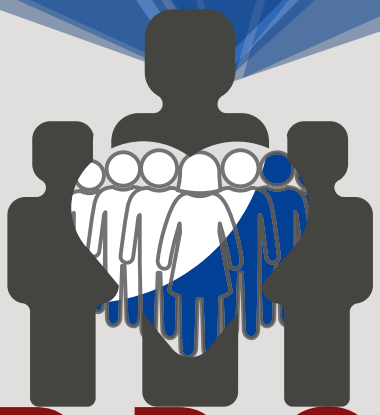


LEPROSY

CLINICAL PRACTICE GUIDELINES

2021

NATIONAL LEPROSY CONTROL PROGRAM

DEPARTMENT OF HEALTH

PHILIPPINES

Philippine Leprosy Clinical Practice Guidelines

Published by

National Leprosy Control Program
Disease Prevention and Control Bureau
Department of Health
San Lazaro Compound, Rizal Avenue, Sta. Cruz
Manila 1003, Philippines

An electronic copy of this publication can be downloaded at:
www.doh.gov.ph

Suggested Citation:

Department of Health. (2021). *Philippine Leprosy Clinical Practice Guidelines*. Manila, Philippines:Department of Health.

Editorial and Publication Team

Technical Advisory Group

Chair:	Dr. Leda M. Hernandez National Leprosy Control Program
Co-chair:	Dr. Francesca Gajete International Leprosy Association
Members:	Dr. Rajendra Prasad Huraj Yadav World Health Organization
	Dr. Gloria Nenita Velasco Health Policy Development and Planning Bureau
	Dr. Ma. Luisa Abad-Venida Philippine Dermatological Society

Technical Team

Principal Investigator:	Dr. Abelaine Venida-Tablizo
Technical Lead:	Mr. Teddy S. Dizon
Technical Co-lead:	Dr. Joseph V. Oraño
Support Team:	Dr. Cherie Grace Quingking Dr. Rosally P. Zamora Dr. Grace Almenor Ms. Seth N. Barce

Implementing Agency

Healthcare Practice and Policy Management (HPPM), Inc.

Funding and Partner Agency

International Leprosy Association – Philippines
Culion Foundation, Inc
Philippine Dermatological Society

Contents

This page was intentionally left blank.

Abbreviation and acronyms

ADR	adverse drug reaction
ALT	alanine aminotransferase
AMR	antimicrobial resistance
AGREE	Appraisal of Guidelines for Research and Evaluation
AST	aspartate aminotransferase
BI	bacterial index
BL	borderline leprosy
CPG	clinical practice guidelines
CI	confidence interval
COI	conflict of interest
CP	Consensus Panel
DOH	Department of Health (Philippines)
ELISA	enzyme-linked immunosorbent assay
ENL	erythema nodosum leprosum
ERE	Evidence Review Experts
G6PD	glucose-6-phosphate dehydrogenase
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GDG	Guideline Development Group
HR	hazard ratio
HDL	high-density lipoprotein
INFIR	ILEP nerve function impairment and reactions
LL	lepromatous leprosy
LDL	low-density lipoprotein
MF	monofilament
MB	multibacillary

MDT	multidrug therapy
NLCP	National Leprosy Control Program
NPV	negative predictive value
NCS	nerve conduction studies
NFI	nerve function impairment
NP	nerve palpation
NT	Northern Territory (Australia)
NNH	number needed to harm
NNT	number needed to treat
OR	odds ratio
PB	paucibacillary
PYAR	person-years at risk
PCR	polymerase chain reaction
PICO	Population, Intervention, Comparison, Outcome
PIPOH	Population, Interventions, Professionals, Outcomes, Health care setting and context
PPV	positive predictive value
qPCR	quantitative polymerase chain reaction
RCT	randomized controlled trial
RR	relative risk
SGPT	serum glutamic pyruvic transaminase (see ALT)
SGOT	serum glutamic-oxaloacetic transaminase (see AST)
SDR	single-dose rifampicin
SSS	slit-skin smear
SC	Steering Committee
TAG	Technical Advisory Group
TG	triglyceride

TB	tuberculosis
T1R	type 1 reaction
T2R	type 2 reaction
VMT	voluntary muscle testing
WHA	World Health Assembly
WHO	World Health Organization
YLD	years lost to disability

Acknowledgements

The Philippine Leprosy CPG was produced by the Department of Health (DOH) under the technical guidance and supervision of the National Leprosy Control Program (NLCP) and the International Leprosy Association (ILA) Philippines. Representatives from the DOH, ILA-Philippines, WHO Philippines and the Philippine Dermatological Society (PDS) comprised the Technical Advisory Group, which provided the technical direction and guidance in the conceptualization, development and finalization of the CPG.

Healthcare Practice and Policy Management, Inc. (HPPM) was contracted as an independent study group to generate the Philippine leprosy CPG through a series of consultations and evidence reviews.

The following partner organizations contributed to the success of this publication: National Leprosy Control Program, Philippine Dermatological Society, Health Policy Development and Planning Bureau, Pharmacy Division, Health Facility Development Bureau, Philippine Health Insurance Corporation, National Council on Disability Affairs, Philippine Institute of Traditional and Alternative Medicine, Philippine Academy of Ophthalmology, Pediatric Infectious Disease Society of the Philippines, Rizal Medical Center, Jose R. Reyes Memorial Medical Center, Southern Philippines Medical Center, St. Luke's Medical Center College of Medicine, East Avenue Medical Center, Research Institute for Tropical Medicine, Culion Sanitarium and General Hospital, Dr. Jose N. Rodriguez Memorial General Hospital and Sanitarium, Association of Municipal Health Officers of the Philippines, Integrated Midwives Association of the Philippines, Philippine Physical Therapy Association, Philippine Academy of Family Physicians, and Culion Foundation.

Contributors

These guidelines were collaborative effort between various guideline committees, methodologists, systematic reviewers. The consensus panel/committee included leprosy advocates, program managers of leprosy program and primary health care givers. All contributors completed the declaration of interest form.

The Technical Advisory Group (TAG) consisted of the following persons: Dr. Leda M. Hernandez (DOH-DPCB), Dr. Francesca Gajete and Ms. Rouselle Gajete (ILA Philippines), Dr. Ma. Luisa Abad-Venida (PDS/JRRMMC), Dr. Rajendra Prasad Juraj Yadav (WHO Western Pacific Region) and Dr. Mae Velasco (DOH-HPDB).

The Steering Committee was composed of representatives from the Department of Health and WHO Philippines, and other stakeholders: Dr. Julie Mart Rubite (DOH-DPCB), Dr. Anna Melissa Guerrero and Joyce Ceria-Perena (DOH-PD), Dr. Hyacinth Balderama (DOH – HFDB), Dr. Marc Anthony Cepeda (PhilHealth), Engr. Emerito L. Rojas (NCDA), Dr. Kalpeshinh Rahevar (WHO Philippines), Dr. Teresita Gabriel (PDS/RITM), Dr Teresita R. Castillo (PAO), Dr. Maylene Agrimano (PIDSP), Dr. Maria Mercedes S. Cauilan (PDS/SPMC), Dr. Malaya P. Santos (PDS/SLMCCM), and Dr. Irene Florentino Farinas (DOH-PD).

Methodologists, systematic reviewers and evidence review experts were provided by the Healthcare Practice and Policy Management, Inc team with background in clinical epidemiology, medical informatics, infectious disease and public health provided the technical guidance for the development of clinical practice guideline and clinical pathway. Dr. Rosally Zamora, Dr. Cherie Grace Quingking, Dr. Grace Almenor and Dr. Joseph Oraño provided the guidance on the implementation, systematic reviews and drafted the recommendations. The team was headed by the project lead, Dr. Abelaine Venida-Tablizo, who also provided her expertise as the technical reviewer and subject matter expert for leprosy. The project was only possible with the administrative, coordination and review services provided by Mr. Teddy Dizon and Ms. Seth Barce.

The Consensus Panel contributed by reviewing the evidence base and affirming recommendation statements. The panel included Ms. Pacita Alano (DOH-DPCB), Dr. Annabelle Pabiona-de Guzman (PITAHC), Dr. Arturo Cunanan Jr (Culion Sanitarium and General Hospital), Dr. Frederica Veronica Marquez Protacio (PDS), Dr. Angela M. Lavadia (PDS/EAMC), Dr. Jessie Mae Cruz (PAFP), Dr. Franz Marie Cruz (PAO), Dr. Sinamar Ann C. Dela Cruz-Abando and Dr. Dimpna Cecilia D. Sare (AMHOP), Ms. Corazon L. Paras (IMAP), Mr. Michael P. Gabilo (PPTA), Ms. Catherine Joy Escuarda, and Mr. Eugene Caccam (Culion Foundation, Inc.)

This page was intentionally left blank.

Executive summary

The Department of Health seeks to further reduce the prevalence of leprosy in the country, and achieve its goal of realizing a "leprosy-free" Philippines by 2022 (Department of Health, 2018). In fact, the Philippines has reached targets for the elimination of leprosy as a public health problem based on national prevalence rates. Notably, pockets of high prevalence and detection rates in the country remain (Leonardo et al., 2020).

As a chronic infectious disease, leprosy negatively influences the physical and psychosocial well-being of the affected individual. In addition to visible lesions that are highly stigmatized, patients may develop significant neuromuscular impairments secondary to peripheral nerve involvement and visible deformities due to injuries caused by sensorimotor impairments (Somar et al., 2020). Globally, the burden of disease is estimated at 21,100 disability-adjusted life-years (Kyu et al., 2018). In fact, the recognition of the lasting impact of leprosy beyond the immediate course of antibiotic treatment has led the WHO to reassert its global strategy to address disability.

The Department of Health developed its own Manual of Procedures of NLCP for 2017-2022 serving as a guide for local program managers and coordinators, health workers in the prevention, and control, diagnosis, management and care of patients and at-risk individuals. Development of a clinical practice guideline (CPG) that is sensitive to the local and community context is desirable to address local clinical practice variations including but not limited to under-, over- and misuse of international recommended interventions.

Recognizing the significant progress in scientific knowledge on leprosy since it was recognized as a public health problem by the WHO, guideline development for the management of leprosy in the Philippines utilized new evidence generated by leprosy research as well as a synthesis of existing international clinical practice guidelines. Program implementers, policy makers, and experts in dermatology and in the management of complications related to leprosy were consulted in generating clinical questions that should be addressed by the Philippine leprosy CPG through a process of prioritization and consensus-building. A consensus panel composed of stakeholders in the management of leprosy validated the findings from a review of evidence.

This Guideline will aid in standardizing the care provided to patients with leprosy in the Philippines, and ensures that diagnosis, treatment and prevention standards are appropriate and contextualized to local policies, needs and capabilities.

Summary of Recommendations

Recommendations will be based on the evidence synthesis from the systematic review of literature utilizing both ADAPTE and de novo synthesis. Results of the ADAPTE will be from the updated source guideline, primarily from the WHO Leprosy clinical practice guidelines. The Philippine Leprosy Clinical Practice Guideline will cover screening, diagnosis, treatment and prevention clinical questions that are relevant to the local practice settings.

AREA OF RECOMMENDATION	CLINICAL QUESTION	RECOMMENDATION	METHOD	STRENGTH	QUALITY OF EVIDENCE
SCREENING	How are leprosy cases best defined? What clinical parameters should be considered when suspecting leprosy?	Leprosy is considered based on the presence of at least one of the three 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; or 3) presence of acid-fast bacilli in a slit-skin smear.	ADAPTE	Weak	Very low
		It is recommended that slit-skin smear or histopathological examination be included in the initial diagnosis of leprosy if available. The unavailability of slit-skin smear should not hamper the initiation of treatment.	ADAPTE	Weak	Very low
	Among patients for treatment of leprosy, what initial clinical and laboratory evaluation should be done?	Clinical evaluation including complete history (close contacts and co-morbidities), physical examination, and disability assessment (to include sensory and motor nerve function assessment and eye examination) are recommended before, during and after treatment to determine presence and progress of disability.	De novo	Strong	Moderate

AREA OF RECOMMENDATION	CLINICAL QUESTION	RECOMMENDATION	METHOD	STRENGTH	QUALITY OF EVIDENCE
		The following laboratory diagnostics may be done, if available, before initiating treatment: slit skin smear, complete blood count, SGPT/SGOT and renal function tests.	De novo	Strong	Low
		G6PD deficiency screening and pathological examination of skin biopsies may be done, if indicated and available.	De novo	Strong	Low
		Electrocardiogram and lipid profile may be done for high-risk patients.	De novo	Strong	Very low to low
		Chest X-ray and sputum smear microscopy may be done to screen for active pulmonary tuberculosis.	Good Practice Statement		
		Fasting blood sugar determination may be done to screen for diabetes.	Good Practice Statement		
		Early referral to a specialist is desirable if with presence of disability and if with derangement of initial diagnostics, but the presence of disability and absence of access to a specialist should not prevent initiation of treatment in primary health care.	Good Practice Statement		
TREATMENT AND MANAGEMENT OF LEPROSY	Among patients diagnosed with paucibacillary and multibacillary leprosy, what is the dose and duration of treatment?	A three-drug regimen with rifampicin, dapsone and clofazimine is recommended for all leprosy patients with duration of treatment of 6 blister packs taken within 6-9 months for PB leprosy and 12 blister packs taken within 12-18 months for MB leprosy.	De novo	Weak	Very low

AREA OF RECOMMENDATION	CLINICAL QUESTION	RECOMMENDATION	METHOD	STRENGTH	QUALITY OF EVIDENCE
	Among patients with MB leprosy, can MDT be extended to 24 months versus 12 months and what are the indications for extension?	There is no strong evidence to extend MDT for MB leprosy patients, but extension of treatment may be done as clinically indicated.	De novo	Weak	Very low
		Patients needing treatment extension should be referred to specialty centers.	Good Practice Statement		
MONITORING AND EVALUATION DURING TREATMENT	What is the recommended monitoring interval during and after treatment?	Active monitoring should be done based on regular clinical evaluation to detect adverse drug events, leprae reaction, disability, treatment failure and relapse.	Good Practice Statement		
		To detect adverse drug events, patients on treatment should have a repeat complete blood count and liver function test one month after initiation of treatment, then quarterly, until end of treatment when available and referred accordingly.	De novo	Weak	Very low
		To detect lepra reactions, patients undergoing treatment are recommended to follow up monthly. Patients who completed treatment are recommended to have follow-up visits every three months for the first two years and annually for five years.	De novo	Strong	Very low
		To detect new or progression of physical disability, patients should be followed up monthly during treatment. For patients who have completed treatment, follow-up visits should be made every three months for the first two years and annually for five years.	De novo	Strong	Very low

AREA OF RECOMMENDATION	CLINICAL QUESTION	RECOMMENDATION	METHOD	STRENGTH	QUALITY OF EVIDENCE
		To detect relapse, patients should be advised to watch out for new lesions, numbness or loss of sensation appearing after release from treatment.	De novo	Strong	Very low
MANAGEMENT OF LEPRA REACTIONS	What is the treatment of complicated/refractory cases of lepra reactions?	In primary health care settings, health workers need to be trained in recognizing leprae reactions, providing initial treatment and initiating possible referral to specialists.	De novo	Strong	Moderate
		The mainstay treatment for type 1 and type 2 leprae reaction is oral corticosteroid. Prednisolone is given for at least 20 weeks (5 months) prednisolone regimen, starting at 0.5 mg/kg to 1 mg/kg daily, tapered by 5 mg every 2 weeks until completion of 20 weeks to prevent early nerve damage or progression of symptoms.	De novo	Strong	Moderate
		For patients with leprae reaction, early treatment with corticosteroids (prednisolone) should be started within six months, after which steroids may be ineffective.	De novo	Strong	Moderate
		Adverse events that need to be monitored for patients on corticosteroids (prednisolone) are gastric pain, steroid-induced hyperglycemia, Cushing syndrome, osteoporosis and infections.	De novo	Strong	Moderate
		Other adverse events that need to be monitored are mental disturbance, growth suppression in children, hypertension, glaucoma and cataract. Patients on steroid should be monitored closely for steroid-induced complications.	Good Practice Statement		

AREA OF RECOMMENDATION	CLINICAL QUESTION	RECOMMENDATION	METHOD	STRENGTH	QUALITY OF EVIDENCE
		For patients who do not respond or cannot tolerate prednisolone, these alternative treatment regimens may be used: a. Type 1 leprae reaction not responding with prednisolone alone: cyclosporine is recommended as additional treatment with prednisolone. b. Type 2 leprae reactions that are not responsive to prednisolone alone: second-line drugs such as clofazimine and cyclosporine can be used with prednisolone as alternative therapy. c. Thalidomide may be used as alternative treatment regimen for ENL, but it is limited in accessibility due to its teratogenic effects and consequently, ethical and legal considerations.	De novo	Strong	Moderate
		Clofazimine monotherapy may be used as alternative treatment if prednisolone is contraindicated.	ADAPTE	Weak	Very low
		Patients with confirmed leprae reaction may receive prednisolone treatment under the supervision of trained community health workers. However, patients with suspected refractory leprae reaction should be referred to specialists for treatment and management.	Good Practice Statement		
		For patients who will receive chronic steroid regimen, they should be referred to specialist for possible side effects.	Good Practice Statement		
CHEMOPROPHYLAXIS	Should contacts exposed to a patient with leprosy be offered chemoprophylaxis versus observation alone?	Eligible contacts (i.e., household contacts) of leprosy patients should be given chemoprophylaxis in the absence of any contraindications.	De novo and ADAPTE	Strong	High

AREA OF RECOMMENDATION	CLINICAL QUESTION	RECOMMENDATION	METHOD	STRENGTH	QUALITY OF EVIDENCE
	What is an effective and safe chemoprophylaxis among contacts of patients with leprosy and high-risk populations?	Single dose rifampicin (300–600 mg) 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 disease and in the absence of other contraindications. This intervention shall be implemented by programs that can ensure adequate management of contacts.	De novo and ADAPTE	Weak	Very low
		It is recommended that surveillance for eligible contacts (i.e., household contact) of patients with leprosy be done in the program level.	Good Practice Statement		
LEPROSY AND DRUG RESISTANCE	How is drug resistance evaluated among leprosy patients?	All patients suspected to have drug resistance should undergo drug susceptibility testing, if available.	De novo	Weak	Very low
		Patients confirmed to have relapsed must be evaluated for drug resistance and referred to a specialty center.	De novo	Weak	Very low
		Drug resistance should be suspected in a patient with prior history of dapsone (monotherapy) intake.	De novo	Strong	Very low
		Drug resistance should be suspected among the following populations: 1) patients who have relapsed; 2) patients with treatment failure; 3) patients living in a community with reported drug-resistant leprosy; and 4) new patients with prior history of intake of dapsone, rifampicin or clofazimine for indications other than leprosy.	Good Practice Statement		
	What is the treatment regimen for drug-resistant leprosy?	Leprosy patients with suspected resistance to dapsone, rifampicin, or clofazimine are recommended to be referred to specialty treatment centers for evaluation and management.	Good Practice Statement		

AREA OF RECOMMENDATION	CLINICAL QUESTION	RECOMMENDATION	METHOD	STRENGTH	QUALITY OF EVIDENCE
		Leprosy patients with confirmed 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.	ADAPTE	Weak	Expert opinion; no evidence retrieved
		Leprosy patients with resistance to both rifampicin and ofloxacin may be treated with the following drugs: clarithromycin, minocycline and clofazimine daily for 6 months, followed by clarithromycin or minocycline plus clofazimine daily for the next 18 months.	ADAPTE	Weak	Expert opinion; no evidence retrieved

Rationale

From 2017 data, leprosy affects approximately 4 per 100,000 population in the Philippines, with an incidence rate of 2.47 per 100,000 population.(Department of Health, 2018; Handog et al., 2011) Albeit low, further reductions in the prevalence of leprosy is sought with the Department of Health's goal of realizing a "leprosy-free" Philippines by 2022 (Department of Health, 2018). Leprosy control made strides with the discovery and establishment of the multi-drug therapy (MDT) regimen by the World Health Organization, along with the continued supply of MDT to the country. In fact, the Philippines has achieved the WHO-recommended targets for leprosy elimination based on national prevalence rates; however, pockets of high prevalence and detection rates in the country remain (Leonardo et al., 2020). The Philippines continues to pour its resources into eliminating leprosy from these areas.

As a chronic infectious disease with cutaneous and nervous manifestations, leprosy causes outsize physical and psychosocial burden on the affected individual. Patients may develop significant neuromuscular impairments secondary to peripheral nerve involvement in leprosy. Globally, the burden of disease is estimated at 21,100 disability-adjusted life-years (Kyu et al., 2018). Moreover, the resulting disabilities and irreversible disfigurements have historically contributed to intense societal stigma and discrimination against patients with leprosy. Psychiatric morbidities and other negative demographic, lifestyle and socioeconomic factors have been identified among leprosy-affected persons (Somar et al., 2020). In fact, the recognition of the lasting impact of leprosy beyond the immediate course of antibiotic treatment has led the WHO to reassert its global strategy to address disability.

On the international front, apart from supplying MDT to countries where leprosy is endemic, the World Health Organization has published its clinical practice guideline in 2018 (World Health Organization [WHO], 2018b) This is the first international CPG on leprosy providing evidence-based recommendations on the diagnosis, treatment and prevention of leprosy, utilizing formal guideline development process using WHO guideline development methods. The CPG was developed for personnel involved in leprosy policy formulation and clinicians who manage leprosy, particularly in low- and middle-income countries.

The Philippines is committed to the eradication of leprosy from the country. The national public health response to leprosy is led by the National Leprosy Control Program (NLCP) of the Department of Health. PhilHealth also covers treatment for leprosy, albeit with case rates only for inpatient care for patients who have leprosy as a comorbidity of up to Php 8,800 (Philippine Health Insurance Corporation, 2017). Based on NLCP data, the country remains the leading contributor of leprosy burden in the Western Pacific Region with 1721 new cases detected in 2016.

The Department of Health developed its own Manual of Procedures of NLCP for 2017-2022 serving as a guide for local program managers and coordinators, health workers in the prevention, and control, diagnosis, management and care of patients and at-risk individuals. While there is corroborative guidance from the WHO and the DOH on leprosy management, there remains considerable practice variations. In an evaluation of clinical practice and knowledge in three hospitals in Metro Manila, there were significant differences in leprosy management, including clinical definitions of concepts such as treatment completion and default and non-standard

extension of treatment up to 24-36 months (Pepito et al., 2018). Development of a clinical practice guideline (CPG) that is sensitive to the local, community and primary care context is desirable to address local clinical practice variations including but not limited to underuse, overuse and misuse of international recommended interventions.

Target audience

This is intended for Filipino healthcare workers who care for patients with leprosy in the primary setting, including general practitioners, dermatologists, and students or trainees.

Scope and objectives of the Guidelines

This guideline included relevant questions on screening, diagnosis, treatment, and prevention of leprosy. The objectives of this guideline are as follows:

1. To present and synthesize the best available evidence on the diagnosis and management of leprosy;
2. To standardize the diagnosis and management of leprosy in the Philippines for the reduction of the burden of disease; and,
3. To complement the existing DOH manual of procedures by providing evidence to its statements for policy implementation.

I. BACKGROUND

Introduction

Leprosy, also referred to as Hansen disease, is caused by *Mycobacterium leprae* complex, which comprises *M. leprae* and *M. lepromatosis* (Maymone et al., 2020). This bacterium that belongs to the genus *Mycobacterium*, which also includes the bacteria that causes tuberculosis. A key feature of bacteria in the *Mycobacteria* genus is their complex cell envelope that renders them poorly permeable to the common laboratory staining procedures, such that "acid-fast" staining techniques are instead preferred (Pfyffer & Inderlied, 2010). Additionally, the *M. leprae* complex is an obligate intracellular pathogen that requires temperatures lower than the core human body temperature for replication (Maymone et al., 2020).

Infection begins with human-to-human respiratory secretions as the most common route of transmission, with rare instances of skin contamination and vertical transmission having been reported as well (Maymone et al., 2020). It is acquired through close contact and prolonged exposure. The bacterium invades a cell and replicates slowly until T cells locate the mycobacterial antigens and a chronic inflammatory reaction begins. Development of the disease depends on the patient's immunologic response to M. leprae (Eichelmann et al., 2013; Maymone et al., 2020). An intense cellular response may be observed in cases in the tuberculoid pole of the spectrum of leprosy, while an absence of a specific immune response is seen at the opposite pole in lepromatous leprosy (Eichelmann et al., 2013). The lepromatous form may present as infiltrated plaques that are anesthetic and annular or ovoid. Histologically, a biopsy of the skin and the region surrounding the affected nerves may reveal granulomas.

Mycobacterium leprae shows a predilection for peripheral nerves (Sabin & Swift, 2014). Within the cells of these nerves, the bacterium is able to induce proliferation of its preferred reservoir cells to ensure long-term bacterial survival (Tapinos & Rambukkana, 2005). The presence of these mycobacteria in the peripheral nerves incites a granulomatous response resulting in early and severe irreversible immune-mediated nerve damage (Sabin & Swift, 2014).

Due to the variable immune response from the infection, patients may also experience leprosy reactions, which feature debilitating systemic symptoms including vasculitis (Eichelmann et al., 2013; Sabin & Swift, 2014). These reactions may be classified into two major types: type 1 reactions (or reversal reactions) and type 2 reactions (or erythema nodosum leprosum) (Nery et al., 2013). The cellular reaction is most severe in regions with greatest bacterial density, such as the peripheral nerves that a leprosy reaction may cause devastating acute neuritis, resulting in sensory loss and/or paralysis. The neurologic deficits may also contribute to deformities such as clawed toes, foot drop and clawed hands (Sabin & Swift, 2014). However, the peripheral neuropathy with loss of temperature and pain sensation, contributes to the risk of progressive damage of limbs from painless injury, followed by ulceration, infection, osteomyelitis and even bone resorption. It causes iritis and episcleritis which may also lead to blindness if left untreated. Deformity in leprosy is preventable with adequate patient support (Eichelmann et al., 2013).

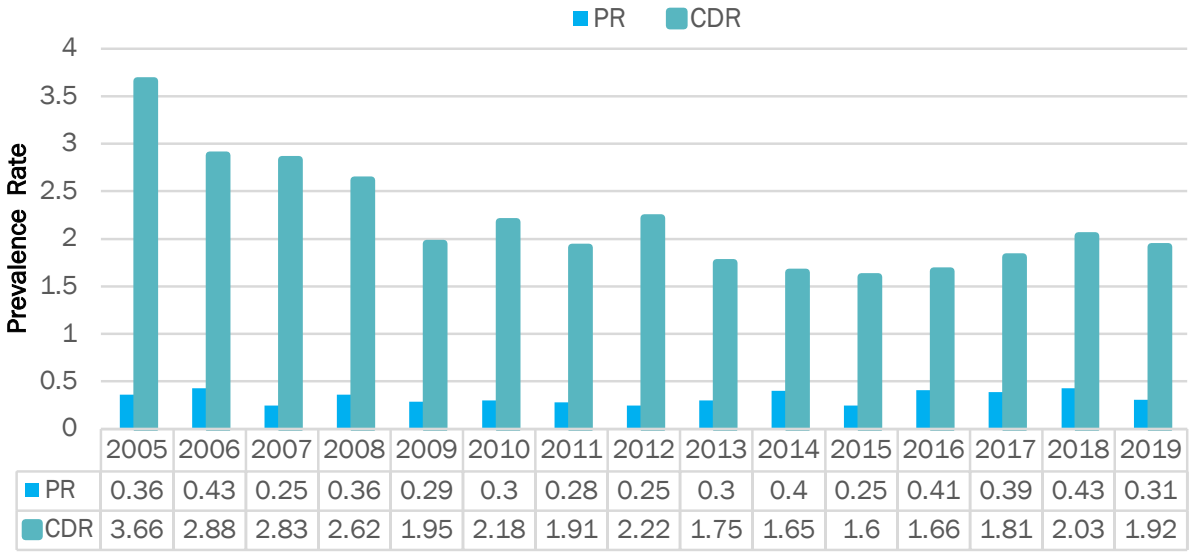
Leprosy was the first infectious disease to be causally associated with its bacterial etiology, when *Mycobacterium leprae* was first identified in 1873 (Maymone et al., 2020). However, records of the disease date back to 600 BC and there are biblical references to leprosy. Patients have historically suffered from stigma, attributed to beliefs regarding the high transmissibility of leprosy and biblical proscriptions against the disease (Robertson, 2016). Stigma against leprosy appears

to be cross-cultural and associated with visible impairments, activity limitations and socioeconomic status (Adhikari et al., 2014; Rathod et al., 2020). Leprosy-affected people have fought against stigma and social exclusion, which has endured through time despite advances in clinical knowledge on the disease (Robertson, 2016).

The burden of leprosy

The World Health Organization considers leprosy as a public health problem to have been sufficiently addressed as of the year 2000, when the registered prevalence of leprosy was less than 1 case per 10,000 persons (WHO, 2019b). Data from the WHO Global Health Observatory for 2019 shows a prevalence of 177 115 cases, but 202 162 new cases of leprosy were detected in the same year.

Data from the DOH NLCP for the same year showed 2,023 new cases of leprosy, with a resulting case detection rate of 1.92 per 100,000 population. Figure 1 below Total prevalence rate for 2019 was 0.31 per 10,000 population. These epidemiologic estimates indicate that the Philippines has achieved WHO targets; however, a study published in 2020 found that there are remaining areas within the country that experience high prevalence rates and case detection rates (Leonardo et al., 2020). The WHO, which provides free pharmacotherapy packs for patients with leprosy, recorded 2,122 cases registered for treatment (Alberts et al., 2011).



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
PR	0.36	0.43	0.25	0.36	0.29	0.3	0.28	0.25	0.3	0.4	0.25	0.41	0.39	0.43	0.31
CDR	3.66	2.88	2.83	2.62	1.95	2.18	1.91	2.22	1.75	1.65	1.6	1.66	1.81	2.03	1.92

FIGURE 1. PREVALENCE RATE (PER 10,000 POPULATION) AND CASE DETECTION RATE (PER 100,000 POPULATION) OF LEPROSY FROM 2005-2019. SOURCE: DOH-NLCP, 2020.

The burden of disease of leprosy extends beyond the diagnosis of the infection and its immediate clinical course. An equally important aspect of the disease is the burden of disability due to secondary impairments arising from the involvement of the peripheral nervous system in leprosy, such as wounds caused by burns, pressure ulcers, contractures and visual impairment (Jan Hendrik Richardus, 2013). Among infectious diseases, leprosy is a leading cause of peripheral neuropathy and disability in the world (Rathod et al., 2020). The Global Burden of Disease 2016

study reported 23.0 thousand disability-adjusted life-years (DALYs), an estimate that includes years of healthy life lost due to disability (YLD) as well as years of life lost (YLD) (Hay et al., 2017).

Specific to leprosy, the WHO has also established the presence of Grade 2 disability in the patient population as an important country indicator of leprosy control. Grade 2 disability in leprosy refers to visible impairments or deformity, such as digital shortening or burns as a result of impaired sensation (Brandsma & Van Brakel, 2003). In 2019, there were 37 adults with grade 2 disabilities according to DOH NLCP data (WHO, 2019a).

Leprosy reactions are crucial aspects of the burden of disease of leprosy, since physical disability is mainly caused by acute episodes and a positive association exists between patients having leprosy reactions and disability (De Paula et al., 2019; Nery et al., 2013). In India, a retrospective study of 16 years from 1994 to 2009 found a range of incidence rates of type 1 reaction at 10-21% per year for patients with paucibacillary leprosy and 6-8% per year for patients with multibacillary leprosy (Tiwary et al., 2011). In a cohort study between 2003-2008 with a site in Cebu, 10.4% of newly detected leprosy patients were diagnosed with type 1 reactions at baseline (Scollard et al., 2015). In a systematic review of epidemiological data, 1.2% of all leprosy cases develop erythema nodosum leprosum (ENL) according to field-based studies, whereas estimates are higher in hospital-based surveillance studies (Voorend & Post, 2013). Moreover, multiple ENL episodes were observed in 39-77% of ENL patients, averaging at 2.6 episodes. Leprosy reactions pose a significant economic burden to households affected by these complications due to medical costs and productivity loss (Chandler et al., 2015).

Population and individual-based health interventions

Since the Third World Health Assembly, leprosy has become a matter of concern for the World Health Organization when it was placed on the regular budget (WHO, 1950). The WHO remarked that leprosy control measures can substantially reduce leprosy prevalence and endorsed population-based interventions such as intensive case detection and disease surveillance as early as 1975 (28th World Health Assembly [WHA], 1975). The indicator for the elimination of leprosy as a public health problem was set at a target of below one case per 10,000 population (44th WHA, 1991). The WHO also monitors the case detection rates and number of cases registered for treatment. The use of disease prevalence has been criticized because the indicator is sensitive to operational factors such as detection delay and case-finding method, and in 2009, the WHO instated as an indicator the number of new cases with grade 2 disability (Alberts et al., 2011). This step also follows a shift in global strategy from elimination of leprosy as a public health problem to reduction of the disease burden, along with an emphasis in reduction of new cases in children (WHO, 2018a).

The WHO also seeks to address the social exclusion associated with the disease, noting the importance of psychosocial factors in the control of leprosy (28th WHA, 1975). Stigmatization hinders early detection (WHO, 2020a). Health education through media and community participation and institution of legal guarantees to protect the rights of patients with leprosy are emphasized as means to eliminate stigma.(40th WHA, 1987)

Leprosy control and mitigation of leprosy-associated disability is closely tied to early diagnosis and closely supervised treatment (28th WHA, 1975). Multidrug therapy (MDT) was introduced in 1981, and since 1995 WHO provided MDT free of cost.(Alberts et al., 2011; WHO, 2019c)

The same pillars of leprosy control of population and individual-based health interventions, as well as prioritizing government ownership of leprosy control programs, were emphasized with the WHO's Global Leprosy Strategy 2016-2020 (WHO, 2016b).

The Department of Health administers the National Leprosy Control Program, which comprises "a multi-agency effort to control leprosy in the country with private and public partnership in achieving its goals to lessen the burden of the disease and its mission to have a leprosy-free country."(NLCP, 2018b) Government efforts under the NLCP mirror the global strategies and priorities promoted by WHO.

Population-based services provided by the NLCP include: case detection, especially mapping of new cases and identification of hotspots of leprosy transmission in the country; active case finding and household contact tracing; community- and patient-directed health education; and, health human resource capacity building through continuing medical education campaigns and lectures (NLCP, 2018b). The NLCP also manages the drug supply and the system of drug provision for the control of leprosy and its complications.

The NLCP's approach to leprosy control is two-pronged and acknowledges both new and old WHO goals of eliminating leprosy as a public health problem, especially in endemic areas, and preventing and managing grade 2 disability among patients with leprosy (NLCP, 2018b). Among its strategic objectives, the NLCP also seeks to prevent leprosy in children below 15 years and increase coverage of MDT in all areas.

Guideline development process

Clinical practice guidelines are recommendations and statements provided to practitioners to optimize care to patients and assist policy makers in creation of policies and pathways. These statements are based on systematic reviews of evidence that are encompassing, cost-effective, adapted to the local setting and culturally appropriate. CPGs are developed using a systematic process of evidence synthesis and multidisciplinary consensus development among experts and stakeholders.

The development process of the Philippine Leprosy Clinical Practice Guidelines adapted the methods in the Department of Health Manual for Clinical Practice Guideline Development (DOH [Philippines], 2018), which prescribed four phases: 1) preparation phase; 2) evidence synthesis; 3) consensus development; and 4) dissemination and evaluation. This document will focus on the first three phases of the CPG development cycle. Figure 2 below summarizes the activities for the preparation phase and the evidence synthesis phase.

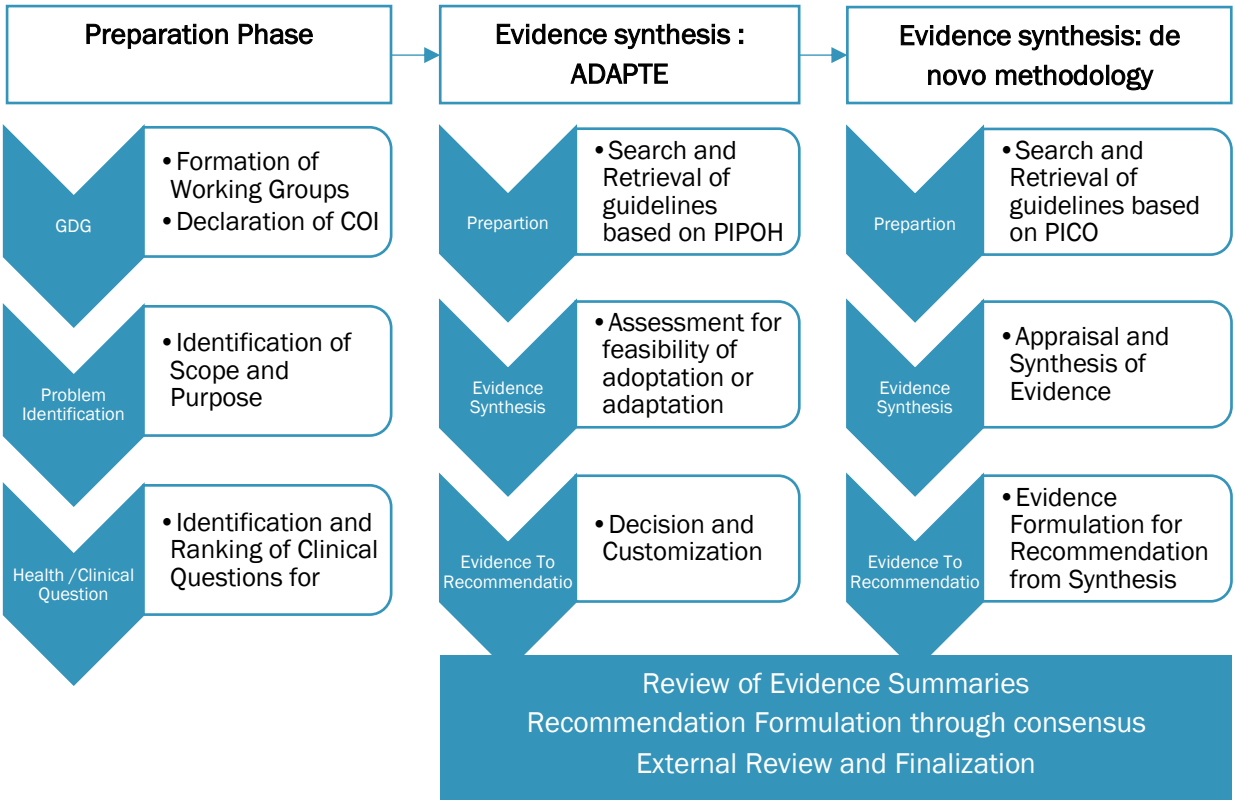


FIGURE 2. FLOWCHART OF ACTIVITIES FOR THE PREPARATION AND EVIDENCE SYNTHESIS PHASES

Preparation phase

Formation of working groups

The guideline development group was composed of smaller working groups of stakeholders, who were identified and convened during the preparation of the guideline development process, which took on unique and complementary responsibilities. These working groups included the CPG Technical Advisory Group (TAG), the Steering Committee, the Evidence Review Experts, and the Consensus Panel.

The Technical Advisory Group (TAG) and the Steering Committee comprised the lead CPG developers. The TAG was created to provide oversight and direction in the CPG development process. Nominated members for the TAG included representatives from the World Health Organization, Department of Health, International Leprosy Association Philippines, and Jose Reyes Memorial Medical Center.

The Steering Committee (SC) drafted the scope and target audience of the CPG and identified and ranked the clinical questions relevant to the management of leprosy in the Philippines. Members identified were multispecialty practitioners—dermatologists, pediatric infectious disease specialists, ophthalmologists, program managers, policy makers and patient advocates on disability.

The Evidence Review Experts (ERE) provided technical assistance in evidence review ranging from the development of the clinical questions, search and identification of evidence, appraisal of relevant literature to answer clinical questions, and synthesis of evidence summaries as basis of recommendation statements. The ERE for this Guideline included consultants with backgrounds

in clinical epidemiology, infectious diseases, information specialists, medical informatics and public health.

The Consensus Panel was a wider group of leprosy control stakeholders, who reviewed the evidence with the ERE group. Establishing a more open and diverse group of stakeholders for the Consensus Panel—including multidisciplinary healthcare practitioners, patient advocates, DOH program managers and other technical content experts—was aimed at promoting transparency, introducing different perspectives to leprosy management and safeguarding against conflicts of interest. The Consensus Panel reviewed and revised the recommendation statements and voted on the adoption of these statements into the Guideline.

Declaration and management of conflicts of interest

Independent review of conflict of interests and positive recommendation, the GDG was formed following the DOH CPG Manual 2018. Only stakeholders who have no or limited COI became part of the GDG. See Annex A for details. The funder of the project is ILA and disbursed by Culion Foundation. Both do not have influence in drafting and finalizing this clinical practice guideline. The scope of work and responsibilities of the institution is limited to fund disbursement upon positive approval of both steering committee and consensus panel.

Identification of the scope of the CPG

The PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes and Health Care Setting (ADAPTE Collaboration, 2009). These five items aided the selection and framing of clinical questions:

- **P**opulation: Adult and pediatric patients with leprosy
- **I**nterventions of interest: Screening, diagnostics, treatment and prevention
- **P**rofessionals to whom the Guideline will be targeted: Health care workers
- **O**utcomes: Sensitivity and specificity, cure rate, treatment completion rate, transmission rate
- **H**ealth care setting and context: Primary care

Generation of CPG questions

The methodology of clinical question generation is based on frameworks of clinical practice guidelines, agenda-setting, and consensus-building (Delbecq et al., 1986; Murphy et al., 1998; The James Lind Alliance, 2020; WHO, 2014). For CPG question development guidelines, we specifically referred to guidance published by the WHO (2014), the Scottish Intercollegiate Guidelines Network (SIGN, 2015) and the UK's National Institute for Health and Care Excellence (NICE, 2014). Due to the COVID-19 pandemic and mobility restrictions at the time of guideline development, all methods of communication were virtual, and no face-to-face, physical gatherings were conducted.

The generation of CPG questions is an essential early step in CPG development. These questions were used as the basis for the subsequent systematic review of the evidence base on leprosy (WHO, 2014). CPG questions were generated using an iterative method of online surveys to solicit clinical questions from multisectoral stakeholders—such as health care professionals, patients or patient advocates, and policy makers or program implementers—regarding evidence uncertainties,

areas of controversy in the management of leprosy and known variations of clinical practice and care. Responses were solicited from the TAG, SC and additional stakeholders according to nominations by existing committee members and further stakeholder mapping.

The initial clinical questions were analyzed by the ERE team and grouped together according to similar themes to form *interim* clinical questions. The SC needed to achieve consensus on which *interim* clinical questions should be adopted as the basis for this Guideline. Consensus-building activities included two consecutive online surveys with anonymous feedback to evaluate the importance of each clinical question. The SC was then convened in a culminatory virtual workshop where the final 10 questions were reviewed, revised and chosen according to a consensus. The top 10 questions that garnered the highest importance scores were adopted as the basis for the subsequent evidence review. The 10 questions addressed by this Guideline are summarized in Table 1 below.

TABLE 1. SUMMARY OF CLINICAL QUESTIONS ADDRESSED BY THE GUIDELINE

AREA	QUESTION
SCREENING	How are leprosy cases best defined? What clinical parameters should be considered when suspecting leprosy?
DIAGNOSIS	Among patients for treatment of leprosy, what initial clinical and laboratory evaluation should be done?
TREATMENT	Among patients with diagnosed PB/MB leprosy, what is the dose and duration of treatment? Among patients with MB leprosy, can MDT be extended to 24 months versus 12 months and what are the indications for extension? What is the recommended monitoring interval post-treatment? What is the treatment of complicated/refractory cases of lepra reactions? What is the treatment regimen for drug-resistant leprosy? How is drug resistance evaluated among leprosy patients?
PREVENTION	Should contacts exposed to a patient with leprosy be offered chemoprophylaxis versus followed with observation alone? What is an effective and safe chemoprophylaxis among contacts of leprosy with patients and high-risk populations?

Evidence synthesis

Overview of evidence synthesis methods

The 10 questions reviewed and selected by the SC were further converted to PICO format. The acronym PICO refers to Population, Intervention, Comparator and Outcome, and is a method of

extracting the subjects of interest from a general clinical or research question (Box 1). Final list of PICO elements for each CPG question is located in Annex B.

BOX 1. THE PICO FRAMEWORK FOR REVISING CPG QUESTIONS(National Institute for Health and Care Excellence, 2014)

Population: Which population are we interested in? How best can it be described? Are there subgroups that need to be considered?

Intervention: Which intervention, treatment or approach should be examined?

Comparators: Are there alternative(s) to the intervention being examined? If so, what are these (for example, other interventions, standard active comparators, usual care or placebo)?

Outcome: Which outcomes should be considered to assess how well the intervention is working (including outcomes on both benefits and harms)? What is really important for people using services?

The approach to CPG development may be through 1) adopting existing recommendations from others; 2) adapting existing recommendations to their own context; or 3) creating recommendations de novo after systematic review (Schünemann et al., 2017). In the development of this CPG, after identification of relevant clinical questions during the preparation phase, evidence synthesis was done by the ERE in two phases to address the clinical questions generated: adaptation using the ADAPTE methodology, and de novo CPG development as shown in Figure 2. The GRADE approach was used to formulate and categorize the strength of recommendations (strong or conditional) (Oxman, 2004). 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 (Oxman, 2004).

With consideration of the time and resources to produce quality CPGs, it is recommended that existing guidelines be adapted to reduce duplication of effort and update existing guidelines in a shorter period of time. In this CPG development process, guideline adaptation by the ADAPTE method was considered to address specific health questions, while the de novo method was used for questions that were not found in existing guidelines.

The first phase of the guideline development is the setup phase for both the ADAPTE and de novo methods. As outlined in the preparation phase, this process involves the process of identifying specific health questions and searching for and retrieving guidelines. Independent methodologists and reviewers determined if adaptation of any existing CPG was feasible and consequently created the adaptation plan.

The combination of these two methods presupposes that there are existing good quality CPGs that may need to be contextualized as well as that there are issues inherent to local settings that may not be observed or taken into consideration in other CPGs (Wang et al., 2018).

ADAPTE methodology

The ADAPTE collaboration has developed a systematic approach to aid in the adaptation of guidelines (ADAPTE Collaboration, 2009). The systematic approach aids in the use and modification of existing guidelines to customize an existing guideline to suit the local context while addressing relevant health questions.

Assessment of the guidelines for consideration for adaptation started with a systematic search of existing guidelines in multiple databases, including PubMed, Google Scholar, Scopus® and Directory of Open Access Journals (DOAJ). Search terms and limits are provided in Annex C. The electronic search yielded three guidelines for review: one clinical practice guideline and two treatment guidelines.

The three guidelines were assessed for guideline quality, currency, content, consistency, and applicability (ADAPTE Collaboration, 2009). These guidelines included the WHO's Guidelines for the Diagnosis, Treatment and Prevention of Leprosy (WHO, 2018b), Guidelines for the Control of Leprosy in the Northern Territory by Australia's Department of Health (2018), and Guidelines for the Treatment of Hansen's disease in Japan 3rd edition (Goto et al., 2013). Within the ADAPTE model, the Appraisal of Guidelines for Research and Evaluation (AGREE II) Instrument (Annex D) was used to rate and select appropriate guidelines. These guidelines were reviewed and evaluated by 2 members of the technical review team in duplicate using the AGREE II reporting checklist. The PIPOH components of the guidelines are shown in Annex C.4. The characteristics and contents of the three guidelines are summarized in Annex C.5.

The AGREE Instrument

The Appraisal of Guidelines Research and Evaluation (AGREE) II instrument provides a framework for assessing the quality of clinical practice guidelines (Brouwers et al., 2013). The 23 items in the AGREE instrument assess the methods used for developing the guideline and quality of reporting. Assessment is focused on the rigor and does not assess the clinical content of the recommendation. The domains and criteria for the AGREE II tool are shown in Annex D.

Upon appraising the CPGs using the 23-item criteria, only the WHO Guideline was found with suitable quality and content for adaptation. The WHO Guideline had an overall rigor, according to the AGREE II tool, of 100% with the two other treatment guidelines both earning only 21.43%. A summary of the AGREE II rigor scores are provided in Annex C.6.

TABLE 2. SUMMARY TABLE FOR AGREE SCORES FOR APPRAISED CLINICAL PRACTICE GUIDELINES AND TREATMENT GUIDELINES

GUIDELINE	AGREE II DOMAIN SCORES						
	Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity & Presentation	Applicability	Editorial Independence	Overall
WHO 2018	100%	97.61%	89.28%	97.61%	82.14	57.14%	100%
NT 2018	30.95%	14.28%	14.28%	40.48	14.28%	14.28%	21.43%
Goto et.al., 2013*	42.85%	19.04%	14.28%	40.48%	14.28%	14.28%	21.43%

Although the WHO CPG achieved the best possible AGREE score, it did not address all the CPG questions generated by the SC, requiring de novo evidence synthesis for the remaining questions. The ADAPTE method does not preclude revision of the recommendations from the WHO Guideline, given that the guideline was published in 2018 and that there may be new data and developments in leprosy management. Further customization of the WHO Guideline recommendations may be advisable to incorporate new evidence found through the de novo process. Additionally, the recommendations should also be contextualized to the local setting.

The guideline developers investigated the currency of the WHO CPG, along with formal and informal direct communication with WHO Philippines. The next leprosy update is scheduled in 2022. The two other treatment guidelines did not mention plans for updating.

Treatment recommendations from Guidelines for the Control of Leprosy in the Northern Territory (2018) and Guidelines for the treatment of Hansen's disease in Japan (2013) were also reviewed as the basis for Good Practice Statements, taken as expert opinion. These two guidelines provided guidance on the diagnosis, treatment and prevention of leprosy but with no mention of the strength of evidence as basis for the recommendation.

De novo process

The de novo process was used to address the remaining health questions that were not found among the source guidelines or if the questions required updating in light of new evidence from the time the source guidelines were published. *De novo* refers to the process of creating *new* recommendations based on either evidence or expert opinion.

The clinical questions were also transmuted to articulate the relevant PICO components for each question. Each clinical question corresponded to at least four different PICO sets to accommodate multiple outcomes of interest. Concepts were extracted from the PICO tables, which served as bases for the keywords that were used in a maximally sensitive literature search. The search was conducted according to the search function rules for each database. In sum, search results corresponded to permutations of the intersections of P-I-C against O items. The complete concept table, including PICO components, is presented in Annex E.

The search results were parsed by two members of the ERE, with a third serving as arbitrator in case of disputes regarding the inclusion or exclusion of a particular article.

Primary and secondary outcomes of the studies identified in the systematic literature search were extracted. The evidence was reviewed for their quality by two members of the ERE, which pertains to the certainty in the estimates of the effect to be adequate to support a recommendation (WHO, 2014).

Evidence to recommendations

The tool developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group was used in evaluating the quality of the evidence (Schünemann et al., 2013). Quality of evidence grades are summarized and defined in Table 3 below. The outcomes relevant to each clinical question and their corresponding quality of evidence grades are provided in full in Annex B.

TABLE 3. QUALITY OF EVIDENCE GRADES.(Schünemann et al., 2013)

GRADE	DEFINITION
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

The ERE drafted the initial recommendation statements, accompanied by suggested strengths of recommendation according to a calculus of the desirable effects of an intervention vis-à-vis its undesirable effects (Schünemann et al., 2013). Recommendations may either be *strong* or *weak*. *Strong* recommendations refer to issues where the guideline development group may be confident that the benefits outweigh the risks or costs of an intervention, or vice versa, whereas *weak* recommendations are those where there is appreciable uncertainty on the calculus of benefits and risks. In terms of value to each stakeholder, the GRADE Working Group provided a summary of the implication of recommendation strength on each type of guideline user, which is reproduced in full in Table 4.

TABLE 4. IMPLICATIONS OF STRONG AND WEAK RECOMMENDATIONS FOR DIFFERENT USERS OF GUIDELINES (WHO, 2014)

	STRONG RECOMMENDATION	WEAK RECOMMENDATION
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Consensus development

The result of ADAPTE and de novo processes of evidence evaluation and recommendation synthesis were presented to the Consensus Panel, composed of leprosy management stakeholders from health care practitioners to patient advocates to program implementers, for validation. The results of the systematic literature review and recommendation synthesis were forwarded to the members of the CP for review, either individually or together with their affiliated organizations.

The CP met in a series of three online workshops in the period of 8 January 2021 to 29 January 2021 to discuss and vote on the recommendation statements. The ERE presented the results of the evidence synthesis from the ADAPTE methodology and the evidence summaries from the de novo methodology. The suggested recommendations were also reiterated to the CP.

Nominal group techniques were applied to direct the discussions (Delbecq et al., 1986). After presentation of the evidence and recommendations, stakeholders were requested one-by-one to provide their inputs on each recommendation within a set time limit. The CP was allowed to revise the recommendation statements within reasonable limits as long as the revision did not alter the value of the underlying evidence.

The strength and content of each recommendation were then put to a vote. Reinforcing the need to reach a higher degree of agreement than a majority vote, the workshops sought to achieve consensus by setting a higher standard when to pass a vote. Consensus markers are proxy quantitative indicators of consensus, usually measured according to standard deviation or percent agreement (Christie & Barela, 2005; Holey et al., 2007; Schively, 2007). In these workshops, consensus was set at 80% agreement on a specific choice. If the CP was unable to reach the consensus marker, the cycle of discussions then voting was repeated up to two times. In the event of no consensus by the third iteration, the majority vote was adopted.

Dissemination and use of the Guideline

The value of a clinical practice guideline is fully appreciated when it is widely adopted, and adoption is contingent on access and distribution of the CPG to its target audience. This clinical practice guideline is available on the DOH website and the NLCP program web page.

In discussions between the GDG and NLCP, the effective implementation of the recommendations contained in this Guideline should be accompanied by capacity-building activities. The NLCP shall disseminate this Guideline to concerned develop monitoring and evaluation processes for the dissemination lead the monitoring and dissemination of this Guideline. This CPG is valid until new significant evidence emerges that would require a change in recommendation. The ERE recommends revisiting the Guidelines regularly every 5 years.

References

28th World Health Assembly. (1975). *WHA28.56 Leprosy control*. https://apps.who.int/iris/bitstream/handle/10665/92994/WHA28.56_eng.pdf

40th World Health Assembly. (1987). *WHA40.35 Towards the Elimination of Leprosy*. https://apps.who.int/iris/bitstream/handle/10665/164105/WHA40_R35_eng.pdf

44th World Health Assembly. (1991). *World Health Assembly Resolution 44.9*. https://www.who.int/neglected_diseases/mediacentre/WHA_44.9_Eng.pdf

ADAPTE Collaboration. (2009). The ADAPTE Process: Resource Toolkit for Guideline Adaptation. *Version 2.0*, 1–95. http://www.g-i-n.net

Adhikari, B., Kaehler, N., Raut, S., Marahatta, S. B., & Ggyanwali, K. (2014). Risk factors of stigma related to leprosy - A Systematic Review. *Journal of Manmohan Memorial Institute of Health Sciences*, *1*(2), 3–11. https://doi.org/10.3126/jmmihs.v1i2.9902

Alberts, C. J., Smith, W. C. S., Meima, A., Wang, L., & Richardus, J. H. (2011). Potential effect of the World Health Organization's 2011–2015 global leprosy strategy on the prevalence of grade 2 disability: a trend analysis. *Bulletin of the World Health Organization*, *89*(7), 487–495. https://doi.org/10.2471/BLT.10.085662

Ashwini, B., Nandakishore, B., Basti, R. S., Martis, J., Hundi, G. K., & Jayaraman, J. (2018). Ultrasound as a diagnostic modality for the involvement of peripheral nerves in leprosy. *Indian Journal of Leprosy*, *90*(1), 1–14.

Balagon, M. F., Cellona, R. V, Cruz, E. dela, Burgos, J. A., Abalos, R. M., Walsh, G. P., Saunderson, P. R., & Walsh, D. S. (2009). Long-term relapse risk of multibacillary leprosy after completion of 2 years of multiple drug therapy (WHO-MDT) in Cebu, Philippines. *The American Journal of Tropical Medicine and Hygiene*, *81*(5), 895–899. https://doi.org/10.4269/ajtmh.2009.09-0189

Bandeira, S. S., Pires, C. A., & Quaresma, J. A. S. (2019). Leprosy Reactions In Childhood: A Prospective Cohort Study In The Brazilian Amazon. *Infection and Drug Resistance*, *12*, 3249–3257. https://doi.org/10.2147/IDR.S217181

Barr, J. (2011). A short history of dapsone, or an alternative model of drug development. *Journal of the History of Medicine and Allied Sciences*, *66*(4), 425–467. https://doi.org/10.1093/jhmas/jrq068

Becx-Bleumink, M. (1992). Relapses in leprosy patients after release from dapsone monotherapy; experience in the leprosy control program of the all Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia [Abstract]. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *60*(2), 161–172. http://www.ncbi.nlm.nih.gov/pubmed/1522358

Becx-Bleumink, M., & Berhe, D. (1992). Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy; experience in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *60*(2), 173–184. http://www.ncbi.nlm.nih.gov/pubmed/1522359

Bell, M. L., Kenward, M. G., Fairclough, D. L., & Horton, N. J. (2013). Differential dropout and bias in randomised controlled trials: when it matters and when it may not. *BMJ (Clinical Research Ed.)*, *346*, e8668. https://doi.org/10.1136/bmj.e8668

Bennett, B. H., Parker, D. L., & Robson, M. (2008). Leprosy: Steps along the journey of eradication. In *Public Health Reports* (Vol. 123, Issue 2, pp. 198–205). Association of Schools of Public Health. https://doi.org/10.1177/003335490812300212

Bhat, I., Madhukara, J., Rout, P., Elizabeth, J., & Kumaran, S. (2015). Comparison of bacillary index on slit skin smear with bacillary index of granuloma in leprosy and its relevance to present therapeutic regimens. *Indian Journal of Dermatology*, *60*(1), 51. https://doi.org/10.4103/0019-5154.147791

Bhattacharya, B., Hasanoor Reja, A., Biswas, N., Biswas, S., Lavania, M., Chaitanya, V., Banerjee, S., Maha Patra, P., Gupta, U., Patra, P., & Sengupta, U. (2015). Report of rpoB mutation in clinically suspected cases of drug resistant leprosy: A study from Eastern India. *Indian Journal of Dermatology, Venereology, and Leprology*, *81*(2), 155. https://doi.org/10.4103/0378-6323.152185

Bhushan, P., Sardana, K., Koranne, R., Choudhary, M., & Manjul, P. (2008). Diagnosing multibacillary leprosy: A comparative evaluation of diagnostic accuracy of slit-skin smear, bacterial index of granuloma and WHO operational classification. *Indian Journal of Dermatology, Venereology and Leprology*, *74*(4), 322. https://doi.org/10.4103/0378-6323.42892

Boerrigter, G., Pönnighaus, J. M., Fine, P. E., & Wilson, R. J. (1991). Four-year follow-up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *59*(2), 255–261. http://www.ncbi.nlm.nih.gov/pubmed/2071983

Brandsma, J. W., & Van Brakel, W. H. (2003). WHO disability grading: Operational definitions. *Leprosy Review*, *74*(4), 366–373. https://doi.org/10.47276/lr.74.4.366

Brouwers, M., Kho, M., Browman, G., Cluzeau, F., Feder, G., Fervers, B., Hanna, S., & Makarski, J. (2013). *Appraisal of Guidelines for Research & Evaluation II: AGREE II Instrument*. https://doi.org/10.1503/cmaj.090449

Cambau, E., Saunderson, P., Matsuoka, M., Cole, S. T., Kai, M., Suffys, P., Rosa, P. S., Williams, D., Gupta, U. D., Lavania, M., Cardona-Castro, N., Miyamoto, Y., Hagge, D., Srikantam, A., Hongseng, W., Indropo, A., Vissa, V., Johnson, R. C., Cauchoix, B., … Nanba, Y. (2018). Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009–15. *Clinical Microbiology and Infection*, *24*(12), 1305–1310. https://doi.org/10.1016/j.cmi.2018.02.022

Chandler, D. J., Hansen, K. S., Mahato, B., Darlong, J., John, A., & Lockwood, D. N. J. (2015). Household Costs of Leprosy Reactions (ENL) in Rural India. *PLoS Neglected Tropical Diseases*, *9*(1). https://doi.org/10.1371/journal.pntd.0003431

Christie, C. A., & Barela, E. (2005). The Delphi technique as a method for increasing inclusion in the evaluation process. *Canadian Journal of Program Evaluation*, *20*(1), 105–122.

Costa, L. G., Cortela, D., Soares, R. C. F. R., & Ignotti, E. (2015). Factors associated with the worsening of the disability grade during leprosy treatment in Brazil. *Leprosy Review*, *86*(3), 265–272. http://www.ncbi.nlm.nih.gov/pubmed/26665362

Costa Queiroz, R. H., de Souza, A. M., Sampaio, S. V., & Melchior, E. (2002). Biochemical and hematological side effects of clofazimine in leprosy patients. *Pharmacological Research*, *46*(2), 191–194. https://doi.org/10.1016/s1043-6618(02)00086-5

Courtright, P., Daniel, E., Sundarrao, Ravanes, J., Mengistu, F., Belachew, M., Celloria, R. V, & Ffytche, T. (2002). Eye disease in multibacillary leprosy patients at the time of their leprosy diagnosis: findings from the Longitudinal Study of Ocular Leprosy (LOSOL) in India, the Philippines and Ethiopia. *Leprosy Review*, *73*(3), 225–238. http://www.ncbi.nlm.nih.gov/pubmed/12449887

da Silva Júnior, G. B., & Daher, E. D. F. (2006). Renal involvement in leprosy: retrospective analysis of 461 cases in Brazil. *The Brazilian Journal of Infectious Diseases : An Official Publication of the Brazilian Society of Infectious Diseases*, *10*(2), 107–112. https://doi.org/10.1590/s1413-86702006000200007

Daher, E. F., Silva, G. B., Cezar, L. C., Lima, R. S. A., Gurjão, N. H., Mota, R. M. S., Abreu, K. L. S., Rocha, N. A., Oliveira, M. J. C., & Libório, A. B. (2011). Renal dysfunction in leprosy: a historical cohort of 923 patients in Brazil. *Tropical Doctor*, *41*(3), 148–150. https://doi.org/10.1258/td.2011.100436

De Paula, H. L., De Souza, C. D. F., Silva, S. R., Martins-Filho, P. R. S., Barreto, J. G., Gurgel, R. Q., Cuevas, L. E., & Santos, V. S. (2019). Risk Factors for Physical Disability in Patients with Leprosy: A Systematic Review and Meta-analysis. *JAMA Dermatology*, *155*(10), 1120–1128. https://doi.org/10.1001/jamadermatol.2019.1768

Delbecq, A. L., Van de Ven, A. H., & Gustafson, D. H. (1986). *Group techniques for program planning: a guide to nominal group and Delphi processes*. Green Briar Press.

Department of Health. (2014). *National TB Control Program: Manual of Procedures* (5th ed.). Department of Health. http://www.doh.gov.ph

Department of Health. (2018). *National Leprosy Control Program*. https://www.doh.gov.ph/leprosy-control-program

Department of Health. (2021). *Administrative Order 2021-0004*.

Department of Health Northern Territory [Australia]. (2018). *Guidelines for the control of leprosy in the Northern Territory*. www.health.nt.gov

Department of Health Philippines. (2018). *Manual for Clinical Practice Guideline Development* (1st ed.).

Diório, S. M., Rosa, P. S., Belone, A. de F. F., Sartori, B. G. C., Trino, L. M., Baptista, I. M. F. D., Marcos, E. V. C., Barreto, J. A., & Ura, S. (2009). Relapse Related To Drug. *Hansen Int*, *34*(1), 43–48.

Dogra, S., Kumaran, M. S., Narang, T., Radotra, B. D., & Kumar, B. (2013). Clinical characteristics and outcome in multibacillary (MB) leprosy patients treated with 12 months WHO MDT-MBR: a retrospective analysis of 730 patients from a leprosy clinic at a tertiary care hospital of Northern India. *Leprosy Review*, *84*(1), 65–75. http://www.ncbi.nlm.nih.gov/pubmed/23741883

Dos Santos, A. R., Silva, P. R. D. S., Steinmann, P., & Ignotti, E. (2020). Disability progression among leprosy patients released from treatment: A survival analysis. *Infectious Diseases of Poverty*, *9*(1), 1–7. https://doi.org/10.1186/s40249-020-00669-4

Eichelmann, K., González González, S. E., Salas-Alanis, J. C., & Ocampo-Candiani, J. (2013). Leprosy. An Update: Definition, Pathogenesis, Classification, Diagnosis, and Treatment. *Actas Dermo-Sifiliográficas (English Edition)*, *104*(7), 554–563. https://doi.org/10.1016/j.adengl.2012.03.028

Elias, J., Nogueira-Barbosa, M. H., Feltrin, L. T., Furini, R. B., Foss, N. T., Marques, W., & dos Santos, A. C. (2009). Role of Ulnar Nerve Sonography in Leprosy Neuropathy With Electrophysiologic Correlation. *Journal of Ultrasound in Medicine*, *28*(9), 1201–1209. https://doi.org/10.7863/jum.2009.28.9.1201

Feenstra, S. G., Pahan, D., Moet, F. J., Oskam, L., & Richardus, J. H. (2012). Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. *Leprosy Review*, *83*(3), 292–304. https://pubmed.ncbi.nlm.nih.gov/23356030/

Ferreira, S. M. B., Yonekura, T., Ignotti, E., Oliveira, L. B. de, Takahashi, J., & Soares, C. B. (2017). Effectiveness of rifampicin chemoprophylaxis in preventing leprosy in patient contacts: a systematic review of quantitative and qualitative evidence. *JBI Database of Systematic Reviews and Implementation Reports*, *15*(10), 2555–2584. https://doi.org/10.11124/JBISRIR-2016-003301

Frade, M. A. C., Nogueira-Barbosa, M. H., Lugão, H. B., Furini, R. B., Marques Júnior, W., & Foss, N. T. (2013). New sonographic measures of peripheral nerves: a tool for the diagnosis of peripheral nerve involvement in leprosy. *Memorias Do Instituto Oswaldo Cruz*, *108*(3). https://doi.org/10.1590/S0074-02762013000300001

Gonçalves, S. D., Sampaio, R. F., & Antunes, C. M. de F. (2009). [Predictive factors of disability in patients with leprosy]. *Revista de Saude Publica*, *43*(2), 267–274. https://doi.org/10.1590/s0034-89102009000200007

Goto, M., Nogam, R., Okano, Y., Gidoh, M., Yotsu, R., Ishida, Y., Kitajima, S., Kai, M., Ishii, N., Ozaki, M., Hatano, K., Ad Hoc Committee on Treatment Guideline, & Japanese Leprosy Association. (2013). [Guidelines for the treatment of Hansen's disease in Japan (third edition)]. *Nihon Hansenbyō Gakkai Zasshi = Japanese Journal of Leprosy : Official Organ of the Japanese Leprosy Association*, *82*(3), 143–184. https://doi.org/10.5025/hansen.82.143

Guerrero-Guerrero, M. I., Muvdi-Arenas, S., & León-Franco, C. I. (2012). Relapses in multibacillary leprosy patients: a retrospective cohort of 11 years in Colombia. *Leprosy Review*, *83*(3), 247–260.

http://www.ncbi.nlm.nih.gov/pubmed/23356026

Guragain, S., Upadhayay, N., & Bhattarai, B. M. (2017). Adverse reactions in leprosy patients who underwent dapsone multidrug therapy: a retrospective study. *Clinical Pharmacology : Advances and Applications*, *9*, 73–78. https://doi.org/10.2147/CPAA.S135846

Gurung, P., Gomes, C. M., Vernal, S., & Leeflang, M. M. G. (2019). Diagnostic accuracy of tests for leprosy: a systematic review and meta-analysis. In *Clinical Microbiology and Infection* (Vol. 25, Issue 11, pp. 1315–1327). Elsevier B.V. https://doi.org/10.1016/j.cmi.2019.05.020

Handog, E. B., Gabriel, M. T. G., & Co, C. C. (2011). Leprosy in the Philippines: A review. *International Journal of Dermatology*, *50*(5), 573–581. https://doi.org/10.1111/j.1365-4632.2011.05044.x

Hay, S. I., Abajobir, A. A., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abdulkader, R. S., Abdulle, A. M., Abebo, T. A., Abera, S. F., Aboyans, V., Abu-Raddad, L. J., Ackerman, I. N., Adedeji, I. A., Adetokunboh, O., Afshin, A., Aggarwal, R., Agrawal, S., Agrawal, A., … Murray, C. J. L. (2017). Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *390*(10100), 1260–1344. https://doi.org/10.1016/S0140-6736(17)32130-X

Health Resources & Services Administration [United States]. (2018, September). *Preparation and Examination of Skin Smears*. Official Web Site of the U.S. Health Resources & Services Administration. https://www.hrsa.gov/hansens-disease/diagnosis/skin-smears.html

Hilder, R., & Lockwood, D. (2020). The adverse drug effects of dapsone therapy in leprosy: a systematic review. *Leprosy Review*, *91*(3), 232–243. https://doi.org/10.47276/lr.91.3.232

Holey, E. A., Feeley, J. L., Dixon, J., & Whittaker, V. J. (2007). An exploration of the use of simple statistics to measure consensus and stability in Delphi studies. *BMC Medical Research Methodology*, *7*(February). https://doi.org/10.1186/1471-2288-7-52

Idema, W. J., Majer, I. M., Pahan, D., Oskam, L., Polinder, S., & Richardus, J. H. (2010). Cost-Effectiveness of a Chemoprophylactic Intervention with Single Dose Rifampicin in Contacts of New Leprosy Patients. *PLoS Neglected Tropical Diseases*, *4*(11), e874. https://doi.org/10.1371/journal.pntd.0000874

International Federation of Anti-Leprosy Associations. (2020). *How to do a skin smear examination for leprosy*.

Jamet, P., & Ji, B. (1995). Relapse after long-term follow up of multibacillary patients treated by WHO multidrug regimen. Marchoux Chemotherapy Study Group. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *63*(2), 195–201. http://www.ncbi.nlm.nih.gov/pubmed/7602214

Kaluarachchi, S. I., Fernandopulle, B. M., & Gunawardane, B. P. (2001). Hepatic and haematological adverse reactions associated with the use of multidrug therapy in leprosy--a five year retrospective study. *Indian Journal of Leprosy*, *73*(2), 121–129. http://www.ncbi.nlm.nih.gov/pubmed/11579648

Khambati, F. A., Shetty, V. P., Ghate, S. D., & Capadia, G. D. (2009). Sensitivity and specificity of nerve palpation, monofilament testing and voluntary muscle testing in detecting peripheral nerve abnormality, using nerve conduction studies as gold standard; a study in 357 patients. *Leprosy Review*, *80*(1), 34–50. http://www.ncbi.nlm.nih.gov/pubmed/19472851

Kumar, A., Girdhar, A., & Girdhar, B. K. (2012). Risk of developing disability in pre and post-multidrug therapy treatment among multibacillary leprosy: Agra MB Cohort study. *BMJ Open*, *2*(2), e000361. https://doi.org/10.1136/bmjopen-2011-000361

Kumar, A., Girdhar, A., & Girdhar, B. K. (2013). Twelve months fixed duration WHO multidrug therapy for multibacillary leprosy: incidence of relapses in Agra field based cohort study. *The Indian Journal of Medical Research*, *138*(4), 536–540. http://www.ncbi.nlm.nih.gov/pubmed/24434261

Kyaw, K., Tsoh, T. M., Swe, S. Y. Y., Nagaoka, Y., Takezaki, S., Suzuki, K., & Ishii, N. (2008). Clinical analysis of multibacillary leprosy patients after 1-year fixed World Health Organization recommended multidrug

therapy at Yangon General Hospital, Myanmar. *The Journal of Dermatology*, *35*(5), 264–269. https://doi.org/10.1111/j.1346-8138.2008.00464.x

Kyu, H. H., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, M., Abebe, Z., Abil, O. Z., Aboyans, V., Abrham, A. R., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., … Murray, C. J. L. (2018). Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1859–1922. https://doi.org/10.1016/S0140-6736(18)32335-3

Lambert, S. M., Alembo, D. T., Nigusse, S. D., Yamuah, L. K., Walker, S. L., & Lockwood, D. N. J. (2016). A Randomized Controlled Double Blind Trial of Cyclosporine versus Prednisolone in the Management of Leprosy Patients with New Type 1 Reaction, in Ethiopia. *PLOS Neglected Tropical Diseases*, *10*(4), e0004502. https://doi.org/10.1371/journal.pntd.0004502

Lemes, R. M. R., Silva, C. A. de M. e, Marques, M. Â. de M., Atella, G. C., Nery, J. A. da C., Nogueira, M. R. S., Rosa, P. S., Soares, C. T., De, P., Chatterjee, D., Pessolani, M. C. V., & de Macedo, C. S. (2020). Altered composition and functional profile of high-density lipoprotein in leprosy patients. *PLOS Neglected Tropical Diseases*, *14*(3), e0008138. https://doi.org/10.1371/journal.pntd.0008138

Leonardo, L., Hernandez, L., Magturo, T. C., Palasi, W., Rubite, J. M., de Cadiz, A., Moendeg, K., Fornillos, R. J., Tabios, I. K., Mistica, M., & Fontanilla, I. K. (2020). Current status of neglected tropical diseases (NTDs) in the Philippines. *Acta Tropica*, *203*(July 2019), 105284. https://doi.org/10.1016/j.actatropica.2019.105284

Lockwood, D. N. J., Darlong, J., Govindharaj, P., Kurian, R., Sundarrao, P., & John, A. S. (2017). AZALEP a randomized controlled trial of azathioprine to treat leprosy nerve damage and Type 1 reactions in India: Main findings. *PLOS Neglected Tropical Diseases*, *11*(3), e0005348. https://doi.org/10.1371/journal.pntd.0005348

Lugão, H. B., Frade, M. A. C., Marques-Jr, W., Foss, N. T., & Nogueira-Barbosa, M. H. (2016). Ultrasonography of Leprosy Neuropathy: A Longitudinal Prospective Study. *PLOS Neglected Tropical Diseases*, *10*(11), e0005111. https://doi.org/10.1371/journal.pntd.0005111

Maghanoy, A., Balagon, M., Saunderson, P., & Scheelbeek, P. (2017). A prospective randomised, double-blind, placebo controlled trial on the effect of extended clofazimine on Erythema Nodosum Leprosum (ENL) in multibacillary (MB) leprosy. *Leprosy Review*, *88*(2), 208–2016. https://doi.org/10.47276/lr.88.2.208

Maghanoy, A., Mallari, I., Balagon, M., & Saunderson, P. (2011). Relapse study in smear positive multibacillary (MB) leprosy after 1 year WHO-multi-drug therapy (MDT) in Cebu, Philippines. *Leprosy Review*, *82*(1), 65–69. http://www.ncbi.nlm.nih.gov/pubmed/21644473

Mangum, L., Kilpatrick, D., Stryjewska, B., & Sampath, R. (2018). Tuberculosis and Leprosy Coinfection: A Perspective on Diagnosis and Treatment. *Open Forum Infectious Diseases*, *5*(7). https://doi.org/10.1093/ofid/ofy133

Matsuoka, M. (2010). Drug resistance in leprosy. *Japanese Journal of Infectious Diseases*, *63*(1), 1–7. http://www.ncbi.nlm.nih.gov/pubmed/20093754

Matsuoka, M., Budiawan, T., Aye, K. S., Kyaw, K., Tan, E. V., Cruz, E. Dela, Gelber, R., Saunderson, P., Balagon, V., & Pannikar, V. (2007). The frequency of drug resistance mutations in Mycobacterium leprae isolates in untreated and relapsed leprosy patients from Myanmar, Indonesia and the Philippines. *Leprosy Review*, *78*(4), 343–352. https://doi.org/10.47276/lr.78.4.343

Maymone, M. B. C., Laughter, M., Venkatesh, S., Dacso, M. M., Rao, P. N., Stryjewska, B. M., Hugh, J., Dellavalle, R. P., & Dunnick, C. A. (2020). Leprosy: Clinical aspects and diagnostic techniques. *Journal of the American Academy of Dermatology*, *83*(1), 1–14. https://doi.org/10.1016/j.jaad.2019.12.080

Moet, F. J., Pahan, D., Oskam, L., & Richardus, J. H. (2008). Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ*, *336*(7647), 761–764. https://doi.org/10.1136/bmj.39500.885752.BE

Mowla, M. R., Ara, S., Mizanur Rahman, A. F. M., Tripura, S. P., & Paul, S. (2017). Leprosy reactions in postelimination stage: the Bangladesh experience. *Journal of the European Academy of Dermatology and Venereology*, *31*(4), 705–711. https://doi.org/10.1111/jdv.14049

Murphy, M., Black, N., Lamping, D., McKee, C., Sanderson, C., Askham, J., & Marteau, T. (1998). Consensus development methods, and their use in clinical guideline development. *Health Technology Assessment*, *2*(3). https://doi.org/10.4135/9781848608344.n24

Naafs, B., & van Hees, C. L. M. (2016). Leprosy type 1 reaction (formerly reversal reaction). *Clinics in Dermatology*, *34*(1), 37–50. https://doi.org/10.1016/j.clindermatol.2015.10.006

Nair, S. P. (2018). A 19-Year Retrospective Study of Adverse Drug Reactions to Multidrug Therapy in Leprosy Requiring a Change in Regime. *Indian Dermatology Online Journal*, *9*(1), 33–36. https://doi.org/10.4103/idoj.IDOJ_116_17

National Institute for Health and Care Excellence. (2014). *Developing NICE guidelines: the manual*. www.nice.org.uk/process/pmg20

National Leprosy Control Program. (2018a). *National Leprosy Control Program (NLCP) Manual of Procedures*.

National Leprosy Control Program. (2018b). *National Leprosy Control Program Medium Term Plan 2017-2022*.

Negera, E., Tilahun, M., Bobosha, K., Lambert, S. M., Walker, S. L., Spencer, J. S., Aseffa, A., Dockrell, H. M., & Lockwood, D. N. (2018). The effects of prednisolone treatment on serological responses and lipid profiles in Ethiopian leprosy patients with Erythema Nodosum Leprosum reactions. *PLoS Neglected Tropical Diseases*, *12*(12), e0007035. https://doi.org/10.1371/journal.pntd.0007035

Nery, J. A. da C., Bernardes Filho, F., Quintanilha, J., Machado, A. M., Oliveira, S. de S. C., & Sales, A. M. (2013). Understanding the type 1 reactional state for early diagnosis and treatment: a way to avoid disability in leprosy. *Anais Brasileiros de Dermatologia*, *88*(5), 787–792. https://doi.org/10.1590/abd1806-4841.20132004

Nunes, M. I. (2001). The relationship between quality of life and adherence to treatment. *Current Hypertension Reports*, *3*(6), 462–465. https://doi.org/10.1007/s11906-001-0007-9

Oliveira, D. T. de, Sherlock, J., Melo, E. V. de, Rollemberg, K. C. V., Paixao, T. R. S. da, Abuawad, Y. G., Simon, M. do V., Duthie, M., & Jesus, A. R. de. (2013). Clinical variables associated with leprosy reactions and persistence of physical impairment. *Revista Da Sociedade Brasileira de Medicina Tropical*, *46*(5), 600–604. https://doi.org/10.1590/0037-8682-0100-2013

Oliveira, R. A., Silva, G. B., Souza, C. J., Vieira, E. F., Mota, R. M. S., Martins, A. M. C., Libório, A. B., & Daher, E. F. (2008). Evaluation of renal function in leprosy: a study of 59 consecutive patients. *Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *23*(1), 256–262. https://doi.org/10.1093/ndt/gfm568

Oxman, A. D. (2004). Grading quality of evidence and strength of recommendations. In *British Medical Journal* (Vol. 328, Issue 7454, pp. 1490–1494). BMJ Publishing Group. https://doi.org/10.1136/bmj.328.7454.1490

Pamba, A., Richardson, N. D., Carter, N., Duparc, S., Premji, Z., Tiono, A. B., & Luzzatto, L. (2012). Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. *Blood*, *120*(20), 4123–4133. https://doi.org/10.1182/blood-2012-03-416032

Pavezzi, P. D., do Prado, R. B., Boin Filho, P. Â., Gon, A. dos S., Tuma, B., Fornazieri, M. A., Scalone, F. de M., Alves, L. R. M., Montero, R. H., & Casella, A. M. B. (2020). Evaluation of ocular involvement in patients with Hansen's disease. *PLOS Neglected Tropical Diseases*, *14*(9), e0008585. https://doi.org/10.1371/journal.pntd.0008585

Pepito, V. C. F., Amit, A. M. L., Samontina, R. E. D., Abdon, S. J. A., Fuentes, D. N. L., & Saniel, O. P. (2018). Variations in the clinical management of multibacillary leprosy patients in selected hospitals in Metro Manila. *Acta Medica Philippina*, *52*(3), 268–276. https://doi.org/10.47895/amp.v52i3.409

Pfyffer, G. E., & Inderlied, C. B. (2010). Mycobacteria. In *Infectious Diseases: Third Edition* (Vol. 2, pp. 1777–1800). Elsevier Inc. https://doi.org/10.1016/B978-0-323-04579-7.00174-X

Philippine Health Insurance Corporation. (2017). *PhilHealth Circular 2017-0019* (Vol. 6). https://www.philhealth.gov.ph/circulars/2017/circ2017-0019.pdf.

Polito, M. G., Moreira, S. R., Nishida, S. K., & Mastroianni Kirsztajn, G. (2015). It is time to review concepts on renal involvement in leprosy: pre- and post-treatment evaluation of 189 patients. *Renal Failure*, *37*(7), 1171–1174. https://doi.org/10.3109/0886022X.2015.1057470

Poojabylaiah, M., Marne, R. B., Varikkodan, R., Bala, N., Dandakeri, S., & Martis, J. (2008). Relapses in multibacillary leprosy patients after multidrug therapy. *Leprosy Review*, *79*(3), 320–324. http://www.ncbi.nlm.nih.gov/pubmed/19009982

Prabu, R., Manickam, P., Mahalingam, V. N., Jayasree, P., Selvaraj, V., & Mehendale, S. M. (2015). Relapse and deformity among 2177 leprosy patients released from treatment with MDT between 2005 and 2010 in South India: A retrospective cohort study. *Leprosy Review*, *86*(4), 345–355. http://www.ncbi.nlm.nih.gov/pubmed/26964430

Rao, P. S. S. S., Sugamaran, D. S. T., Richard, J., & Smith, W. C. S. (2006). Multi-centre, double blind, randomized trial of three steroid regimens in the treatment of type-1 reactions in leprosy. *Leprosy Review*, *77*(1), 25–33. http://www.ncbi.nlm.nih.gov/pubmed/16715687

Rathod, S. P., Jagati, A., & Chowdhary, P. (2020). Disabilities in leprosy: an open, retrospective analyses of institutional records. *Anais Brasileiros de Dermatologia*, *95*(1), 52–56. https://doi.org/10.1016/j.abd.2019.07.001

Ravanes, J. M., Cellona, R. V, Balagon, M., Abalos, R. M., Walsh, G. P., & Walsh, D. S. (2011). Longitudinal ocular survey of 202 Filipino patients with multi-bacillary (MB) leprosy treated with 2 year WHO-multiple drug therapy. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *42*(2), 323–330. http://www.ncbi.nlm.nih.gov/pubmed/21710853

Reed, N. K., van Brakel, W. H., & Reed, D. S. (1997). Progress of impairment scores following commencement of chemotherapy in multibacillary leprosy patients. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *65*(3), 328–336. http://www.ncbi.nlm.nih.gov/pubmed/9401485

Renault, C. A., & Ernst, J. D. (2015). Mycobacterium leprae (Leprosy). In *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* (Vol. 2, pp. 2819-2831.e2). Elsevier. https://doi.org/10.1016/B978-1-4557-4801-3.00252-6

Reveiz, L., Buendía, J. A., & Téllez, D. (2009). Chemoprophylaxis in contacts of patients with leprosy: Systematic review and meta-analysis. In *Revista Panamericana de Salud Publica/Pan American Journal of Public Health* (Vol. 26, Issue 4, pp. 341–349). Pan American Health Organization. https://doi.org/10.1590/S1020-49892009001000009

Richardus, Jan H, Nicholls, P. G., Croft, R. P., Withington, S. G., & Smith, W. C. S. (2004). Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up. *International Journal of Epidemiology*, *33*(2), 337–343. https://doi.org/10.1093/ije/dyg225

Richardus, Jan H, Withington, S. G., Anderson, A. M., Croft, R. P., Nicholls, P. G., Van Brakel, W. H., & Smith, W. C. S. (2003). Adverse events of standardized regimens of corticosteroids for prophylaxis and treatment of nerve function impairment in leprosy: results from the "TRIPOD" trials. *Leprosy Review*, *74*(4), 319–327. http://www.ncbi.nlm.nih.gov/pubmed/14750577

Richardus, Jan Hendrik. (2013). Leprosy remains an important public health challenge in India. In *The Indian journal of medical research* (Vol. 137, Issue 5, pp. 878–879). Wolters Kluwer -- Medknow Publications. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3734677/

Robertson, J. (2016). Leprosy, Historical. In *International Encyclopedia of Public Health* (Second Edi, Vol. 4). Elsevier. https://doi.org/10.1016/B978-0-12-803678-5.00252-6

Rosa, P. S., D'Espindula, H. R. S., Melo, A. C. L., Fontes, A. N. B., Finardi, A. J., Belone, A. F. F., Sartori, B. G. C., Pires, C. A. A., Soares, C. T., Marques, F. B., Branco, F. J. D., Baptista, I. M. F. D., Trino, L. M., Fachin, L. R. V, Xavier, M. B., Floriano, M. C., Ura, S., Diório, S. M., Delanina, W. F. B., … Mira, M. T. (2020). Emergence and Transmission of Drug-/Multidrug-resistant Mycobacterium leprae in a Former Leprosy Colony in the Brazilian Amazon. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *70*(10), 2054–2061. https://doi.org/10.1093/cid/ciz570

Sabin, T. D., & Swift, T. R. (2014). Neurologic Complications of Leprosy. In *Aminoff's Neurology and General Medicine* (pp. 845–856). Elsevier. https://doi.org/10.1016/B978-0-12-407710-2.00042-4

Sales, A. M., Sabroza, P. C., Nery, J. A. da C., Dupprè, N. C., & Sarno, E. N. (2007). No difference in leprosy treatment outcomes comparing 12- and 24-dose multidrug regimens: a preliminary study. *Cadernos de Saúde Pública*, *23*(4), 815–822. https://doi.org/10.1590/S0102-311X2007000400009

Schively, C. (2007). A quantitative analysis of consensus building in local environmental review. *Journal of Planning Education and Research*, *27*(1), 82–98. https://doi.org/10.1177/0739456X07305794

Schreuder, P. A. (1998). The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in northeastern Thailand, 1987-1995 [correction of 1978-1995]. I. Overview of the study. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *66*(2), 149–158. http://www.ncbi.nlm.nih.gov/pubmed/9728447

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013, October). *GRADE Handbook*. https://gdt.gradepro.org/app/handbook/handbook.html

Schünemann, H., Wiercioch, W., Brozek, J., Etxeandia-Ikobaltzeta, I., Mustafa, R. A., Manja, V., Brignardello-Petersen, R., Neumann, I., Falavigna, M., Alhazzani, W., Santesso, N., Zhang, Y., Meerpohl, J. J., Morgan, R. L., Rochwerg, B., Darzi, A., Rojas, M. X., Carrasco-Labra, A., Adi, Y., … Akl, E. A. (2017). GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *Journal of Clinical Epidemiology*, *81*, 101–110. https://doi.org/10.1016/j.jclinepi.2016.09.009

Scollard, D. M., Martelli, C. M. T., Stefani, M. M. A., De Fatima Maroja, M., Villahermosa, L., Pardillo, F., & Tamang, K. B. (2015). Risk factors for leprosy reactions in three endemic countries. *American Journal of Tropical Medicine and Hygiene*, *92*(1), 108–114. https://doi.org/10.4269/ajtmh.13-0221

Scottish Intercollegiate Guidelines Network (SIGN). (2015). *SIGN 50 Guideline Developer's Handbook*. *November*. http://www.sign.ac.uk/guidelines/fulltext/50/section1.html,

Sharma, P., Kar, H. K., Beena, K. R., Kaur, H., & Narayan, R. (1996). Disabilities in multibacillary leprosy patients: before, during and after multidrug therapy. *Indian Journal of Leprosy*, *68*(2), 127–136. http://www.ncbi.nlm.nih.gov/pubmed/8835580

Smith, C. M., & Smith, W. C. (2000). Chemoprophylaxis is effective in the prevention of leprosy in endemic countries: a systematic review and meta-analysis. MILEP2 Study Group. Mucosal Immunology of Leprosy. *The Journal of Infection*, *41*(2), 137–142. https://doi.org/10.1053/jinf.2000.0698

Solanki, J., Thesia, A., Mehta, H., Shah, C., & Mehta, H. (2016). Evaluation of cardiac autonomic status using QTc interval in patients with leprosy. *Asia Pacific Clinical and Translational Nervous System Diseases*, *1*(3), 144. https://doi.org/10.4103/2468-5577.187081

Somar, P., Waltz, M., & van Brakel, W. (2020). The impact of leprosy on the mental wellbeing of leprosy-affected persons and their family members – a systematic review. *Global Mental Health*, *7*. https://doi.org/10.1017/gmh.2020.3

Srinivas, G., Muthuvel, T., Lal, V., Vaikundanathan, K., Schwienhorst-Stich, E.-M., & Kasang, C. (2019). Risk of disability among adult leprosy cases and determinants of delay in diagnosis in five states of India: A case-control study. *PLoS Neglected Tropical Diseases*, *13*(6), e0007495. https://doi.org/10.1371/journal.pntd.0007495

Suchonwanit, P., Triamchaisri, S., Wittayakornrerk, S., & Rattanakaemakorn, P. (2015). Leprosy Reaction in Thai Population: A 20-Year Retrospective Study. *Dermatology Research and Practice*, *2015*, 253154.

https://doi.org/10.1155/2015/253154

Tabri, F., Maskur, Z., Amiruddin, M. D., & Makalew, H. L. (2017). Analysis of SGOT, SGPT, and IgM anti PGL-1 in Multibacillary Leprosy Patient after Multi Drug Therapy. *Global Journal of Health Science*, *9*(9), 36. https://doi.org/10.5539/gjhs.v9n9p36

Tamez-Pérez, H. E. (2015). Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World Journal of Diabetes*, *6*(8), 1073. https://doi.org/10.4239/wjd.v6.i8.1073

Tapinos, N., & Rambukkana, A. (2005). Insights into regulation of human Schwann cell proliferation by Erk1/2 via a MEK-independent and p56Lck-dependent pathway from leprosy bacilli. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(26), 9188–9193. https://doi.org/10.1073/pnas.0501196102

The James Lind Alliance. (2020). *The James Lind Alliance Guidebook* (9th ed.). http://www.jla.nihr.ac.uk/jla-guidebook/

Thompson, K. J., Allardice, G. M., Babu, G. R., Roberts, H., Kerketta, W., & Kerketta, A. (2006). Patterns of ocular morbidity and blindness in leprosy--a three centre study in Eastern India. *Leprosy Review*, *77*(2), 130–140. http://www.ncbi.nlm.nih.gov/pubmed/16895069

Tiwary, P. K., Kar, H. K., Sharma, P. K., Gautam, R. K., Arora, T. C., Naik, H., & Dhir, V. (2011). Epidemiological trends of leprosy in an urban leprosy centre of Delhi: A retrospective study of 16 years. *Indian Journal of Leprosy*, *83*(4), 201–208. http://europepmc.org/article/med/22783754

Umpierrez, G. E., Murphy, M. B., & Kitabchi, A. E. (2002). Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome. *Diabetes Spectrum*, *15*(1), 28–36. https://doi.org/10.2337/diaspect.15.1.28

Van Brakel, W. H., Anderson, A. M., Withington, S. G., Croft, R. P., Nicholls, P. G., Richardus, J. H., & Smith, W. C. S. (2003). The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2). *Leprosy Review*, *74*(4), 300–310. http://www.ncbi.nlm.nih.gov/pubmed/14750575

van Brakel, W. H., Nicholls, P. G., Wilder-Smith, E. P., Das, L., Barkataki, P., & Lockwood, D. N. J. (2008). Early Diagnosis of Neuropathy in Leprosy—Comparing Diagnostic Tests in a Large Prospective Study (the INFIR Cohort Study). *PLoS Neglected Tropical Diseases*, *2*(4), e212. https://doi.org/10.1371/journal.pntd.0000212

Van Veen, N. H., Nicholls, P. G., Smith, W. C. S., & Richardus, J. H. (2016). Corticosteroids for treating nerve damage in leprosy. In N. H. Van Veen (Ed.), *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd. https://doi.org/10.1002/14651858.CD005491.pub3

Voorend, C. G. N., & Post, E. B. (2013). A Systematic Review on the Epidemiological Data of Erythema Nodosum Leprosum, a Type 2 Leprosy Reaction. *PLoS Neglected Tropical Diseases*, *7*(10), e2440. https://doi.org/10.1371/journal.pntd.0002440

Wagenaar, I., Post, E., Brandsma, W., Bowers, B., Alam, K., Shetty, V., Pai, V., Husain, S., Sigit Prakoeswa, C. R., Astari, L., Hagge, D., Shah, M., Neupane, K., Tamang, K. B., Nicholls, P., & Richardus, J. H. (2017). Effectiveness of 32 versus 20 weeks of prednisolone in leprosy patients with recent nerve function impairment: A randomized controlled trial. *PLOS Neglected Tropical Diseases*, *11*(10), e0005952. https://doi.org/10.1371/journal.pntd.0005952

Walker, S. L., Sales, A. M., Butlin, C. R., Shah, M., Maghanoy, A., Lambert, S. M., Darlong, J., Rozario, B. J., Pai, V. V., Balagon, M., Doni, S. N., Hagge, D. A., Nery, J. A. C., Neupane, K. D., Baral, S., Sangma, B. A., Alembo, D. T., Yetaye, A. M., Hassan, B. A., … Lockwood, D. N. J. (2017). A leprosy clinical severity scale for erythema nodosum leprosum: An international, multicentre validation study of the ENLIST ENL Severity Scale. *PLOS Neglected Tropical Diseases*, *11*(7), e0005716. https://doi.org/10.1371/journal.pntd.0005716

Wang, Z., Norris, S. L., & Bero, L. (2018). The advantages and limitations of guideline adaptation frameworks. *Implementation Science*, *13*(1), 72. https://doi.org/10.1186/s13012-018-0763-4

World Health Organization. (1950). *WHA3.71 Adjustment of Operating Programme for 1951 The Third World Health Assembly*.

World Health Organization. (2014). *Handbook for guideline development* (2nd ed.). http://www.who.int/kms/handbook_2nd_ed.pdf (accessed 15 May 2015)

World Health Organization. (2016a). *Classification of leprosy*. https://www.who.int/lep/classification/en/

World Health Organization. (2016b). Global Leprosy Strategy 2016-2020: accelerating towards a leprosy-free world. In *Weekly Epidemiological record* (Vol. 1, Issue 35). http://apps.who.int/iris/bitstream/10665/205149/1/B5233.pdf?ua=1

World Health Organization. (2016c). *MDT: relapse after treatment FAQ*. https://www.who.int/lep/mdt/relapse/en/

World Health Organization. (2016d). *Microbiology of M. leprae*. https://www.who.int/lep/microbiology/en/

World Health Organization. (2016e). *WHO recommended MDT regimens*. https://www.who.int/lep/mdt/regimens/en/

World Health Organization. (2017). *A guide for surveillance of antimicrobial resistance in leprosy: 2017 update*. World Health Organization, Regional Office for South-East Asia.

World Health Organization. (2018a). Global leprosy update, 2017: reducing the disease burden due to leprosy. *Weekly Epidemiological Record*, *93*(35), 445–456. http://apps.who.int/iris/bitstream/hand%0Ahttp://www.who.int/wer/2009/wer8440.pdf?ua=1

World Health Organization. (2018b). *Guidelines for the diagnosis, treatment and prevention of leprosy*. World Health Organization, Regional Office for South-East Asia.

World Health Organization. (2019a). *Leprosy - Number of new G2D cases*. The Global Health Observatory. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/leprosy---number-of-new-g2d-cases

World Health Organization. (2019b). *Leprosy (Hansen's disease)*. The Global Health Observatory. https://www.who.int/data/gho/data/themes/topics/leprosy-hansens-disease

World Health Organization. (2019c, September 10). *Leprosy*. https://www.who.int/news-room/fact-sheets/detail/leprosy

World Health Organization. (2020a). Global leprosy (Hansen disease) update, 2019: time to step-up prevention initiatives. *Weekly Epidemiological Record*, *95*(36), 417–440. http://www.who.int/wer

World Health Organization. (2020b). *Leprosy/Hansen Disease: Management of reactions and prevention of disabilities*.

Youngster, I., Arcavi, L., Schechmaster, R., Akayzen, Y., Popliski, H., Shimonov, J., Beig, S., & Berkovitch, M. (2010). Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety*, *33*(9), 713–726. https://doi.org/10.2165/11536520-000000000-00000

II. CLINICAL PRACTICE GUIDELINES

Clinical and laboratory evaluation in leprosy

Question 1: How are leprosy cases best defined? What clinical parameters should be considered when suspecting leprosy?

Recommendation 1.a

Leprosy is considered based on the presence of at least one of the three cardinal signs:

- Definite loss of sensation in a pale (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

Weak recommendation, very low quality of evidence

Background

Due to the involvement of diverse structures in the human body and the effect of the individual's immune system on the progression of the disease, leprosy has a variable presentation. The diagnosis of leprosy may be made by clinical examination alone, by histopathological examination of a skin specimen, or both.

Skin lesions from leprosy may be flat (macule/patch) or raised (papule/plaque), and they may appear to be lighter than normal skin (hypopigmented), reddish, or coppery. Leprosy may also manifest as nodules or infiltrated lesions, which appear to arise from deeper regions of the skin. Skin lesions in leprosy largely vary in size, shape, location and number, and vigilance is essential in documenting all lesions suspected to be due to leprosy. Leprosy in early disease may be found anywhere on the body.

Loss of sensation (hypoesthesia) in these skin lesions should be documented by proper and complete history-taking and physical examination. Ideally, a graded monofilament would be used to test for hypoesthesia, but in field conditions, a ballpoint pen or a piece of cotton made to have a point at the end can be used (National Leprosy Control Program, 2018a).

Peripheral nerves may also be thickened or enlarged in leprosy. Nerve palpation must be performed when a patient is examined for leprosy at the time of diagnosis, and even if the diagnosis is certainly based on the presence of skin lesions (NLCP, 2018a). The two most commonly affected nerves are the ulnar nerve and the peroneal nerve, but any peripheral nerve may be involved. Signs of nerve damage should be noted, such as numbness, tingling or muscle weakness.

Slit-skin smears, or biopsies of the skin, may also be obtained. These specimens are stained by acid-fast techniques, which are the same used for the identification of *Mycobacterium* in tuberculosis. A negative slit-skin smear does not rule out leprosy, unless the other cardinal signs are also absent; however, a positive slit-skin smear would indicate that the patient has multibacillary leprosy (NLCP, 2018a). Technical expertise, facilities and equipment for obtaining slit-skin smears are not yet widely available in the primary care setting.

Summary of evidence

This recommendation utilized the ADAPTE methodology given the remarkable rigor of the WHO Guideline where this statement is founded upon. Among the three guidelines identified through database searching, the WHO guideline was the only guideline that directly answered this question and gave consensus recommendations. The slit-skin smear requires an expert in this procedure that may not be available in all primary care settings. No other diagnostic tools were recommended. Other diagnostic modalities were evaluated for their diagnostic accuracies in a meta-analysis of 78 studies (Gurung et al., 2019).

TABLE 5. SUMMARY OF THE DIAGNOSTIC ACCURACIES OF SEROLOGICAL TESTS FOR LEPROSY (GURUNG ET AL., 2019)

OUTCOME	TEST	STUDIES INCLUDED	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)
DETECTION OF IGM ANTIBODIES AGAINST PHENOLIC GLYCOLIPID I	ELISA	39	63.8% (55.0 -71.8)	91.0% (86.9-93.9)
	Conventional PCR	17	75.3% (67.9-81.5)	94.5% (91.4-96.5)
	qPCR	5	78.5% (61.9-89.2)	89.3% (61.4-97.8)
CLASSIFICATION TO MB FORM	ELISA	30	84.1% (77.8-88.9)	-
	Lateral Flow	6	87.4% (78.6 - 92.9)	-
	Agglutination	5	82.1% (71.6-89.3)	-
	Conventional PCR	16	92.6% (87.5-95.6)	-
	qPCR	5	91.6% (58.5-98.8)	-
CLASSIFICATION TO PB FORM	ELISA	30	65.2% (54.2-74.8)	-
	Lateral Flow	6	71.1% (65.0-76.6)	-
	Agglutination	5	78.6% (54.3-91.9)	-
	Conventional PCR	16	41.4% (31.9-51.6)	-
	qPCR	5	58.3% (22.1 -87.3)	-

Rationale

This definition of leprosy is also consistent with the case definition provided by the World Health Organization (WHO). To provide accurate epidemiologic estimates of the burden of disease of leprosy, the Philippine definition must abide by international definitions as well.

The consensus panel acknowledges that a diagnosis of leprosy may be made using clinical findings, given the first two cardinal signs of leprosy. The ability to make the diagnosis is therefore accessible to health care professionals in the primary care setting. When a diagnosis of leprosy can be definitively made based only on clinical signs (i.e., the presence of hypoesthetic skin lesions or thickened peripheral nerves with associated sensory or motor deficits), a slit-skin smear or a histopathological examination is no longer necessary. However, it is recommended that in settings where SSS are available, this histopathological test may be obtained to complement the initial clinical diagnosis. Determining the pre-treatment bacillary index is also helpful for monitoring of the patient and identifying treatment failure or resistance to multidrug treatment (MDT).

The consensus panel also acknowledges the high sensitivity and sensitivity of serological tests for leprosy. However, facilities and equipment in primary care settings considered, these tests may not be widely available.

Recommendation 1.b

It is suggested that slit-skin smear or histopathological examination be included in the initial diagnosis of leprosy if available. The unavailability of slit skin smear should not hamper the initiation of treatment.

Weak recommendation, very low quality of evidence

Background

A slit-skin smear is a test in which a sample of material is collected from a tiny cut in the skin and then stained for *M. leprae* (ILEP Federation, 2020). The smear is a means of estimating the number of acid-fast bacteria present, reported as the bacterial index (BI) which pertains to the extent of the bacterial load (WHO, 2016d). It is important in determining the type and severity of disease as well as assessing the response to treatment (Health Resources & Services Administration [United States], 2018).

Rationale

Leprosy can be classified on the basis of clinical manifestations and skin smear results (WHO, 2016a). In the classification of leprosy based on clinical manifestations, patients with 1-5 skin lesions are grouped as paucibacillary (PB) leprosy, while patients with more than 5 skin lesions or with nerve involvement are grouped as multibacillary leprosy (WHO, 2018b).

On the basis of skin smear results, patients with PB leprosy are those that have negative skin smears at all sites (WHO, 2016a). Patients with MB leprosy may show bacilli in skin smears, and the classification of MB leprosy is irrespective of the number of skin lesions when the patient has a positive slit-skin smear (WHO, 2018b). Therefore, a diagnosis of PB leprosy may be changed to MB leprosy when slit-skin smears test positive for acid-fast bacilli. This classification has

implications on the duration of treatment, which will be discussed in subsequent sections of the Guideline.

The consensus panel notes that the BI is also used for monitoring response to treatment and detection of relapse (ILEP Federation, 2020) in certain leprosy control programs in other countries (HRSA [USA], 2018) and dermatology practices.

Although BI is valuable in leprosy treatment because it is simple and representative of many lesions, obtaining an accurate BI is affected by the depth of the skin incision, the thoroughness of the scrape and the thickness of the film (WHO, 2016d). Thus, the BI is contingent on technical skill, which may not yet be available widely in primary care settings.

Considering the limitations on expertise and resources, the recommendation to obtain slit-skin smears or other histopathological examination at the time of initial leprosy diagnosis should not be taken as a requirement for the initiation of treatment. **The inability to obtain a slit-skin smear should not delay the initiation of treatment for leprosy, especially since the diagnosis of leprosy may also be made based on clinical manifestations only.**

Question 2: Among patients for treatment of leprosy, what initial clinical and laboratory evaluation should be done?

Recommendation 2.a

> Clinical evaluation including complete history (close contacts and co-morbidities), physical examination, and disability assessment (to include sensory and motor nerve function assessment and eye examination) are recommended before, during and after treatment to determine presence and progress of disability.
>
> *Strong recommendation, moderate quality of evidence*

Background

The success of leprosy management requires a well-founded diagnosis, which is fortunately possible even with clinical evaluation only. As the previous recommendation statements described, two out of the three cardinal signs of leprosy are based on clinical findings. However, the patient's contact with the health care system should not be limited to finding a basis to initiate treatment.

A complete clinical evaluation is needed which includes history-taking especially for close contacts and other comorbidities. Drug interventions may be warranted for close contacts, and treatment may also have effects on the patients coexisting comorbidities. Thorough history-taking can aid in contact tracing. Complete physical examination is also necessary. For instance, one of the criteria for the diagnosis of MB leprosy is the number of lesions, and accounting for these lesions relies on a thorough examination of the patient.

Disability, one of the highly troublesome chronic effects of leprosy infection, should also be documented. While patients may present with visible impairments, such as when leprosy is long-

standing and has indirectly contributed to significant injuries, it falls upon the health care worker to investigate for other more insidious patterns of involvement. Sensory and motor nerve function testing should be performed to document the absence or presence of impairment and to serve as a baseline for subsequent monitoring of disability. Mitigation and minimization of deformities and disabilities are essential. Eye examination should also be performed, which includes visual acuity, lid examination, and assessment of cornea, uvea and lens. Primary health workers can be trained to examine visual acuity and lid examination.

Summary of evidence

Neurofunction assessment

Peripheral nerve damage is prevalent in leprosy leading to neuromuscular disability. Nerve function assessment, to involve motor nerve function (voluntary muscle testing [VMT], grip dynamometry, motor nerve conduction measurements) and sensory nerve function (sensory testing with monofilaments and sensory nerve conduction measurement on 4 nerves [radial cutaneous, ulnar, median and sural nerve]) should be included in baseline and monitoring for early diagnosis of neuropathy or detecting changes in nerve function prior to a clinical nerve damage event. Findings of the INFIR (ILEP Nerve Function Impairment and Reactions) Cohort study (van Brakel et al., 2008) documented the use of neurofunction assessments relevant to the detection of peripheral nerve neuropathy associated with leprosy.

Clinical neurologic assessments (monofilament testing, VMT, nerve palpation) in combination can increase the detection sensitivity of clinical tests comparable to that detected by nerve conduction studies (Khambati et al., 2009). More importantly, these clinical neurological assessments are applicable even in low-resource settings such as that of the Philippines.

Sonography has been described as a useful tool in the diagnosis of leprosy neuropathy. A highly correlated finding is a fusiform thickening of the peripheral nerves that are generally compromised in patients affected with leprosy, including the ulnar, median, and posterior tibial nerves (Elias et al., 2009). The thickening may be measured in the corresponding cross-sectional areas (CSAs) of the affected regions. One cohort study of 100 leprosy patients utilized ultrasound of peripheral nerves (ulnar, median and common peroneal nerve) for detection of peripheral nerve neuropathy demonstrated as nerve enlargement (Lugão et al., 2016); however, this modality is not available in most primary care settings in the country.

TABLE 6. SUMMARY OF EVIDENCE FOR NEUROFUNCTION ASSESSMENT

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
van Brakel et al. (2008)	Cohort with follow-up to 2 years; India	303 newly diagnosed patients with MB leprosy	188 patients were included for follow up for 2 years	Nerve function impairment (NFI) without skin signs of reaction was the most frequent outcome event in 23% of the cohort, and 60% of all events. Sensory impairment was much more frequent than motor impairment (19% vs. 2.1%).	Low

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
Khambati et al. (2009)	Cross-sectional study; India	357 untreated multibacillary (MB) leprosy patients	Sensitivity and specificity of clinical tools viz. nerve palpation (NP), monofilament (MF), and voluntary muscle testing (VMT), for assessing peripheral NFI in leprosy, using nerve conduction studies (NCS) as gold standard	The sensitivity of NP for NFI ranged between 71% to 88% for all nerves, except the median (43%) and sural (59%) nerves. Specificity was 60% for all, but low for ulnar (34%) and common peroneal (40%) nerves. The specificity of MF testing was 80% and of VMT assessment was 90% for all nerves. The sensitivity of MF testing ranged between 35–44%, while that of VMT assessment was very low at 4–5%. The maximum was for the ulnar nerve (25%).	Very Low
Frade et al. (2013)	Cross-sectional Study; Brazil	A total of 126 patients, with 77 leprosy patients and 49 healthy volunteers as control group	Ultrasound (US) evaluation was done with cross-sectional areas (CSAs) of peripheral nerves, indexes of the differences between CSAs at the same point (ΔCSAs) and between tunnel (T) and pre-tunnel (PT) ulnar CSAs (ΔTPTs) as well as along the median (M) and common fibular (CF) nerves	The ROC analysis of CSAs showed the best specificity and sensitivity at the PT point of the ulnar and CF nerves, respectively, with ulnar specificity = 85% and sensitivity = 68%, and CF sensitivity = 81% and specificity = 72%. The ΔCSAs of the PT and T points of the ulnar nerve showed high specificity (>80%) and the ΔTPTs showed the highest specificity (>90%).	Low
Ashwini et al. (2018)	Case control; India	35 patients with leprosy as cases,	Clinical evaluation of bilateral ulnar,	Comparing clinical examination to ultrasound revealed specificity of	Very low

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
		and 30 healthy controls	median, and common peroneal nerves was performed by two observers, compared with US of these nerves for both populations of cases and controls	72.63% (95% CI: 65.71–78.84%); specificity of 100% (95% CI: 95.01%–100%); positive predictive value of 58.06% (95% CI: 52.34%–63.58%); and, negative predictive value of 58.06% (95% CI: 52.34%–63.58%)	

Eye examination

Eye examination is recommended to be done at baseline and during monitoring. This includes visual acuity, lid examination, assessment of cornea, uveal and lens. Primary health workers can be trained to examine visual acuity and lid examination. Prevalence of ocular involvement in patients with leprosy are also described in Table 7. Early detection of leprosy-related eye problems can address the disability related to disease progression.

TABLE 7. SUMMARY OF EVIDENCE FOR EYE ASSESSMENT

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
Pavezzi et al. (2020)	Cross-sectional study; India	86 patients were evaluated, with a mean age of 50.1 years, and with multibacillary leprosy (92%)	All patients diagnosed with leprosy, in the course of treatment or with treatment already completed, irrespective of whether they had ocular complaints.	The prevalence of ophthalmologic changes was 100%, with the most common findings as dysfunction of the Meibomian glands (89.5%) and dry eye syndrome (81.4%). Cataracts were observed in 22 patients (25.6%), but best corrected visual acuity was normal or near normal in 84 patients (97.7%).	Moderate
Thompson et al. (2006)	Observational study; India	1137 patients diagnosed with leprosy, with 54% of the sample having MB leprosy	Patients underwent ophthalmic examination according to a standard format.	Thirty-three out of 1137 (2.9%) subjects were blind according to the WHO classification, and 232/1137 (20.7%) had moderate visual impairment.	

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
				Longer duration of disease, more advanced treatment stage and older age were independently associated with blindness based on multiple regression analysis.	
Courtright et al. (2002)	Cohort study; India, Philippines, Ethiopia	691 patients diagnosed with MB leprosy		Age-adjusted prevalence of blindness and visual impairment was 2.8% and 5.2%, respectively. 115 (95%CI 8.5-13.2%) of newly enrolled MB patients have potentially blinding related ocular pathology (e.g. lagophthalmos, uveal conditions, trichiasis).	
Ravanes et al. (2011)	Cohort study; Philippines	202 Filipino MB leprosy patients	Comprehensive eye examinations before, during, and after WHO 2 year MDT with follow up for 5 years	Eye abnormalities consisted mostly of diminished corneal sensitivity before MDT (6%) and lagophthalmos (n = 7, 3.4%)	Moderate

Rationale

The CP recognizes that the establishment of baseline conditions of a patient is necessary in order to track the progress of treatment. Additionally, given the significant impact of leprosy on disability, assessment of baseline function is important in the identification of disability to initiate prompt management and monitoring for the development or further deterioration of disability.

Recommendation 2.b

The following laboratory diagnostics may be done, if available, before initiating treatment: slit skin smear, complete blood count, SGPT/SGOT and renal function tests.

Strong recommendation, low quality of evidence

Recommendation 2.c

G6PD deficiency screening and pathological examination of skin biopsies may be done, if indicated and available.

Strong recommendation, low quality of evidence

Background

The slit-skin smear provides a counter-diagnosis to PB leprosy when the SSS is positive; in this case, the diagnosis would be changed to MB leprosy. Additionally, the SSS provides a measure of the bacterial index of a leprosy case, which is used a basis for determining relapse according to the WHO definition (WHO, 2020b). In other guidelines, the BI was also used to dictate the need for follow-up among patients with leprosy (Department of Health Northern Territory [Australia], 2018). The BI is used in other guidelines to guide decisions for extending MDT.

Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are sensitive towards dapsone and may develop hemolytic anemia. A G6PD screening test may be prudent prior to initiating treatment with MDT. However, cases of dapsone-induced hemolytic anemia have been recorded even among those with normal G6PD activity (Costa Queiroz et al., 2002; Kaluarachchi et al., 2001). A complete blood count may serve as a useful baseline for patient records.

Baseline measures of SGPT/SGOT (ALT/AST) and renal function can be obtained and kept as reference values. Rare instances of drug-induced hepatitis (Nair, 2018; Tabri et al., 2017) and renal dysfunction (da Silva Júnior & Daher, 2006; Daher et al., 2011; R. A. Oliveira et al., 2008; Polito et al., 2015) have been documented as a result of pharmacotherapy.

This recommendation includes a caveat for availability. The intended setting for this guideline is in primary care, which may not be equipped to perform the laboratory examinations. There may be undesirable, added costs to the patient and the health care system. Finally, these tests are not necessary. The need for these tests should always be informed by a trained health care professional with knowledge of the patient's clinical history and risk factors.

Summary of evidence

Slit-skin smear and the bacillary index

For areas with available resources, it is recommended to measure the initial bacillary index of each patient. Additionally, the bacillary index of granuloma (BIG) appears to be more sensitive than slit-skin smear alone (Bhushan et al., 2008). Table 8 shows the sensitivity and specificity of BI through SSS and BIG in the diagnosis of MB leprosy.

TABLE 8. SUMMARY OF EVIDENCE FOR SLIT-SKIN SMEARS AND BACILLARY INDEX

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
Bhushan et al. (2008)	Cross-sectional study; India	141 patients with leprosy with 67 (47.5%) PB	A total of 76 patients were truly MB with either positive smears, BIG	SSS correctly identified MB patients in 43 of 76 *true*-MB cases with a sensitivity of 56.58%, while skin biopsy showed AFB in 65	Moderate

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
		and 74 (52.2%) MB.	positivity or with a typical histology of BB, BL or LL. Among these 76 true-MB patients, WHO operational classification correctly identified multibacillary status in 56 (73.68%), and SSS in 43 (56.58%), while BIG correctly identified 65 (85.53%) true-MB cases	of 76 *true*-MB cases with sensitivity of 85.53%. The specificity and the positive predictive value (PPV) for both BI and BIG would naturally be 100% as they directly demonstrate AFB; however, the negative predictive value (NPV) of SSS was 66.33% as compared to 85.53% of BIG.	
Bhat et al. (2015)	Cross-sectional study; India	45 newly diagnosed patients with leprosy, with 33 (73%) of borderline tuberculoid spectrum (BT) of leprosy, 5 borderline lepromatous (BL), and 7 lepromatous leprosy (LL). Among BT patients, 18 had PB leprosy and 15 had MB leprosy.	A slit skin smear (SSS), from where the bacillary index was calculated. Another skin biopsy from a clinical lesion where the bacillary index of granuloma (BIG) was calculated.	All patients who were SSS-positive were BIG positive. In the BT group, three patients who had ≤5 lesions who were negative on SSS were found to be BIG-positive. BIG may be a better indicator of the true bacillary load in leprosy as compared to bacillary index on slit smear (BIS)	Low

Complete blood count and glucose-6-phosphate dehydrogenase (G6PD) deficiency screening

It is recommended to do a baseline complete blood count and monitoring before and during ongoing treatment of MDT for leprosy patients. Two studies showed adverse drug reactions with MDT/dapsone, resulting in hemolytic anemia even in patients with normal G6PD activity, with

reticulocyte count elevated (Costa Queiroz et al., 2002; Kaluarachchi et al., 2001). Hemolytic anemia were noted in the studies shown in Table 9 and monitoring is recommended within the first 3 months of treatment with MDT (Kaluarachchi et al., 2001). Other hematologic adverse reactions included agranulocytosis, severe leukopenia (Guragain et al., 2017).

With the known association of hemolytic anemia among patients with G6PD deficiency receiving dapsone, a G6PD deficiency screening test is recommended prior to initiation of treatment (Pamba et al., 2012; Youngster et al., 2010).

TABLE 9. SUMMARY OF EVIDENCE FOR COMPLETE BLOOD COUNT AND G6PD DEFICIENCY SCREENING

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
Costa Queiroz et al. (2002)	Retrospective cross-sectional study; Nepal	2205 leprosy patients	ADRs to dapsone were normally seen after 3 weeks of intake of dapsone. Hemolytic anemia and agranulocytosis events were noted	Occurrence of dapsone ADRs was 0.82% in 4 years with hemolysis (5 out of 18 patients [27%])	Very low
Nair, SP. (2018)	Retrospective cross-sectional study; India	901 new leprosy cases	Prevalence of adverse drug reactions (ADR) to MDT was reviewed. 28 cases ADR to MDT were documented. Borderline tuberculoid was the commonest type of leprosy in which ADR were seen (46.43%).	3 out of 17 (18%) had hemolytic anemia	Very low

Tests for liver damage

It is recommended to evaluate for liver damage prior to starting MDT among patients with leprosy. One prospective cohort study among patients with leprosy measured SGOT (also known as aspartate transaminase [AST]) and SGPT (also known as alanine transaminase [ALT]) before initiation of MDT and 3 and 6 months after initiation of MDT. The study found significant increases in SGOT and SGPT levels (Tabri et al., 2017). (Level of evidence – very low)

Adverse drug reactions (ADRs) were also noted in two studies. A retrospective study of 901 new leprosy cases given MDT recorded hepatic involvement in the form of drug-induced hepatitis as the most common presentation of ADR, accounting for 13 cases (46.43%) out of 17 cases of ADR

(Nair, 2018). It was posited that the culprit drugs were rifampicin and dapsone. (Level of evidence – very low).

Renal function tests and urinalysis

Functional and urinary abnormalities have been reported in association with lepromatous reactive episodes and erythema nodosum leprosum (ENL) development. Baseline and post-treatment evaluation are recommended to include laboratory (serum urea and creatinine, estimated glomerular filtration rate, urinalysis, and microalbuminuria) and clinical features of renal disease. Renal dysfunction was mostly associated with patients having lepromatous leprosy and patients developing ENL as seen in Table 10.

TABLE 10. STUDIES ON RENAL FUNCTION OF PATIENTS WITH LEPROSY

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
Oliveira et al. (2008)	Cross-sectional study; Brazil	59 consecutive PB and MB leprosy patients with no history of hypertension and diabetes, compared with controls	Functional and urinary abnormalities were compared; however, no matching for age and gender was done	Leprosy patients had lower glomerular filtration rate (GFR) (86.25 vs 112,18 ml/min/1.73m2, p-value=0.000) compared to controls Hematuria (27%), proteinuria (11.95) and microalbuminuria (8.4%) were noted.	Very low
Polito et al. (2015)	Prospective cohort; Brazil	189 consecutive patients, with all forms of leprosy	Laboratory (serum urea and creatinine, estimated GFR, urinalysis, microalbuminuria, urinary RBP) and clinical features of renal disease were evaluated, previously and after onset (3 and 8 months later) of MDT	Microhematuria and microalbuminuria were detected in 7.5% and 9.6% of the cases, respectively. Elevated serum creatinine was detected in 34% pre-MDT and among patients with erythema nodosum lepromatosum, 45.5% by the time of diagnosis, 18% after 3 months, and 9% after 8 months of MDT.	Very low
da Silva Júnior & Daher (2006)	Cross-sectional study; Brazil	461 leprosy patients without any co-morbidity	Review of records done among patients admitted from 1976 to 2002	Urinary abnormalities were found in all clinical presentations of leprosy. Proteinuria was found in 7.8%, hematuria in 60 13%, hemoglobinuria in	Very low

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
				7.3% and leukocyturia in 16.4%. Nephrotic levels of proteinuria (>3.5g/dL) were found in four patients (0.8%). Levels of creatinine above 1.4 mg/dL were detected in 8.6% and levels of urea above 40 mg/dL in 11.2% of patients. Among the patients with renal failure (serum creatinine >1.4 mg/dL), 45% were lepromatous, 17.5% tuberculoid, 17.5% indeterminate, 7.5% borderline lepromatous, 7.5% borderline tuberculoid and 5% mid-borderline.	
Daher et al. (2011)	Historical cohort; Brazil	923 patients diagnosed with leprosy, with 65% PB and 35% MB	Retrospective study was conducted among patients with confirmed leprosy followed at tertiary hospitals. Laboratory data in the medical records were reviewed.	Renal dysfunction was found in 35 cases (3.8%). Among these patients, cases could be classified into: 23 (65.7%) lepromatous; three (8.6%) tuberculoid; five (14.3%) indeterminate; and, four (11.4%) borderline. Urinary abnormalities were found in all clinical presentations of leprosy. Proteinuria was found in 44 cases (4.8%), hematuria in 63 (6.8%), and leukocyturia in 96 (10.4%).	Very low

Recommendation 2.d

Electrocardiogram and lipid profile may be done for high-risk patients.

Strong recommendation, very low to low quality of evidence

Background

Leprosy may contribute to the development or worsening of comorbidities. The management of leprosy complications may even exacerbate existing conditions in the patient. A study found leprosy

patients to be at higher risk for cardiac autonomic neuropathy than healthy controls based on prolonged QTc intervals on electrocardiography (Solanki et al., 2016).

Leprosy patients may also experience reduced high-density lipoprotein (HDL) levels compared to healthy controls (Lemes et al., 2020). Corticosteroids, which are administered to patients with leprosy reactions, also contribute to significant increases in triglycerides (TG) and low-density lipoproteins (LDL) (Negera et al., 2018). Low HDL cholesterolemia, increased TG and increased LDL contribute to cardiovascular risk. The latter two also contribute to diabetes and hypertension. The possible derangements that are present or that may develop among leprosy patients prior to and during the course of treatment support the need for monitoring lipid profiles.

The Recommendation adds that these may be performed for "high-risk" patients. The assessment of *high risk* must be based on the fair and adequate evaluation of the health care provider who also has knowledge of the patient's clinical history and comorbidities, taking into consideration the additional burden on patient's time and financial resources.

Summary of evidence

Electrocardiogram

Cardiac autonomic neuropathy may be present among patients with leprosy which can lead to repolarization abnormality. A small case-control study, assessed to be have a very low quality of evidence, with 30 leprosy patients and 30 age- and sex-matched healthy controls showed an odds ratio of 6 for prolonged QTc (95% CI: 1.17–30.72, p-value = 0.03) (Solanki et al., 2016).

Lipid profile

It is recommended that lipid profile should be done at baseline and on follow-up, especially among patients with multibacillary leprosy and on treatment with prednisolone for ENL.

Among patients with MB leprosy, pre-MDT high-density lipoprotein (HDL) levels were 50% lower compared to healthy controls, with HDL cholesterol levels in pre-MDT MB patients at 31.5 (21–39) mg/dL and in HC at 62 (55–74) mg/dL with a p-value <0.0001 (Lemes et al., 2020). In the study, HDL is highly affected during infection and these functions can be slightly recovered after MDT, but not to the levels of healthy individuals. (Level of evidence – very low)

In one prospective matched case-control study of 30 patients with ENL and 30 non-reactional LL patient controls, the use of prednisolone for prolonged time in chronic ENL (occurring for 24 weeks or more) was correlated with increased triglycerides (TG) and low-density lipoproteins (LDL) (Negera et al., 2018). These derangements in cholesterol values support the need for monitoring lipid profiles, particularly during prednisolone treatment to avoid the risks associated with increased TG and LDL, such as diabetes and hypertension. (Level of evidence – very low)

Good Practice Statement 2.a

Chest x-ray and sputum smear microscopy may be done to screen for active pulmonary tuberculosis.

Rationale

There is considerable overlap between leprosy and tuberculosis, not only in terms of microbial taxonomy but also in its similar geographic endemicity (Mangum et al., 2018). In the Philippine primary care setting, Tuberculosis–Directly-Observed Treatment Short-Course (TB-DOTS) facilities, which may be rural health units or community health centers, already provide diagnostic services and treatment for patients with pulmonary tuberculosis (Department of Health, 2014). The health care worker responsible for the management of a patient with leprosy may request for a chest X-ray and sputum smear microscopy to diagnose TB and exclude coinfection. Patients with active pulmonary TB may need modified treatment with MDT for both TB and leprosy.

Good Practice Statement 2.b

Fasting blood sugar determination may be done to screen for diabetes.

Rationale

There is no known association between leprosy and diabetes. However, the management of leprosy, specifically the administration of corticosteroids for the treatment of leprosy reactions, may impair glucose control. Hyperglycemia is one of the most common and representative side effects of corticosteroid intake (Tamez-Pérez, 2015). Steroids may cause diabetes in patients without documented hyperglycemia. Moreover, due to its promotive effects on insulin resistance, corticosteroids may precipitate life-threatening hyperglycemic crises in patients with diabetes, such as diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome (Umpierrez et al., 2002). Diabetes may also contribute to peripheral neuropathy, and it is important to manage diabetes alongside leprosy to prevent the development or the progression of disability.

Good Practice Statement 2.c

Early referral to a specialist is desirable if with presence of disability and if with derangement of initial diagnostics, but the presence of disability and absence of access to a specialist should not prevent initiation of treatment in primary health care.

Rationale

Health care workers who serve as the frontliners in managing leprosy patients may not have the necessary training and expertise to manage the derangements identified during laboratory, radiologic and histopathologic testing. Disability may also portend advanced disease and require physical therapy and rehabilitation which may be beyond the capacity and capability of the HCW and the facility in the primary care setting. Referrals to specialists may be prudent.

Treatment and management of leprosy

Question 3: Among patients diagnosed with paucibacillary and multibacillary leprosy, what is the dose and duration of treatment?

A three-drug regimen with rifampicin, dapsone and clofazimine is recommended for all leprosy patients with duration of treatment of 6 blister packs taken within 6-9 months for PB leprosy and 12 blister packs taken within 12-18 months for MB leprosy.

Weak recommendation, very low quality of evidence

Background

Rifampicin, clofazimine and dapsone are provided in multi-drug treatment (MDT) regimen blister packs by the WHO. The regimens require classification of patients into either PB or MB leprosy (WHO, 2018b). For adults, monthly doses include rifampicin 600 mg and clofazimine 300 mg, while daily doses include dapsone 100 mg and clofazimine 50 mg. Children 10-14 years old have access to lower doses of rifampicin 450 mg once a month, clofazimine 150 mg once a month and 50 mg every other day, and dapsone 50 mg daily. Children younger than 10 years or who weigh less than 40 kg may be given weight-adjusted treatment regimens. The latter requires single formulation medications because no MDT combination packs are available (WHO, 2018b). The summary of dosages for the current WHO-MDT regimen are provided in Table 11 below.

TABLE 11. RECOMMENDED TREATMENT REGIMEN FOR ADULT AND CHILDREN ADAPTED FROM WHO (2018b) TREATMENT GUIDELINES

AGE GROUP	DRUG	DOSAGE AND FREQUENCY	DURATION (MONTHS)	
			MB	PB
ADULT	Rifampicin Clofazimine Dapsone	600 mg once a month 300 mg once a month and 50 mg daily 100 mg daily	12	6
CHILDREN (10-14 YEARS)	Rifampicin Clofazimine Dapsone	450 mg once a month 150 mg once a month, 50 mg on alternate days 50 mg daily	12	6
CHILDREN <10 YEARS OR <40 KG	Rifampicin Clofazimine Dapsone	10 mg/kg once a month 100 mg once a month, 50 mg twice weekly 2mg/kg daily	12	6

Summary of evidence

The WHO Guideline (2018b) provided the foundation for this recommendation. It should be acknowledged that WHO distributes MDT regimen packs to national leprosy programs. Furthermore, the NLCP Manual of Procedures (2018a) served as foundation for allowing a longer period of drug intake due to the aforementioned different socioeconomic contexts of patients.

The three-drug regimen for PB leprosy is a departure from previous treatments endorsed by WHO, which had been for a two-drug regimen of monthly rifampicin and daily dapsone for a period of six months (WHO, 2016e). There is evidence to show that there is a potential increase in risk of relapse in PB patients with the two-drug regimen (WHO, 2018b). The use of a three-drug regimen for both MB and PB leprosy also reduces the consequences of misclassification of MB patients as PB patients. This weak recommendation takes into account patient preferences, where 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." (WHO, 2018b)

In the analysis conducted by the WHO (2018b), six studies on PB leprosy were included showing evidence of better clinical outcomes with a 3-drug compared to 2-drug regimen. There was also not enough evidence supporting shortening treatment duration. For MB patients, one RCT found a three-drug, six-month regimen to offer a risk of relapse of 2.2% versus 0.3% in a three-drug, six-month regimen. Estimates were imprecise with a relative risk of 6.3 and a 95% CI 0.78–61. A non-randomized study comparing a six-month regimen to a 12-month regimen showed a non-statistically significant clinical response at 24 months (25% vs 77%, RR 0.33 [95% CI 0.06-1.8]).

Rationale

The WHO guidelines recommend stringent periods of drug intake at 6 months for PB leprosy and 12 months for MB leprosy. The consensus panel stressed that the delivery of treatment should be adapted to the needs of patients, and this Guideline is cognizant of the different circumstances surrounding each patient in the Philippines. Patients may live in difficult-to-access areas or be unable to visit the health facility regularly due to social, cultural, or economic reasons (NLCP, 2018a). Flexible treatment options supported by health teaching for the patient and their family plays an important role in compliance and early cure.

Noting that occasional irregularity does not affect the efficacy of MDT (NLCP, 2018a), this Guideline acknowledges that the allotted MDT regimens may be completed within 9 months in PB leprosy and within 18 months in MB leprosy. **However, there should not be a substantial gap nor a long break between doses.** Regular drug intake should still be included in counselling at the time of diagnosis, and **it remains ideal to finish allotted blister packs within 6 months for PB leprosy and within 12 months for MB leprosy.**

Question 4: Among patients with MB leprosy, can MDT be extended to 24 months versus 12 months and what are the indications for extension?

Recommendation 4.a

There is no strong evidence to extend MDT for MB leprosy patients, but extension of treatment may be done as clinically indicated.

Weak recommendation, very low level of evidence

Summary of evidence

There is no head-to-head randomized controlled trial comparing outcomes of patients with MB leprosy given WHO-MDT for 12 months against those given 24 months. One cohort study was done comparing untreated MB patients given 12 months (N=128) and 24 months (N=85) of MDT (Sales et al., 2007); however, this study had very low methodological quality due to imprecision and a small sample size. There was no statistical difference in bacillary index of both arms at baseline, at 12 months follow-up, and at 24 months follow-up. There was no association between treatment regimen and bacillary index after controlling other study variables. There were significantly more patients with reaction in those who received 12 months of treatment at 24 and 36 months of surveillance. The study concluded the risks of developing reactions is dependent on having more skin lesions (OR 2.5, 95% CU 1.192–5.343) and presence of edema (OR 2.919, 95% CI 1.539–5.537). Disability grade also showed no significant difference in both treatment arms.

A few studies published were case series of patients with MB leprosy who were given 12 months of treatment (Table 12). Outcomes differ in terms of relapse rates and reduction of bacillary index over time.

TABLE 12. CASE SERIES STUDIES OF PATIENTS WITH MB LEPROSY WHO WERE GIVEN 12 MONTHS OF MDT

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	OUTCOME	QUALITY OF EVIDENCE
Poojabylaiah et al. (2008)	Case series; India	163 MB leprosy patients		3 out of 163 with relapse	Very low
Kumar et al. (2013)	Case series; India	267 MB leprosy patients	High drop-out rate	Incidence of relapse is highest among cases without any nerve thickening and significantly higher than in cases with 3 or more nerve thickening	Very low
Dogra et al. (2013)	India	730 MB patients		Relapse rate 1.7% 54.9% lepra reactions	Very low

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	OUTCOME	QUALITY OF EVIDENCE
Maghanoy et al. (2011)	Case series; Cebu	300 MB leprosy patients	Case series with 1-year follow-up after the completion of treatment	Absolute relapse rate of 0.3% (0.52 per 1000 patient-years at risk). Subset with pretreatment bacterial indices of 4 and above the rate of relapse was 0.6%.	Very low
Kyaw et al. (2008)	Case series; Myanmar	200 MB leprosy patients	Case series followed up for 3 years	Acute neuritis: 5.0% Worsening of previous neural involvement: 1.5% BI reduction: 45% Increased BI: 1%	Very low

Rationale

In clinical practice in the Philippines, there are reports of treatment extension beyond the maximum recommended duration of 12 months (in the case of MB leprosy) due to a lack of clinical response among leprosy patients. In the Northern Territory (NT) in Australia, the NT Centre for Disease Control includes a 24-month treatment option for cases with a high BI ≥ 4+, based on an association with a higher rate of relapse in this patient population (Department of Health Northern Territory [Australia], 2018).

There is evidence from a study comparing two cohorts of MB leprosy patients undergoing 12 months versus 24 months of MDT that shows there is no statistical difference in BI nor in disability grade (Sales et al., 2007). There is limited data on the incidence of relapse that compare 12 months to 24 months of MDT.

Drug supply is also a matter of concern if treatment were to be extended beyond 12 months. Leprosy control programs in countries such as Australia may be able to fund and provide extended treatment courses (Department of Health Northern Territory [Australia], 2018). However, for the Philippines, the consensus panel acknowledges that the WHO allocates and distributes MDT drugs to the country based on the case load and the WHO formally recommends only up to 12 months of MDT for MB leprosy.

Good Practice Statement 4.a

Patients needing treatment extension should be referred to specialty centers.

Rationale

Health care workers in the primary care setting may not have access to a surplus of MDT regimen packs to extend leprosy treatment. Furthermore, it is likely that when the need to extend treatment is entertained that the health care provider has encountered a complicated leprosy case. The primary care setting may not have the necessary training, facilities and supplies to accommodate and manage treatment extension. The consensus panel asserts that referral to specialty centers is prudent.

Monitoring and evaluation during treatment

Question 5: What is the recommended monitoring interval during and after treatment?

Good Practice Statement 5.a

Active monitoring should be done based on regular clinical evaluation to detect adverse drug events, leprae reaction, disability, treatment failure and relapse.

Rationale

Active monitoring refers to an active, targeted search for relevant clinical phenomenon, as opposed to passive monitoring which only includes regular clinical evaluation. The consensus panel emphasizes that the patient should be requested to attend regular follow-up visits, which improve drug adherence and patient compliance. Adverse drug events (ADEs) may be addressed when detected during follow-up clinic visits; addressing ADEs may improve patient compliance by ensuring that the patient would not be deterred by these ADEs and continue the treatment regimen. Lepra reactions, which are the main contributors to disability in leprosy, must be evaluated at every consultation. Evaluation of disability, including sensorimotor deficits, must also be performed. Finally, the response of the patient to MDT must be monitored to identify any treatment failure and even relapse after the completion of MDT.

Recommendation 5.a

To detect adverse drug events, patients on treatment should have a repeat complete blood count and liver function test one month after initiation of treatment, then quarterly, until end of treatment when available and referred accordingly.

Weak recommendation, very low quality of evidence

Background

During scheduled patient follow-up visits during treatment, the clinician conducts history-taking and a physical examination of the patient. In addition to clinical evaluation, there are certain laboratory tests that are useful for the diagnosis of ADEs.

This recommendation supplements the recommendation on *baseline* diagnostic tests to be obtained at the time of leprosy diagnosis. Laboratory monitoring should be continued after the initiation of MDT. However, the clinician must also take into account the accessibility, availability and affordability of the desired test for the patient and for the primary care setting.

Summary of evidence

A systematic review of adverse effects of dapsone therapy in leprosy patients was conducted, which included 114 studies (Hilder & Lockwood, 2020). Most of the included articles were from India (n=48), Brazil (n=21), USA (n=5) and China (n=5). The average duration of symptom onset is 32.65 days with a range of 9–133 days. The most common adverse drug reactions (ADRs) were dapsone hypersensitivity (n=871), hemolytic anemia (n=240), anemia (n=140), gastrointestinal side effects (n=130), hepatitis (n=93), flu-like symptoms (n=54), and fixed drug eruptions (n=49). The estimated incidence rate of dapsone hypersensitivity was 1.22% (range 0.8%–3.0%) with an estimated fatality rate of 11.24% (range 9.6%–13.3%). The study did not include among the outcomes the frequency of monitoring done in each of the included cohort articles.

In a cross-sectional 19-year study done in India, only 28 cases of documented ADRs were found (Nair, 2018). Mild cutaneous reactions were not included. Dapsone was the most common cause of adverse drug events, and there were no reactions reported to clofazimine. Baseline investigations in the study included liver function tests, CBC, renal function tests, chest X-ray and ultrasound of the abdomen.

Rationale

Monitoring in the leprosy control program serves two functions: clinical monitoring of a patient's progress in treatment and data collection for program success indicators. Adverse drug reactions may occur at any point of treatment. The CP revised the original recommendation to test "every 4-8 weeks for the first three months" to "one month after initiation of treatment, then quarterly, until end of treatment." The most common ADRs in the systematic review by Hilder & Lockwood (2020) included dapsone hypersensitivity, hemolytic anemia, anemia, gastrointestinal side-effects, hepatitis, flu-like symptoms and fixed drug eruptions.

The CP recommends continued laboratory monitoring during ongoing treatment, as opposed to only during the first three months of MDT. The studies that were identified in the evidence base described epidemiological estimates of adverse events in leprosy treatment based on the WHO-recommended duration and based on prior MDT regimens (i.e., PB leprosy was treated with a two-drug regimen prior to 2018).

The CP acknowledges that some clinicians may opt to extend treatment of leprosy, such that it would be prudent to extend the recommendation of laboratory monitoring to cover the entire treatment period. Additionally, given that the old MDT regimens in these studies were different than current recommendations, the CP judged it advisable to increase the frequency of monitoring, especially during the early program implementation of the new MDT regimens. The ability of the clinician to anticipate and address these adverse drug events and provide health education will positively influence drug adherence. Finally, ADR incidence rates were measured in clinical trials, which assured patient follow-up compared to actual practice.

The CP adds a caveat to the recommendation where the availability of these laboratory tests is considered. Not all patients and primary care settings will have access to complete blood counts and liver damage tests. The clinician must consider time and financial resources of the patient and the health care facility in planning follow-ups.

Recommendation 5.b

To detect lepra reactions, patients undergoing treatment are recommended to follow up monthly. Patients who completed treatment are recommended to have follow-up visits every three months for the first two years and annually for five years.

Strong recommendation, very low quality of evidence

Background

Leprosy reactions are caused by changes in the immune system, and are the most common causes of physical disability in leprosy (World Health Organization, 2020b). There are two types of reactions: type 1 reactions manifest clinically as skin and nerve inflammation due to sudden alterations in cell-mediated immunity, and type 2 reactions (or ENL) are caused by humoral responses, as a multisystem and relapsing disorder seen in patients with high bacillary index in BL-LL leprosy (Voorend & Post, 2013). Knowing the subset of patients at risk for lepra reactions enables the clinician and the patient to formulate a follow-up plan that allows early intervention.

Summary of evidence

A systematic review of 65 articles, predominantly from India (24) and Brazil (9) showed the global incidence of ENL (Voorend & Post, 2013). In field-based studies, 1.2% developed ENL, with 4.5% being MB cases and 15.4% being LL cases. Hospital-based studies revealed a higher number of reported ENL cases among MB patients (13.7%). Multiple ENL episodes can occur with an average of 2.6 episodes in 39–77% of ENL patients. It was shown that the peak of ENL incidence was during the first year of treatment.

Two studies from Brazil examined the lepra reactions among patients with leprosy. In a cross-sectional study done in 440 patients, 57% had leprosy reactions during and/or after MDT, with 80.5% of patients with reactions presented with MB leprosy (Gonçalves et al., 2009). In a retrospective study of 494 patients from 2005–2011, reactional episodes were detected in 40% (95% CI: 35.6–44.1) of the patients and were more frequently observed in MB forms (57.2%; p-value < 0.0001) (D. T. de Oliveira et al., 2013). Type 1 reactions were the most common (75.1% [148/197]). Moreover, they occurred more frequently during treatment for leprosy. The studies did not state the frequency of monitoring of the subjects.

In a cohort study by Becx-Bleumink (1992) in Ethiopia, a total of 405 reactions were seen during a 3.5-year period with 90.1% (N=365) being RR and 9.9% (N=40) were ENL. T1R was observed in 43.6% of BL patients and 19.2% in LL patients. Among BL patients, T1R was observed 4.9% at the time of diagnosis, 26.3% during the first year of MDT, and 12.4% during the second year of MDT. Among LL patients, RR was observed 0% at the time of diagnosis, 12.8% during the first year of MDT, and 6.4% during the second year of MDT. Among 438 BT patients, T1R was diagnosed in 21.0% with 3.4% occurring at the time of diagnosis, 10.3% during MDT, and 7.3% during the first release from MDT.

In a recent retrospective cohort study of 108 leprosy patients done in Thailand from 1995–2015, reactions were documented in 56.5% (N=61) of patients. The onset of leprosy reactions was most commonly observed during MDT (n=44, 72.1%), with the frequency being highest at the 6th to

12th month of MDT treatment (34.4%) (Suchonwanit et al., 2015). After release from treatment, only 6.6% had leprosy reactions. The average time to development of leprae reaction was 8.9 months, and majority were type 1 reactions (68.85% vs ENL 31.2%). The risk factor for the development of reaction were female gender (OR 1.87, 95% CI: 1.05–3.31), positive BI status at diagnosis (OR 1.75, 95% CI: 1.19–2.56), MB treatment regimen (OR 1.45, 95% CI 1.06–4.21). In a cohort study by Schreuder (1998) in Thailand, incidence rate for severe type 1 reaction among patients with PB leprosy was 1.4 (CI 0.46–4.5) per 100 person-years at risk (PYAR) during MDT for PB and an incidence rate of 12 (CI 9.0–16) per 100 PYAR during the first 24 months of MDT for MB. Late type 1 reactions were seen in 2.7% of PB patients (95% CI 1.1–4.3) and 9% (95% CI 5–13) among MB patients. Late reactions in PB group were seen in borderline tuberculous patients; in MB patients, most were seen in borderline lepromatous patients. Around 72% of the reversal reactions appeared during the first two years after release from treatment.

In a retrospective study of records of 670 patients done between 2004–2013 done in Bangladesh, the prevalence of reactions was 55.33% (N=166) for type 1 reactions, 16.57% (N=49) for type 2 reactions, and 28.33% (N=85) for neuritis (Mowla et al., 2017). Reactions were observed in 28.33% of patients during MDT, while 15.33% developed leprosy reactions after MDT. Patients in the study received 6 months of MDT for PB leprosy and 12 months of MDT for MB leprosy. Patients were followed up monthly for the first year and every second month during the second year.

In a prospective cohort study of 34 patients under 15 years old, six children (33.3%) had lepra reactions (Bandeira et al., 2019). The occurrence of lepra reactions was significantly associated with age group 8–14 years old; borderline and lepromatous clinical forms; patients with MB leprosy; and patients with 10 or more skin lesions. The frequency of monitoring was not stated.

Rationale

The evidence shows that patients may develop leprae reactions during and after MDT. Since patients undergoing MDT are advised to follow-up monthly, evaluating for the presence of lepra reactions should be done during each clinic visit. Although the likelihood of developing leprae reactions may decrease over time, the CP advises to monitor for signs and symptoms of these reactions to avoid the complications of unmanaged reactions. It should be noted that these epidemiological estimates of lepra reactions were conducted prior to the 2018 recommendation to adopt a three-drug regimen for MDT in PB leprosy, and the observed incidence rates of these reactions may change.

Recommendation 5.c

To detect new or progression of physical disability, patients should be followed up monthly during treatment. For patients who have completed treatment, follow-up visits should be made every three months for the first two years and annually for five years.

Strong recommendation, very low quality of evidence

Summary of evidence

In a retrospective study done in Brazil assessing the progression of physical disability, it was revealed that the mean time for progression of the PD grade was 162 months for PB leprosy and

151 months for MB leprosy, although the risk of PD grade progression was not significant among MB and PB patients (Dos Santos et al., 2020). The greatest risk in development of progression in PD were leprosy reactions during treatment (HR 1.6, 95% CI: 1.1–2.4) and those with leprosy-related complaints during treatment (HR 1.8, 95% CI: 1.3–2.4). The survival curve showed that the rate of progression to PD after release of treatment was 35%. In another retrospective study done in 2009, patients with initial grade 2 PD progressed to grade 0 (21.3%) and grade 1 (20%). Progression of PD grade was significantly associated with disability grade upon admission, type of physiotherapy treatment, age, higher doses of prednisone, number of damaged nerves, and type of reactional state (Gonçalves et al., 2009). In another study by Costa (2015) of cases that were discharged after being declared cured with chemotherapy, improvement of PD was significant among those with higher educational attainment (OR 2.46; 95% CU: 1.75–2.91, p-value < 0.001) and those without reactions at initial diagnosis (OR 2.4; 95% CI: 2.21–2.62, p-value < 0.001).

In a retrospective study done in Nepal, the risk of developing new impairment was doubled among patients who had impairment at diagnoses compared to those without (OR 2.05; 95% CI: 1.4–3, p-value = 0.0002), as well as those with visible deformity (OR 1.98; 95% CI: 1.15–3.40, p-value = 0.014) (Reed et al., 1997).

A population-based cohort study done in Thailand, the incidence of nerve function impairment (NFI) among PB patients without impairment at first examination was 1.7 (95% CI: 0.45–4.4) per 100 person-years at risk (PYAR) and 12 (95% CI: 8.4–17) per 100 PYAR among MB patients. The incidence rates of new impairments among patients without impairments at release from treatment during the first 3 years of surveillance were 0.3 per 100 PYAR for PB leprosy and 0.5 per 100 PYAR for MB leprosy. In a study done in Bangladesh 5 years after persons were released from treatment (6 months of MDT for PB leprosy and 24 months of MDT for MB leprosy), the incidence rates of NFI were 16.1 per 100 PYAR among MB leprosy patients and 0.9 per 100 PYAR among PB leprosy patients (Jan H Richardus et al., 2004). For PB patients, the first NFI event was within 3 years after registration (89%). For 121 patients with MB leprosy, 64% of NFI was recorded within a year after diagnosis, 29% during the second year, and 7% after two years.

In a study by Sharma (1996) in India among 151 patients, the deformity incidence was 59.2 per 1000 person-years. There was no significant difference observed between the incidence of Grade 2 deformity developed before, during, and after MDT. In a 2012 study, the incidence of disability was lower at 2.74 per 100 PYAR, with higher disability among early defaulters than late defaulters (Kumar et al., 2012). In a recent case control study (Srinivas et al., 2019), among 1400 leprosy patients 18 years old and above, the risk factor for development of grade 2 or grade 1 PD were age more than 60 years old (OR 2.2; 95% CI: 1.3–3.6); daily wage laborer/agriculture (OR 1.95; 95% CI: 1.1–2.2); diagnosis of MB leprosy (OR 9.1; 95% CI: 6.2-13.3); more than 3 months delay in treatment initiation (OR 1.95; 95% CI: 1.3-2.1); and, healthcare provider delay more than 1 month (OR 1.4; 95% CI: 1.1-1.9).

Rationale

The evidence suggests that annual follow-up may be effective in monitoring physical disability. Physical disability is preventable if managed promptly. However, given that patients may have inadequate follow-ups and that monthly follow-ups are already recommended during the MDT course for other indications, the CP found it prudent to recommend monthly evaluations of physical disability during the MDT regimen.

The CP also acknowledges that lepra reactions contributing to nerve function impairment is the primary contributor to physical disability in leprosy. Since evaluation of lepra reactions is performed monthly according to Recommendation 5.b, it is also prudent to assess physical disability in the same clinic visit.

Recommendation 5.d

> To detect relapse, patients should be advised to watch out for new lesions, numbness or loss of sensation appearing after release from treatment.
>
> *Strong recommendation, very low quality of evidence*

Summary of evidence

Relapse rate varies according to year and country (table 1). Most of the studies conducted on relapse rates were passive surveillance. The study done in Malawi followed up their subjects quarterly for four years, while a study done in India followed up their subjects monthly during treatment and every 6 months after release from treatment for five years and annually thereafter. A study done in the Philippines did slit skin smear yearly or for every reported new lesions. Studies with definite follow-up showed higher rates of relapse compared to passive surveillance.

A retrospective cohort study of 3791 subjects done in India (Prabu, 2015) evaluated the rate of relapse among patients with signs and symptoms of relapse who were released after completion of full course of treatment of MDT. The study was of very low quality because of high dropout rate as it only examined 58% of the patients released from treatment. Out of the 2177 patients, 58 patients were diagnosed with clinical relapse, and 9.3% of the patients who relapsed showed positive for M. leprae in the slit skin smear. No significant difference in rate of relapse between classification of leprosy (MB 7.5 vs PB 5.1 per 1000 patient-year, p-value = 0.15). The study observed that the relapse rate declined over years after release from treatment.

In a prospective cohort study done in India among 267 patients with MB leprosy, the initial smear status did not affect the rate of relapse. The study was of poor quality due to many patients refusing skin smear testing. Also, no test on the viability of the bacilli found on the skin smears was conducted.

TABLE 13. INCIDENCE AND RISK OF RELAPSE AFTER MDT TREATMENT IN LEPROSY PATIENTS

REFERENCE	YEARS OF STUDY	COUNTRY AND POPULATION	FREQUENCY OF FOLLOW-UP	RELAPSE RATE
Prabu et al. (2015)	2005–2010	India 2177 patients released from treatment with follow-up data	Once only after release from treatment	Overall incidence rate of relapse was 6.1 per 1000 patient year (95% CI: 4.67–7.83) or
Kumar et al. (2013)	2001–2006	India 267 patients with leprosy given FDT for 12 months	Monthly during treatment Every 6 months after release from treatment	Overall incidence of rate of relapse 1.97 per 100 patient-year

REFERENCE	YEARS OF STUDY	COUNTRY AND POPULATION	FREQUENCY OF FOLLOW-UP	RELAPSE RATE
			for 5 years and then annually thereafter	
Poojabylaiah et al. (2008)	1986–2002	India 163 patients with MB leprosy, with data on follow-up	Passive surveillance	Relapse rate of 0.26 per 100 person-years of follow-up (95% CI: 0.235–0.285)
Guerrero-Guerrero et al. (2012)	1994–2004	Colombia 299 MB leprosy cases given WHO-MDT for 24 months	Not stated	Overall Incidence of relapse was 6.70 per 100 patient-years
Balagon et al. (2009)	1987–1994	Philippines 500 MB leprosy patients followed up after 2 years of WHO-MDT	Follow-up frequency not stated. Whole body clinical done examinations and slit-skin smears were at yearly or every 2 years interval or when new lesions were noted.	Cumulative risk of relapse among all subjects (6.6% at 16 years; 95% CI: 5.0–8.2%)
Schreuder (1998)	1987–1990	Thailand PB 6 months of treatment, and MB 24 months of treatment	Every 3 months	Relapse rates for PB at 0.41 (0.21–0.82) per 100 PYAR, and for MB at 0.33 (0.08–1.3) per 100 PYAR
Jamet & Ji (1995)	1984–1986	Brazil 75 MB leprosy patients, with 35 cases eligible for relapse. Received different treatment: 14 no prior treatment; 15 had DDS monotherapy, 5 with DDS monotherapy followed by various durations of DDS plus RMP, and 1 with 6 months of treatment with a combination of RMP, DDS and CLO. 29 followed up for 5 years and 17 for more than 7 years	Passive surveillance No specified follow-up schedule.	Overall relapse rate was 20.0% (or, 3.3 per 100 patient-years), which is very significantly higher than the figures obtained from the same group of patients analyzed 2½ years earlier, indicating that relapses occurred late (at least 5 ± 2 years) after stopping MDT.
Boerrigter et al. (1991)	1983	Malawi 499 PB leprosy patients released from treatment followed-up for 4 years	3, 6 and 12 months	Overall relapse rate 6.5 per 1000 person years (95% CI 3.4-11.4)

Rationale

These epidemiological estimates of the incidence and risk of relapse used follow-up intervals at the 3rd, 6th and 12th after release from treatment for the first two years, or 6 months thereafter for five years. However, the CP acknowledges that this frequency of clinic visits was performed in the controlled environment of research and may not be necessary in clinical practice. Additionally, the CP advises that relapse usually occurs after 1-2 years for PB leprosy and 3-5 years in MB leprosy (NLCP, 2018a).

Relapse is defined as the re-occurrence of the disease at any time after the completion of a full course of treatment (NLCP, 2018a). However, the detection of relapse is dependent on finding a marked increase (at least 2+ over the previous value) in the BI at any single site, which usually manifests with evidence of clinical deterioration, such as new skin patches or nodules and/or new nerve damage (WHO, 2016c). The CP acknowledges that it would be taxing on health system resources and the patient to undergo slit-skin smears at too frequent intervals.

The CP acknowledges that the patient is a stakeholder in their own care and well-being. Additionally, it is more practicable to empower the patient to identify clinical signs and symptoms of relapse after release of treatment. The clinician should provide appropriate patient education that covers common signs and symptoms of relapse such as, but not limited to, new lesions, numbness or loss of sensation. The patient must be advised to return to the health care provider with the appearance of any of these new symptoms after completing treatment.

Management of lepra reactions

Question 6: What is the treatment of complicated/refractory cases of lepra reactions?

Background

A type 1 reaction is the result of increased cell-mediated hypersensitivity reaction against *M. leprae* antigens, causing inflammation in the skin and nerves, due to changes in a patient's immune status (Eichelmann et al., 2013; Nery et al., 2013). Because the immune response initially appears to be declining and "reverses" to become more intense, type 1 reactions are also called reversal reactions (WHO, 2020b). These are recognized clinically by increased erythema, warmth, edema, and occasional ulceration of preexisting cutaneous plaques and nodules, in combination with increased swelling and tenderness of peripheral nerves (Renault & Ernst, 2015).

Erythema nodosum leprosum (type 2 reaction) is defined by systemic symptoms with fatigue, weakness, fever, joint pain, and weight loss (Eichelmann et al., 2013). ENL is clinically distinguished from type 1 reactions by the acute development of new painful, tender and erythematous subcutaneous nodules (Renault & Ernst, 2015). It is thought to be due to circulating immune complexes with widespread effects throughout the body (WHO, 2020b).

Lepra reactions can occur before, during, or after the completion of treatment, but these should be treated immediately upon first recognition to prevent progression of disability. Reactions are often present at the time of diagnosis, and starting MDT also often appears to precipitate a type 1 reaction (WHO, 2020b). Resolution of these leprosy reactions occurs over a period of a few weeks, although severe cases of type 1 and type 2 reactions may result in ulceration of inflamed skin lesions. A severity scale of ENL is conceived as such (WHO, 2020b):

- Acute ENL: episode of ENL lasting less than six months in which treatment was slowly withdrawn, with no recurrence of ENL while on treatment;
- Recurrent ENL: at least one further episode of ENL occurring 28 days or more after withdrawal of treatment for ENL;
- Chronic ENL: episode of ENL lasting longer than six months during which the patient is on continuous ENL treatment, or any treatment-free periods are less than 28 days.

Complicated leprosy reactions for this Guideline refer to severe cases of type 1 reactions, and non-acute types of ENL. Patients with refractory reactions are those that are being or have been treated but do not show clinical signs of improvement.

Recommendation 6.a

In primary health care settings, health workers need to be trained in recognizing leprae reactions, providing initial treatment, and initiating possible referral to specialists.

Strong recommendation, moderate quality of evidence

Rationale

Leprae reactions are a significant cause of physical disability (De Paula et al., 2019; Naafs & van Hees, 2016; Nery et al., 2013). Early recognition and treatment are key to preventing the development or progression of disability (WHO, 2020b). While this Guideline provides an outline of the management of leprae reactions, more complicated cases may warrant management by a specialist, who may not be present in primary care settings. Health care workers in the primary care setting are the first-line, first responders to leprosy patients in the community. Their role in early recognition, early treatment and referral is uncontested.

The CP emphasizes that primary health care workers who are sufficiently trained, such as nurses or midwives in leprosy programs, can start prednisolone as soon as leprae reactions are recognized. Twenty-two percent of new leprosy cases may present with leprae reactions at the time of initial diagnosis (WHO, 2020b).

Diagnostic procedures indicated in type 1 reactions include tests of nerve function to identify any accompanying neuritis, and tests to look for contraindications to treatment with steroids (WHO, 2020b). Type 2 reactions may be evaluated as mild, moderate or severe ENL using the ENLIST ENL Severity Scale (Walker et al., 2017). Components of the EESS include pain, fever, number of ENL skin lesions, degree of inflammation of ENL skin lesions, extent of distribution of ENL skin lesions, peripheral edema, bone pain, inflammation of joints and/or digits due to ENL, lymphadenopathy and nerve tenderness.

Training programs and leprosy control programs must strive to provide the necessary training for health workers in the primary care setting to enable them to contribute to better health outcomes for leprosy patients. The CP recognizes that primary health care workers who cannot provide treatment or suspect a complicated or refractory leprae reaction should refer to specialists, e.g. dermatologists. The CP notes that the emerging telemedicine platforms may be used in the referral system.

Recommendation 6.b

> The mainstay treatment for type 1 and type 2 leprae reactions is oral corticosteroid. Prednisolone is given for at least 20 weeks (5 months) prednisolone regimen, starting at 0.5 mg/kg to 1 mg/kg daily, tapered by 5 mg every 2 weeks until completion of 20 weeks to prevent early nerve damage or progression of symptoms.
>
> *Strong recommendation, moderate quality of evidence*

Background

Nerve damage leading to impairment and permanent disability is the major concern during leprosy reactions (Naafs & van Hees, 2016). Corticosteroids are commonly used for treating nerve damage, which may accompany a mild or severe type 1 reaction (WHO, 2020b). Their use in leprosy reactions and neuritis has been standardized despite a lack of randomized control trials (WHO, 2020b). Steroids address the disproportionate immunological response that is responsible for the clinical manifestation of leprosy reactions. Corticosteroid treatment must begin as soon as the leprosy reaction is diagnosed. Recommendations on the dosage of prednisolone are consistent with the management of leprosy reactions according to the WHO (2020b). Meanwhile, adjuvant or new therapies are also being investigated as treatment for reactions.

Summary of evidence

The following evidence addresses the treatment of neuritis, with or without leprosy reactions. There is one Cochrane meta-analysis included five RCTs involving 576 patients with reviewing any corticosteroid treatment for nerve damage in leprosy with the following comparators: no treatment, placebo, or a different corticosteroid regimen (Van Veen et al., 2016). Review of main outcomes included in the meta-analysis is shown in Table 14.

The TRIPOD trial included three trials studying prevention of nerve function impairment among patients with leprosy (Jan H Richardus et al., 2003; Van Brakel et al., 2003). A total of 815 patients were included with 414 patients randomly allocated to the placebo arms and 401 to the prednisolone arms. The treatment group was assigned to either a starting dose of prednisolone at 20 mg/day or at 40 mg/day. There is no significant improvement in sensory nerve function compared to placebo, although there is also no significant difference in the rate of adverse events.

TABLE 14. SUMMARY OF EVIDENCE FOR PREDNISOLONE VERSUS PLACEBO IN THE MANAGEMENT OF NERVE FUNCTION IMPAIRMENT IN NEURITIS

REFERENCE	STUDY DESIGN	SYNOPSIS	OUTCOME	QUALITY OF EVIDENCE
Van Brakel et al. (2003)	Randomized, double-blind, placebo-controlled, parallel-group trial	Prednisolone started at 40mg/day and thereafter gradually tapered at 5 mg for 2 weeks until 16 weeks completed (total administered 2520 mg), versus placebo for an	Improvement in sensory nerve function at 1 year: RR 1.01 (95% CI: 0.81–1.27)	Moderate

REFERENCE	STUDY DESIGN	SYNOPSIS	OUTCOME	QUALITY OF EVIDENCE
		equivalent number of tablets for 16 weeks		
			Adverse event rate: Occurrence of one or more major adverse event requiring withdrawal of treatment with RR of 0.83 (95% CI: 0.05–12.77)	Moderate
Richardus et al. (2003)	Randomized, double-blind, placebo-controlled, parallel-group trial	Prednisolone started at 40mg/day and thereafter gradually tapered at 5 mg for 2 weeks until 16 weeks completed (total administered 2520 mg), versus placebo for an equivalent number of tablets for 16 weeks	Improvement in sensory nerve function at 1 year: RR 0.97 (95% CI: 0.65–1,4)	Moderate
			Improvement in motor nerve function at 1 year: Assessed with MRC scale, the mean improvement in motor nerve function at 1 year was -0.30 ± 1.6 point, favoring placebo	Low
			Adverse event rate: RR 1.87 (95% CI: 0.33–10.64)	Moderate

Two randomized controlled trials showed that a 20-week (5-month) duration of treatment for improving and restoring recent clinical NFI in leprosy patients was effective, using a high or low dose of prednisolone gradually tapered for 20 weeks (Rao et al., 2006; Wagenaar et al., 2017). The summary of the outcomes of these RCTs are shown in Table 15.

TABLE 15. EVIDENCE ON TREATMENT DURATION OF PREDNISOLONE FOR NEURITIS

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	OUTCOME	QUALITY OF EVIDENCE
Rao et al. (2006)	RCT ; India	334 patients with leprosy with severe type 1 reactions requiring steroid with 3 treatment arms analyzed with a total of 269	The primary endpoint was the requirement for additional corticosteroids during the 12-month trial	At the end of the 12-month period, 41 out of 90 participants (46%) in the short-regimen group (2940 mg	Low

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	OUTCOME	QUALITY OF EVIDENCE
		patients (a: 88, b: 91, c: 90) (a) Prednisolone started at 60 mg/day and thereafter gradually tapered with 10 mg or 5 mg for 2 or 4 weeks until 5 months completed (total 3500 mg) (b) Prednisolone started at 30 mg/day and thereafter gradually tapered with 5 mg for 2, 4, or 8 weeks until 5 months completed (total 2310 mg) (c) Prednisolone started at 60 mg/day and thereafter gradually tapered with 20 mg or 10 mg for 2 weeks until 3 months completed (total 2940 mg) plus 2 months of placebo	period. A poor outcome was defined as a failure to respond to treatment in terms of changes to skin lesions, nerve pain or tenderness, or nerve function, or recurrences of skin or nerve lesions and needing extra corticosteroids.	over three months) needed extra corticosteroids. The difference between the high-dose and low-dose five-month regimen was not significant (RR 0.78, 95% CI 0.48 to 1.26, n = 179) The RR of needing additional corticosteroids was significantly less with the high-dose five-month course than with the three-month course (RR 0.52, 95% CI 0.34 to 0.81, n = 178) The RR of needing additional corticosteroids was just significantly less with the low dose five-month course than with the three-month course (RR 0.68, 95% CI 0.46 to 0.99, n = 181)	
Wagenaar et al. (2017) TENLEP trial	RCT; India, Nepal, Bangladesh, and Indonesia	875 patients diagnosed with leprosy and NFI symptoms with less than 6 months history, randomized into 2	For the 2 treatment arms, prednisolone was started at either 45 or 60 mg/day, depending on	The proportion of patients with restored or improved nerve function at week 78 was almost similar in both	High

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	OUTCOME	QUALITY OF EVIDENCE
		groups assigned to 20 weeks (n=432) and another assigned to 32 weeks (n=443)	the patient's body weight, and was then tapered. Primary outcome as proportion of patients with restored or improved nerve function. Additional prednisolone was required by 9% of patients assigned to 20 weeks and 1% assigned to 32 weeks.	groups: 78.1% in the 20-week arm and 77.5% in the 32-week arm (p=0.821). In the 20-week arm, more patients showed completely restored nerve function than in the 32-week arm, 23.5% against 18.7%.	

Rationale

A starting dose of 0.5 mg/kg daily of prednisolone is appropriate for a first course, meaning 30 or 40 mg daily for most adults (WHO, 2020b). Prednisolone can be given as high as 60 mg depending upon the patient's condition or computed at 1 mg/kg body weight (NLCP, 2018a). The NLCP describes the total duration of a standard course of corticosteroids as 12 weeks, although guidance provided by the WHO describes studies that suggest that a course lasting 20 weeks provides the best results (WHO, 2020b).

There was considerable hesitation among the CP to extend the course of treatment from 12 weeks to 20 weeks. The CP also acknowledges that the longer the patient is put on corticosteroids, the higher the risk of dose-related ADEs. The ability to taper corticosteroids will heavily rely on the ability of the patient to follow-up and the clinician to monitor. A longer course of steroid treatment would require more time and resources for clinic follow-ups, for both the patient and the healthcare system.

Recommendation 6.c

For patients with leprae reaction, early treatment with corticosteroids (prednisolone) should be started within six months, after which steroids may be ineffective.

Strong recommendation, moderate quality of evidence

Background

Prevention of NFI is a primary outcome of interest in the treatment of leprosy reactions. Early treatment with corticosteroids is desirable before nerve damage becomes irreversible. The

effectivity of steroids on preserving nerve function decreases as treatment initiation is delayed, and the difference is prominent before and after the six-month mark.

Summary of evidence

Based on the meta-analysis by Van Veen et al. (2016), there is moderate-quality evidence from two RCTs showing that treating either longstanding or mild nerve function impairment did not show corticosteroids to have a superior effect to placebo on nerve function improvement. Hence, treating NFI with prednisolone that occurred more than six months previously was no longer beneficial (Jan H Richardus et al., 2003; Van Veen et al., 2016).

Rationale

The CP reiterates the evidence that shows maximum benefit to be gleaned from corticosteroid treatment when it is started within 6 months of NFI. The CP recommends early initiation of steroid treatment for leprosy reactions by healthcare workers in the primary care setting. Additionally, the CP recognizes that prednisolone and prednisone have equivalent anti-inflammatory activity. According to the NLCP, prednisone may be more widely available since the program procures prednisone and not prednisolone. However, acknowledging the evidence that favors the use of prednisolone, the NLCP may consider procuring prednisolone over prednisone for the program.

Recommendation 6.d

Adverse events that need to be monitored for patients on corticosteroids (prednisolone) are gastric pain, steroid-induced hyperglycemia, Cushing syndrome, osteoporosis and infections.

Strong recommendation, moderate quality of evidence

Background

After patients are started on corticosteroids for the treatment of leprosy reactions, they must be closely monitored for the development of adverse events that may be life-threatening, such as steroid-induced hyperglycemia, Cushing syndrome or infections. Adverse events may also be minor, but they may impact the patient's quality of life. It is increasingly recognized that patient-reported outcomes are important predictors of adherence to treatment (Bell et al., 2013; Nunes, 2001). In the TRIPOD study (Jan H Richardus et al., 2003), minor adverse events in corticosteroid treatment in leprosy included moon face, acne, fungal infection and gastric pain. Major adverse events included peptic ulcer, diabetes, infections, and infected ulcer. The WHO recommends examination every week.

Summary of evidence

The adverse drug events associated with prednisolone administration in the prevention or treatment of neuritis in leprosy were studied by Richardus et al. (2003). Effect estimates are published in Table 16 and Table 17. The synthesis of Richardus et al. on adverse events associated with prednisolone intake consisted of consolidated monitoring and follow-up records of all patients receiving corticosteroids in the three TRIPOD trials. Treatment was not entirely performed on patients with neuritis in flare or patients having leprosy reactions. Patients who received a starting dose of prednisolone 20 mg/day were enrolled in TRIPOD 1, which investigated whether there was

a reduction in the rate of type 1 leprae reaction among patients who were given daily then tapered prednisolone during the first four months of MDT treatment, compared to those who received placebo. Patients who received a starting dose of prednisolone 40 mg/day were enrolled in the therapeutic trials of TRIPOD 2 (which investigated whether prednisolone prevents or mitigates sensory function impairment) and TRIPOD 3 (which investigated whether prednisolone treatment given 6-24 months after start of NFI resulted in better treatment outcomes compared to placebo). Data on both prophylactic and therapeutic uses of prednisolone in leprosy are summarized in Table 16 and Table 17.

TABLE 16. MINOR ADVERSE EVENTS RECORDED IN THE TRIPOD STUDY

OUTCOME	EFFECT ESTIMATE	LEVEL OF EVIDENCE
Prednisolone 20 mg vs placebo		
Moon face	RR 1.7308 [0.6366 to 4.7053, 95% CI] NNT (Harm) 73.895 [26.416 (Harm) to ∞ to 92.671 (Benefit), 95% CI]	High
Acne	RR 9.3462 [1.1910 to 73.3417, 95% CI] NNT (Harm) 38.820 [153.298 (Harm) to 22.224 (Harm)), 95% CI]	High
Fungal infection	RR11.4217 [0.6342 to 205.7095, 95% CI] NNT (Harm) 62.370 [906.371 (Harm) to 32.296 (Harm)), 95% CI]	High
Gastric pain	RR 1.5976 [1.1014 to 2.3175, 95% CI] NNT (Harm) 13.901 [63.076 (Harm) to 7.811 (Harm), 95% CI]	High
Prednisolone 40 mg vs placebo		
Moon face	RR 0.6593 [0.1128 to 3.8529, 95% CI] NNT (Benefit) 88.065 [27.495 (Harm) to ∞ to 16.926 (Benefit)), 95% CI]	High
Acne	RR 0.2000 [0.0097 to 4.1091, 95% CI] NNT (Benefit) 46.000 [67.916 (Harm) to ∞ to 17.181 (Benefit))), 95% CI]	High
Fungal Infection	-	-
Gastric pain	RR 1.1868 [0.5402 to 2.6072, 95% CI] NNT (Harm) 48.176 [8.627 (Harm) to ∞ to 13.440 (Benefit), 95% CI]	High

TABLE 17. MAJOR ADVERSE EVENTS IN THE TRIPOD STUDY

OUTCOME	EFFECT ESTIMATE	LEVEL OF EVIDENCE
Peptic ulcer	RR 2.0648 [0.1880 to 22.6831, 95% CI] NNT (Harm) 388.792 [91.855 (Harm) to ∞ to 174.137 (Benefit), 95% CI]	High
Diabetes	RR 3.0973 [0.3235 to 29.6529, 95% CI] NNT (Harm) 197.401 [68.228 (Harm) to ∞ to 220.991 (Benefit), 95% CI]	High
Infections	RR 0.5162 [0.0951 to 2.8028, 95% CI] NNT (Benefit) 213.936 [141.624 (Harm) to ∞ to 60.940 (Benefit), 95% CI]	High
Infected ulcer	RR 1.0324 [0.0648 to 16.4506, 95% CI] NNT (Harm) 12770.308 [145.498 (Harm) to ∞ to 148.891 (Benefit)), 95% CI]	High

Rationale

The major adverse events observed among patients with leprosy who received corticosteroid treatment describe risks associated with steroid intake. The CP cautions that the appearance of these adverse events in any patient should prompt a reevaluation of the current corticosteroid treatment, especially given the months-long course of treatment. The CP also opted to restate diabetes as “steroid-induced hyperglycemia.”

Good Practice Statement 6.a

Other adverse events that need to be monitored are mental disturbance, growth suppression in children, hypertension, glaucoma and cataract.

Patients on steroid should be monitored closely for steroid-induced complications.

Rationale

Certain adverse drug events attributable to corticosteroid administration were not documented in the above studies on corticosteroid in leprosy. However, the causative relation between corticosteroids and these events is well-established. These events were also classified in the TRIPOD study as major adverse effects. These events may include psychiatric disturbance, impaired growth in children, hypertension, glaucoma and cataracts.

Recommendation 6.e

For patients who do not respond or cannot tolerate prednisolone, these alternative treatment regimens may be used:

a. Type 1 leprae reaction not responding with prednisolone alone: cyclosporine is recommended as additional treatment with prednisolone.

b. Type 2 leprae reactions that are not responsive to prednisolone alone: second-line drugs such as clofazimine and cyclosporine can be used with prednisolone as alternative therapy.

c. Thalidomide may be used as alternative treatment regimen for ENL but it is limited in accessibility due to its teratogenic effects and consequently, ethical and legal considerations.

Strong recommendation, moderate quality of evidence

Summary of evidence

There are two randomized controlled trials that showed other treatment regimens as alternative or adjunct to prednisolone for patients who do not respond to steroids or experience steroid adverse

effects as shown in Table 18. Cyclosporine with prednisolone have shown effectiveness in the improvement of symptoms and prevention of relapse.

TABLE 18. TREATMENT OPTIONS FOR TYPE 1 LEPRAE REACTIONS

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
Lambert et al. (2016)	RCT; Ethiopia	73 patients with new T1R were randomized to receive cyclosporine + prednisolone (CnP) or prednisolone (P) for 20 weeks.	Patients assigned to P received Prednisolone 40mg+ PC while patients assigned to CnP received Cyclosporine 7.5mg/kg + Prednisolone 40mg. Doses were tapered in the period of 20 weeks. Improvements in nerve function both, new and old, sensory (66% vs 49%) and motor (75% vs 74%) loss were higher (but not significantly so) in the patients on CnP. Recurrences rates of T1R (85%) were high in both groups, and recurrences occurred significantly earlier (8 weeks) in patients CnP, who needed 10% more additional prednisolone.	General T1R status showed: **Recovered** RR 0.2714 (95% CI: 0.0318–2.3132) NNT 13 (95% CI: -18 to 5) **Improved** RR 1.2945 (95% CI: 1.0116–1.6566) NNT -5 (95% CI: 3 to -101]) **Maintained improvement after treatment** RR 1.9905 (95% CI: 1.1683–3.3912) NNT -3 (95% CI: -2 to -12) **Relapse** RR 0.6286 (95% CI: 0.3507–1.1267) NNT -3 (95% CI: 2 to -12)	Moderate
Lockwood et al. (2017)	RCT; India	345 patients with a new leprosy Type 1 reaction affecting either skin or nerve	Patients were randomized to receive concomitant medication for 48 weeks with azathioprine (A) 50 mg fixed dose for 24, 36 or 48 weeks	76% of patients had improvements in their CCS the end of the study, 22% had no change and 1.1% deteriorated and 36% needed	Moderate

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
			(APC) for a total of 3 treatment arms as intervention or a placebo on top of a 20-week course of prednisolone. Default (20–26%) and withdrawal rates (5.7%–25.5%) were lowest (20%) in the prednisolone only arm. Adverse events noted: Cushingoid features (43%) and infections (35%) were the commonest events occurring at comparable rates across the four arms	extra steroids due to a recurrence of their skin and/or nerve reaction. RRs cannot be ascertained in the published text. For adverse events: RR = 3.64 (95% CI 1.4–8.81) and NNT (harm) 6.5 (95% CI 16.194–4.134)	

Analgesics and steroids are the mainstay of treatment for type 2 leprae reactions (or ENL), but additional or second line therapy is recommended for patients not responding to corticosteroids. A Cochrane Review looked at 13 studies involving 445 participants. The overall quality of the studies was poor, and the samples sizes were often small. Prednisolone, thalidomide and clofazimine generally gave better results than other treatments (such as NSAIDs and pentoxifylline) (Van Veen et al., 2016). Relevant outcomes mentioned were remission to skin lesions (3 studies) with the use of thalidomide vs aspirin (RR 2.43; 95% CI: 1.28-4.59), thalidomide 100 mg vs thalidomide 300 mg (RR 1.33; 95% CI: 0.64–2.79) and pentoxifylline vs thalidomide (RR 1.05; 95% CI: 0.74–1.49). Table 19 shows relevant studies in the treatment of ENL.

TABLE 19. SECOND-LINE TREATMENT FOR ENL

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
CYCLOSPORINE					
LAMBERT ET AL. (2016)	2 RCTs 1 RCT–patients with new ENL (Study 1)	Study 1 n=13 with two treatment arms as cyclosporine arm vs prednisolone arm	Patients were randomly assigned to two treatment interventions: prednisolone	Mean number of ENL recurrences per patient were not significantly different between the two groups of	Low

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
	1 RCT– patients with chronic ENL (Study 2) Ethiopia	Study 2 n=20 with two treatment arms as cyclosporine arm vs prednisolone arm	arm starting at 60mg/day and tapered up to week 16, experimental arm was cyclosporine 7.5mg/kg plus prednisolone from 40 mg/day tapered up to 4 weeks Adverse events were also noted with the primary outcome of the number of ENL recurrence episodes per patient for each treatment arm,	patients (Mann-Whitney U Test, p = 0.684). Patients with acute ENL had a delay of 16 weeks in the occurrence of ENL flare-up episode, with less severe flare-ups and decreased requirements for additional prednisolone. Patients with chronic ENL on cyclosporine had the first episode of ENL flare-up 4 weeks earlier than those on prednisolone, as well as more severe ENL flare-ups requiring 2.5 times more additional prednisolone Occurrence of Infection is greater in prednisolone treatment arms (RR 0.3376 (CI 95% 0.0163)	
THALIDOMIDE					
KAUR ET AL 2009	RCT India	Sixty patients with a histologically confirmed diagnosis of erythema nodosum leprosum with a clinical score of 4 or more (i.e.	Group 1 patients were given thalidomide at a dose of 300 mg/ day for 1 week and the dose was gradually reduced, and	Faster clinical response with thalidomide (cutaneous as well as systemic) compared with prednisolone. With a mean time of 2.04 days	Moderate

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
		moderate to severe type 2 reaction) were randomly allocated to two groups comprising 30 patients each.	Group 2 received prednisolone 40 mg daily for 2 weeks, which was tapered by 10 mg every 2 weeks. Follow up every 4 weeks was done for up to 1 yr.	RR of 0.1576 (95% CI 0.0398-0.6239) for recurrence	
THALIDOMIDE + PREDNISOLONE VERSUS CLOFAZIMINE +PREDNISOLONE					
KAR ET AL , 2015	Prospective cohort India	N= 20 per group for a total of 80 2 cohorts of patients with first attack of T2R and chronic/recurrent T2R were observed for 4 regimens Gr1: Prednisolone was administered at 1 mg/kg/day for 2 weeks, tapering 10 mg at every 2 weeks interval upto 20 mg, and then tapering every 5 mg every 2 weekly to zero over a period of 20 weeks. Grp2: Thalidomide was started at dose of 400 mg/day (200mg BD) for the first week, then 300 mg/day (100mg in the	Comparative efficacy of Prednisolone alone or thalidomide alone for the first attack of T2R, and combination of prednisolone plus thalidomide or prednisolone plus clofazimine for chronic and recurrent T2R and monitored for 3 months with clinical recovery of T2R as primary outcome	For first attack of T2R, Comparing Grp 1 and 2 with Group Thalidomide as intervention, RR was 0.15 (CI 95% 0.0209-1.1004) With NNT of 2.8 (95% 1.62 (Benefit) to 12.18 (Benefit). For recurrent or chronic of T2R, Comparing Grp 3 and 4 with Group Clofazimine +prednisolone as intervention, RR was 2.12 (CI 95% 0.636-7.098) With NNT (Harm) of 5 (95% CI 2.02 (Harm) to 10. 21 (Harm)	Low

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
		morning and 200mg in the evening) for next 4 weeks, then 200 mg OD at bed time for the next 4 weeks. It was further reduced to 100 mg OD at bed time for next 4 weeks. Finally the dose was tapered to 50 mg OD at bed time for 7 weeks over a period of 20 weeks. Group 3 Prednisolone was given in the same dose as in Group 1. Along with prednisolone, thalidomide was given at dose of 400 mg/day for the first week and subsequently tapered as in Group 2 over a same period of 20 weeks. Group 4 Prednisolone was given in the same dose as in Group 1. Along with prednisolone clofazimine was started at 300 mg/day for first 12 weeks. Then it was tapered to 200 mg/day for			

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
		next 4 weeks and then reduced to 100 mg/day for next 4 weeks for a period of 20 weeks			
PENTOXIFYLLINE VS CLOFAZIMINE					
ROY ET AL 2015	RCT India	n=20 patients with T2R Group A received pentoxifylline 400 mg t.d.s, group B received clofazimine 100 mg t.d.s. for 12 weeks. Both groups received prednisolone 40 mg o.d., tapered over 12 weeks. The	Outcome measures were the days required for complete remission of skin lesions, days required for complete remission of systemic symptoms	RR of 3 (95% CI 0.37-24.17) for non remission in pentoxifylline group There were no statistically significant differences in 2 groups on average days of resolution of cutaneous, systemic symptoms and relapse	Low
PENTOXIFYLLINE VS THALIDOMIDE					
SALES ET AL, 2007	RCT Brazil	44 patients with T2R with 2 treatment arms: two groups of patients to compare the results of treatment regimens consisting of 300 mg thalidomide vs 1.2 g pentoxifylline.	All patients were clinically evaluated on the 1st, 7th, 14th, 21st, and 30th days of treatment, were given as needed basis of prednisone and removed from the study free when, at the end of 30 days of treatment, the following criteria were satisfactorily met: complete elimination of type II reactional skin lesion	General improvement of symptoms of T2R at 30 days of treatment, Comparing Thalidomide and pentoxifylline as intervention, RR was 7.5 (CI 95% 1.036-54) With NNT (Harm) of 3 (95% CI 10.46 (Harm) to 1.80 (Harm	Low

REFERENCE	STUDY DESIGN AND LOCATION	POPULATION	SYNOPSIS	KEY OUTCOMES	QUALITY OF EVIDENCE
			inflammation, normal body temperature and/or regression of systemic symptoms.		

There are case reports of biologics such as etanercept, are therapeutic alternatives in management of severe ENL but still with poor strength of evidence.

Rationale

The CP acknowledges the treatment effect of thalidomide in studies; however, the administration of thalidomide carries the immense risk of teratogenesis among women of reproductive age. Access to thalidomide is also restricted in the country. Ethical and legal considerations limit the applicability of the recommendation for thalidomide in the primary care setting. Thalidomide can only safely be given in a controlled environment, carefully monitored clinical trial.

Recommendation 6.f

Clofazimine monotherapy may be used as alternative treatment if prednisolone is contraindicated.

Weak recommendation, very low quality of evidence

Summary of evidence

A recent study in Cebu by Maghanoy et al. (2017) sought to determine the effectiveness of clofazimine in ENL treatment. Clofazimine 100 mg/day versus placebo showed no significant benefit based on endpoints of ENL severity.

Rationale

To be specific to the Philippine context, drug supply is an important aspect of this recommendation. Clofazimine is widely available through the NLCP, which is receiving the drug as a donation from the WHO. The WHO reports on a widely used regimen of clofazimine for ENL management, and clofazimine is already being prescribed to patients in clinics. Although the locally conducted study on clofazimine did not report benefit in favor of clofazimine, the regimen reported by WHO starts clofazimine at 300 mg daily—a markedly higher dose than the 2017 study.

Good Practice Statement 6.b

Patients with confirmed leprae reaction may receive prednisolone treatment under the supervision of trained community health workers. However, patients with suspected refractory leprae reaction should be referred to specialists for treatment and management.

Rationale

Trained health workers in the community may prescribe prednisolone for the treatment of lepra reactions. Early corticosteroid treatment offers better outcomes in terms of preservation of nerve function. However, health workers must also be trained on monitoring adverse events and detecting or suspecting refractory disease. Refractory lepra reactions are suspected when a patient does not exhibit clinical improvement even after appropriate treatment. Clinical manifestations of refractory disease include fever, joint pains, appearance of new lesions and non-resolution of existing lesions.

Second-line drugs, as alternative or adjunctive therapy for corticosteroids, may be warranted in cases of refractory leprae reactions or contraindications to steroid therapy. Given the expertise required to manage the risk of adverse events with these second-line drugs, the CP reaffirms Recommendation 6.a that healthcare workers must recognize when to make appropriate referrals. For severe and refractory cases, a referral to a specialist for treatment is recommended.

Good Practice Statement 6.c

For patients who will receive chronic steroid regimen, they should be referred to a specialist for possible side effects.

Rationale

Longer exposure to corticosteroids increases the risk of adverse events. Because primary health care facilities might not be equipped in terms of expertise and testing facilities to plan and monitor the administration of chronic steroid regimens to patients, the CP emphasized that these patients must be referred to a specialist.

Chemoprophylaxis

Question 7: Should contacts exposed to a patient with leprosy be offered chemoprophylaxis versus observation alone?

> Eligible contacts (i.e., household contacts) of leprosy patients should be given chemoprophylaxis in the absence of any contraindications.
>
> *Strong recommendation, high quality of evidence*

Background

Chemoprophylaxis has been defined as the administration of chemicals, including antibiotics, to prevent the development of an infection or the progression of an infection to active manifest disease (Smith & Smith, 2000). Prevention is preferable to treating patients after clinical presentation and presents public health benefits in indirectly reducing transmission of the disease (WHO, 2018b).

Administration of chemoprophylaxis is supported in a recent DOH Administrative Order 2021-0004 (2021), which supports the reduction of clinical leprosy in household contacts of new cases. The DOH guidance reflects and adheres to recent developments in chemoprophylaxis that have been identified by the WHO.

Summary of evidence

Three systematic reviews were identified that compared chemoprophylaxis versus no chemoprophylaxis for contacts of patients affected with leprosy. The studies are summarized in Table 20. These systematic reviews show not only the current preferred chemoprophylaxis (i.e. rifampicin), but also historical chemoprophylaxis regimens.

TABLE 20. SYSTEMATIC REVIEWS FOR PROVISION OF CHEMOPROPHYLAXIS TO CONTACTS OF PATIENTS WITH LEPROSY

REFERENCES	STUDIES INCLUDED	INTERVENTION	CONTROL	EFFECT SIZE	QUALITY OF EVIDENCE
Smith & Smith (2000)	6 randomized controlled trials from 1965 to 1977 6 clinical trials from 1968 to 1996	Dapsone/ acedapsone Dapsone	Placebo Placebo	RR 0.46 (95% CI: 0.32–0.66) Chi-square 12.93 (df = 5) Z = 4.20 RR 0.28 (95% CI: 0.13–0.59) Chi-square 33.67 (df = 11) Z = 5.46	High
Reveiz et al. (2009)	21 711 participants	Single-dose rifampicin	Placebo	RR 0.43 (95% CI: 0.28–0.67) Number needed to treat = 285	High

REFERENCES	STUDIES INCLUDED	INTERVENTION	CONTROL	EFFECT SIZE	QUALITY OF EVIDENCE
	3 RCTs, 43 137 participants	Dapsone once or twice weekly, for at least 2 years	Placebo	RR 0.60 (95% CI: 0248–0.76, I^2 = 0)	
	2 RCTs, 1 259 participants	Acedapsone every 10 weeks for 7 months	Placebo	RR 0.49 (95% CI: 0.33–0.72, I^2 = 0)	
Ferreira et al. (2017)	3 965 participants in 1 community-based controlled trial	Double-dose of rifampicin (600 mg for adults and 300 mg for children aged 6–14 years old, with 3.5 months between doses Follow-up: 33.5 months	Blanket	No difference was found between the contact and control groups (p-value = 0.93)	Moderate
	21 526 participants in 1 RCT (part of COLEP study)	Single-dose rifampicin (SDR) combination with Bacillus Calmette-Guérin (BCG) vaccine Follow-up: 2 years	None or placebo	BCG protective effect was 57% (95% CI: 25–75%); for rifampicin 58% (95% CI: 30–74%); and both BCG and rifampicin 80% (95% CI: 50–92%)	High
	21 711 participants in 1 RCT (part of COLEP study)	SDR 600 mg for adults weighing 35 kg and over; SDR 450 mg for adults weighing less than 35 kg and for children older than 9 years; and SDR 300 mg for children aged 5 to 9 years Follow-up: 4 years	Placebo	Reduction in incidence in the rifampicin group was 56.5% (95% CI: 32.9–71.9%, p < 0.0002) in two years and 34.9% (95% CI: 9.8–53%, p < 0.02) in four years. Overall NNT to prevent one new case of leprosy was 265 (95% CI: 176–537) after two years	High

Rationale

The CP acknowledges that the current population-based health intervention strategy of the DOH is to reduce clinical leprosy in household contacts of new cases (DOH, 2021). The DOH shall provide chemoprophylaxis to all household contacts, which is defined as "any person who has had direct contact or exposure with a leprosy case and has been living in the same household with the leprosy case for more than 30 days in the past 2 years." The CP notes that contact should be described according to the distance between the individuals and the length of time of exposure.

Question 8: What is an effective and safe chemoprophylaxis among contacts of patients with leprosy and high-risk populations?

Recommendation 8.a

> Single dose rifampicin (300–600 mg) may be used as leprosy preventive treatment for contacts of leprosy patients (children aged 2 years and above and adults), after excluding leprosy and tuberculosis disease and in the absence of other contraindications.
>
> This intervention shall be implemented by programs that can ensure adequate management of contacts.
>
> *Weak recommendation, very low quality of evidence*

Background

The WHO Guidelines recommend single-dose rifampicin (SDR) as chemoprophylaxis for contacts of leprosy patients. Prevention of leprosy is preferable to treating patients after clinical presentation, and it would provide additional public health benefits by reducing the spread of disease.

Contacts of patients affected by leprosy should undergo clinical examination, because the presence of leprosy infection or coexisting tuberculosis must be excluded. In the event the contact has developed signs and symptoms of leprosy, they should be started on the appropriate MDT regimen instead. Leprosy and tuberculosis also share similar geographic endemicity (Mangum et al., 2018). The WHO GDG remarked that it would be prudent to exclude TB before administering SDR, although they made note of a published expert meeting report which found that SDR does not increase the risk of rifampicin-resistant *M. tuberculosis* (WHO, 2018b).

Provision of chemoprophylaxis to contacts is also contingent on the effectiveness of a contact management program. The administration of SDR to contacts first requires disclosing the rationale behind the need for chemoprophylaxis, which would be the contact's proximity to a patient affected with leprosy. With leprosy being a highly stigmatized disease, caution must be exercised when providing SDR to contacts. If a patient does not authorize disclosure of their diagnosis to contacts, the WHO (2018b) "[Guideline Development Group] does not recommend identification or screening of contacts or prescribing preventive treatment to contacts."

Summary of evidence

The WHO Guidelines provided the recommendation and the evidence for this statement. One double-blind RCT (Moet et al., 2008) in Bangladesh with moderate quality of evidence showed SDR to be effective in reducing the risk of leprosy among leprosy contacts. In this RCT, contacts were provided SDR or placebo on the second month of the index patient's MDT regimen and were followed up until a period of six years (Feenstra et al., 2012; Moet et al., 2008). A protective effect was observed in the first 2 years, and SDR was also cost-effective in another analysis (Idema et al., 2010). The WHO Guidelines summarized the results of the 2008 article in Table 21 ci-dessous.

Rationale

There is strong evidence to support the administration of SDR as post-exposure chemoprophylaxis for leprosy, such that it was recommended by the WHO in their 2018 leprosy guidelines. The consensus panel also fully supports SDR, with the caveat that follow-up of contacts who took SDR as chemoprophylaxis should still be followed up to identify if leprosy has developed.

TABLE 21. SDR VERSUS PLACEBO EFFECT ESTIMATES (MOET ET AL., 2008)

OUTCOME	EFFECT ESTIMATE	QUALITY OF EVIDENCE
Leprosy diagnosis 1-2 years	0.3% vs 0.7% RR 0.43 (0.28–0.67)	Moderate
Leprosy diagnosis 3-4 years	0.6% vs. 0.9% RR 0.65 (0.47–0.90)	Moderate
Leprosy diagnosis 5-6 years	0.8% vs 1.1% RR 0.72 (0.54–0.6)	Moderate

Good Practice Statement 8.a

It is recommended that surveillance for eligible contacts (i.e., household contact) of patients with leprosy be done in the program level.

Rationale

The effectiveness of SDR for preventing leprosy will require a programmatic approach to ensure high coverage of contact screening. The program level approach to surveillance will allow for a wider scope of contact screening and tracing (e.g. community level), that may be more feasible in the context of high stigma and discrimination and would not require disclosure of the identity of index cases (WHO, 2018b). The program should also account for leprosy-related stigma in the community and make efforts to address the burden of actual and anticipated stigma, that typically discourages patients from providing consent for disclosure and SDR prophylaxis.

Drug resistance in leprosy

Question 9: How is drug resistance evaluated among leprosy patients?

Recommendation 9.a

All patients suspected to have drug resistance should undergo drug susceptibility testing, if available.

Weak recommendation, very low quality of evidence

Background

Drug resistance can either be primary (seen in patients without prior treatment to any of the MDT), or secondary (seen in patients with prior history of treatment for leprosy) (World Health Organization, 2017). Since the drug susceptibility testing in leprosy can only be cultivated with live specimens, testing for drug resistance is difficult. This is because the test used to detect drug resistance, the mouse-foot pad, is not readily accessible in most centers. Furthermore, it is time-consuming—requiring 6-8 months—and requires considerable technical expertise (Matsuoka, 2010). With the advent of DNA amplification, molecular surveillance is now possible, allowing a more rapid turnaround time to the result of drug susceptibility testing.

Because antimicrobial resistance (AMR) is a threat to the control of leprosy, it is important that these cases of leprosy be identified by having drug susceptibility testing performed when drug resistance is suspected in a patient. The Philippines was part of a network of sentinel drug-resistance surveillance implemented jointly by the WHO and The Nippon Foundation (WHO, 2017). Using polymerase chain reaction testing, WHO launched the surveillance network in 2009 that studied resistance patterns globally (Cambau et al., 2018). Even so, there are no international reference laboratories for AMR in leprosy in the country. The narrow accessibility of drug susceptibility testing for leprosy necessitated the addition of availability as a caveat to this recommendation. Indeed, the surveillance system recommended by the WHO should test a certain number out of the total number of new leprosy cases detected per year, but this is contingent on several conditions, such as if the country has representative baseline data, sufficient financial resources or high laboratory capacity (WHO, 2017).

Summary of evidence

Studies that directly determine the accuracy of clinical findings with susceptibility of *M. leprae* are scarce. Most trials that evaluated drug resistance include patients who relapsed. A cross-sectional study of 25 MB patients with prior five-year history of treatment for leprosy who showed signs of reactivation, showed an incidence of 42.8% susceptible to dapsone and rifampicin and 10.7% resistance to dapsone (Diório et al., 2009). No rifampicin resistant bacilli were isolated. In the said study, the investigators used mouse foot pad to cultivate the bacteria, hence the results were obtained after a 10-month delay from obtaining specimens.

Rationale

The consensus panel expressed their concern about the availability of leprosy drug resistance testing in the Philippines. The test to identify drug resistance requires serological tests, such as PCR, which are not readily available in the primary care setting nor in the country in general. However, given the impact of drug resistance on disease transmission and treatment of leprosy with respect to public health, it is recommended that drug resistance be followed up and confirmed through testing when suspected if these tests are somehow available and accessible to the patient or the health care provider.

Expert opinion offered by the CP notes that suspicion for drug-resistant leprosy may be supported by clinical, bacteriologic or histopathologic findings. For clinical findings, the persistence of hypoesthetic skin lesions or the appearance of new lesions after completion of a full course of MDT should raise a concern for drug resistance. Based on bacteriologic and histopathologic examination, drug resistance may also be suggested by a non-decreasing BI; or presence of solid-staining bacilli on slit-skin smear or Fite Faraco stain after completion of a full course of MDT. Further research is recommended. As part of the global surveillance network, the WHO (2017) also prescribes testing of all retreatment leprosy cases, which pertain to patients diagnosed with leprosy who have abandoned treatment before completion and return to the healthcare facility to complete treatment.

Recommendation 9.b

Patients confirmed to have relapsed must be evaluated for drug resistance and referred to a specialty center.

Weak recommendation, very low quality of evidence

Background

Relapse is confirmed among patients who have completed a full course of treatment for leprosy in the past, and who returns with signs and symptoms of leprosy which is not deemed to be due to a leprosy reaction according to the clinician (WHO, 2017). Certain studies link the history of relapse with drug resistance. However, not all cases of relapse may be due to resistance to the drugs in the WHO-MDT regimen. Definitive identification of drug resistance, as opposed to relapse, would support subsequent management options for the patient affected with leprosy. Furthermore, given the more complicated management of drug-resistant leprosy that may involve drugs unfamiliar to the primary health care worker, referral to a specialty center is recommended.

Summary of evidence

In a cross-sectional study of 50 patients with history of relapse, a mutation in the gene coding for rifampicin was detected in two patients who manifested a stable bacteriological index even after completion of 24 months of multi-drug therapy (Bhattacharya et al., 2015). In another analysis of data collected by the WHO surveillance network from 2009–2015 (Cambau et al., 2018), 1 932 specimens were collected from 19 countries of new and relapse leprosy cases, of which 1 143 were from relapse cases and 780 from new cases. The global rifampicin resistance (Rif-R) rate among all types of leprosy was 3.8%; among relapse cases, 5.1%; and among new cases, 2.0%.

Colombia had the highest Rif-R rate at 24.3% (N=125). Brazil, India and the Philippines were the top three contributors of specimens.

Recently, in a population-based search for *M. leprae* resistance in suspected relapse cases and contacts in Brazil, 37 leprosy cases (18 relapse and 19 new) showed 43.24% drug resistance patterns (Rosa et al., 2020). Resistance to both rifampicin and dapsone was observed in 8 relapse cases and 4 new cases, while single resistance to rifampicin was detected in one new case.

Rationale

The reappearance of leprosy after WHO-MDT completion rightfully raises concerns on drug resistance as a feature of the relapsed leprosy case. However, not all relapsed patients would be due to drug resistance. For patients who may have signs of relapse due to a lack of improvement with MDT, the concerns for drug resistance should be accompanied by a suspicion of other factors, that include poor drug compliance or other concomitant, intercurrent infection (WHO, 2016c). The problem of poor compliance may be addressed by supervised drug administration and health education. A concomitant infection requires thorough investigation and appropriate treatment.

The consensus panel acknowledges the potential impact of drug-resistant leprosy on disease transmission, especially as it relates to public health. The CP also recognizes the complications created by drug-resistant leprosy for the NLCP, because these cases require a treatment regimen different from the regimen provided by the WHO. There is also room for the Philippine health care system to contribute to the scarce data on drug resistance in leprosy. Early and appropriate intervention to prevent the development of drug-resistant leprosy into a difficult public health problem will require identification of antimicrobial resistance in leprosy.

Recommendation 9.c

Drug resistance should be suspected in a patient with prior history of dapsone (monotherapy) intake.

Strong recommendation, very low quality of evidence

Background

Prior to the implementation of WHO-MDT treatment, dapsone has been used as monotherapy for leprosy as well as for a variety of diseases. Dapsone monotherapy was previously recommended for the treatment of leprosy patients, with MDT arriving afterwards in 1982 upon the emergence of treatment relapses and drug resistance to dapsone in the 1970s (Bennett et al., 2008). The use of dapsone in malaria and *Pneumocystis jiroveci* pneumonia is also recorded (Barr, 2011).

Summary of evidence

In the Philippines, there is a scarcity in studies examining resistance patterns and response to treatment. A cross-sectional study was done in 2007 in Myanmar, Indonesia and the Philippines, which collected samples from patients before starting MDT (new cases), patients treated with MDT for 4 months (recent cases), and patients with relapse (patients who developed new skin lesions after completion of MDT and whose BI has increased by more than 2 log units at any site) (Matsuoka et al., 2007). The result showed a dapsone resistance rate of 2.6% among new and recent cases and 26% among relapse cases. No resistance to rifampicin and ofloxacin was

detected in the studied population (Matsuoka et al., 2007). The study reported previous monotherapy with dapsone in two cases, although no significant association was made to link dapsone monotherapy as a risk factor for drug resistance. In the WHO surveillance network study by Cambau et al. (2018), resistance rate to dapsone was lower at 2.2%, all of which were from new leprosy cases. There were no cases of rifampicin and ofloxacin resistance identified.

In a study conducted among leprosy patients who were skin-smear negative and treated with dapsone monotherapy before the implementation of multidrug therapy, there was a strong suspicion of relapse with dapsone-resistant bacilli in 40.4% of MB leprosy relapses (Becx-Bleumink, 1992).

Good Practice Statement 9.a

Drug resistance should be suspected among the following *populations*: 1) patients who have relapsed; 2) patients with treatment failure; 3) patients living in a community with reported drug-resistant leprosy; and 4) new patients with prior history of intake of dapsone, rifampicin or clofazimine for indications other than leprosy.

Rationale

The GDG, including the consensus panel, acknowledges the lack of reliable association between drug resistance and patient factors, which is affirmed by the WHO given that "the number of leprosy patients tested for resistance globally is too small to allow for accurate estimates of drug resistance" (WHO, 2018b). Expert opinion provided by the CP recognizes the resistance patterns described in the foregoing studies. Appropriate action should be taken for patients who have relapsed and who experienced treatment failure. Drug-resistant infection may also be transmitted, raising the possibility of drug-resistant leprosy for new leprosy cases from communities with a previously reported drug-resistant leprosy case. Finally, antimicrobial exposure promotes the development of antimicrobial resistance, especially when surviving bacteria develop the necessary mutations to counter the effects of antibiotics. Drug-resistant leprosy may also be suspected among patients who have a history of intake of the drugs included in MDT for indications other than leprosy.

Question 10: What is the treatment regimen for drug-resistant leprosy?

Good Practice Statement 10.a

Leprosy patients with suspected resistance to dapsone, rifampicin, or clofazimine are recommended to be referred to specialty treatment centers for evaluation and management.

Rationale

While this Guideline provides a general outline of possible treatment regimens for drug-resistant leprosy, primary care may not be equipped in terms of access to medication and training for the management of this more complicated progression of disease. The regimens recommended below are only based on expert opinion and resistance patterns, which may be different per community or health care facility. Hence, it is desirable to receive care under a health care professional with knowledge of local resistance patterns in the Philippines. This Guideline recommends referral to specialty treatment centers for drug-resistant leprosy.

Recommendation 10.a

Leprosy patients with confirmed 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.

Weak recommendation, based on expert opinion; no evidence retrieved

Recommendation 10.b

Leprosy patients with resistance to both rifampicin and ofloxacin may be treated with the following drugs: clarithromycin, minocycline and clofazimine daily for 6 months, followed by clarithromycin or minocycline plus clofazimine daily for the next 18 months.

Weak recommendation, based on expert opinion; no evidence retrieved

Summary of evidence

Recommendations 10.a and 10.b are sourced from the WHO guidelines on leprosy treatment (WHO, 2018b). There are no studies on second-line treatment for patients with drug-resistant leprosy. The surveillance system endorsed by the WHO is geared towards identifying rifampicin resistance, either alone or combined with dapsone or ofloxacin. The WHO identified five studies

that reported the prevalence of rifampicin resistance to be 1.36% among new cases and 8% among relapsed cases. The WHO Guidelines also cite unpublished data from a surveillance network coordination meeting in 2016 that reported resistance to rifampicin, comprising 2.1% among new cases and 5.2% among relapse cases.

Rationale

The consensus panel notes that some of the drugs recommended for drug-resistant leprosy are procured by the NLCP. In particular, the DOH is procuring ofloxacin while the WHO provides clofazimine. The other drugs may also be acquired by the local government units depending on the need of their jurisdiction. The consensus panel expressed their concerns about the unreliable availability of these drugs in accessible primary care settings. Consistent with Good Practice Statement 10.a, patients affected by drug-resistant leprosy will need to consult with specialty treatment centers. Hence, the management of drug-resistant leprosy may cause undue financial burden on the patient who will need to allocate personal time and financial resources to treatment and follow-up. Drug resistance must be confirmed before prescriptions to treat drug-resistant leprosy are started for these patients.

References

28th World Health Assembly. (1975). *WHA28.56 Leprosy control*. https://apps.who.int/iris/bitstream/handle/10665/92994/WHA28.56_eng.pdf

40th World Health Assembly. (1987). *WHA40.35 Towards the Elimination of Leprosy*. https://apps.who.int/iris/bitstream/handle/10665/164105/WHA40_R35_eng.pdf

44th World Health Assembly. (1991). *World Health Assembly Resolution 44.9*. https://www.who.int/neglected_diseases/mediacentre/WHA_44.9_Eng.pdf

ADAPTE Collaboration. (2009). The ADAPTE Process: Resource Toolkit for Guideline Adaptation. *Version 2.0*, 1–95. http://www.g-i-n.net

Adhikari, B., Kaehler, N., Raut, S., Marahatta, S. B., & Ggyanwali, K. (2014). Risk factors of stigma related to leprosy - A Systematic Review. *Journal of Manmohan Memorial Institute of Health Sciences*, *1*(2), 3–11. https://doi.org/10.3126/jmmihs.v1i2.9902

Alberts, C. J., Smith, W. C. S., Meima, A., Wang, L., & Richardus, J. H. (2011). Potential effect of the World Health Organization's 2011–2015 global leprosy strategy on the prevalence of grade 2 disability: a trend analysis. *Bulletin of the World Health Organization*, *89*(7), 487–495. https://doi.org/10.2471/BLT.10.085662

Ashwini, B., Nandakishore, B., Basti, R. S., Martis, J., Hundi, G. K., & Jayaraman, J. (2018). Ultrasound as a diagnostic modality for the involvement of peripheral nerves in leprosy. *Indian Journal of Leprosy*, *90*(1), 1–14.

Balagon, M. F., Cellona, R. V, Cruz, E. dela, Burgos, J. A., Abalos, R. M., Walsh, G. P., Saunderson, P. R., & Walsh, D. S. (2009). Long-term relapse risk of multibacillary leprosy after completion of 2 years of multiple drug therapy (WHO-MDT) in Cebu, Philippines. *The American Journal of Tropical Medicine and Hygiene*, *81*(5), 895–899. https://doi.org/10.4269/ajtmh.2009.09-0189

Bandeira, S. S., Pires, C. A., & Quaresma, J. A. S. (2019). Leprosy Reactions In Childhood: A Prospective Cohort Study In The Brazilian Amazon. *Infection and Drug Resistance*, *12*, 3249–3257. https://doi.org/10.2147/IDR.S217181

Barr, J. (2011). A short history of dapsone, or an alternative model of drug development. *Journal of the History of Medicine and Allied Sciences*, *66*(4), 425–467. https://doi.org/10.1093/jhmas/jrq068

Becx-Bleumink, M. (1992). Relapses in leprosy patients after release from dapsone monotherapy; experience in the leprosy control program of the all Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia [Abstract]. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *60*(2), 161–172. http://www.ncbi.nlm.nih.gov/pubmed/1522358

Becx-Bleumink, M., & Berhe, D. (1992). Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy; experience in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *60*(2), 173–184. http://www.ncbi.nlm.nih.gov/pubmed/1522359

Bell, M. L., Kenward, M. G., Fairclough, D. L., & Horton, N. J. (2013). Differential dropout and bias in randomised controlled trials: when it matters and when it may not. *BMJ (Clinical Research Ed.)*, *346*, e8668. https://doi.org/10.1136/bmj.e8668

Bennett, B. H., Parker, D. L., & Robson, M. (2008). Leprosy: Steps along the journey of eradication. In *Public Health Reports* (Vol. 123, Issue 2, pp. 198–205). Association of Schools of Public Health. https://doi.org/10.1177/003335490812300212

Bhat, I., Madhukara, J., Rout, P., Elizabeth, J., & Kumaran, S. (2015). Comparison of bacillary index on slit skin smear with bacillary index of granuloma in leprosy and its relevance to present therapeutic regimens. *Indian Journal of Dermatology*, *60*(1), 51. https://doi.org/10.4103/0019-5154.147791

Bhattacharya, B., Hasanoor Reja, A., Biswas, N., Biswas, S., Lavania, M., Chaitanya, V., Banerjee, S., Maha Patra, P., Gupta, U., Patra, P., & Sengupta, U. (2015). Report of rpoB mutation in clinically suspected cases of drug resistant leprosy: A study from Eastern India. *Indian Journal of Dermatology, Venereology, and Leprology*, *81*(2), 155. https://doi.org/10.4103/0378-6323.152185

Bhushan, P., Sardana, K., Koranne, R., Choudhary, M., & Manjul, P. (2008). Diagnosing multibacillary leprosy: A comparative evaluation of diagnostic accuracy of slit-skin smear, bacterial index of granuloma and WHO operational classification. *Indian Journal of Dermatology, Venereology and Leprology*, *74*(4), 322. https://doi.org/10.4103/0378-6323.42892

Boerrigter, G., Pönnighaus, J. M., Fine, P. E., & Wilson, R. J. (1991). Four-year follow-up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *59*(2), 255–261. http://www.ncbi.nlm.nih.gov/pubmed/2071983

Brandsma, J. W., & Van Brakel, W. H. (2003). WHO disability grading: Operational definitions. *Leprosy Review*, *74*(4), 366–373. https://doi.org/10.47276/lr.74.4.366

Brouwers, M., Kho, M., Browman, G., Cluzeau, F., Feder, G., Fervers, B., Hanna, S., & Makarski, J. (2013). *Appraisal of Guidelines for Research & Evaluation II: AGREE II Instrument*. https://doi.org/10.1503/cmaj.090449

Cambau, E., Saunderson, P., Matsuoka, M., Cole, S. T., Kai, M., Suffys, P., Rosa, P. S., Williams, D., Gupta, U. D., Lavania, M., Cardona-Castro, N., Miyamoto, Y., Hagge, D., Srikantam, A., Hongseng, W., Indropo, A., Vissa, V., Johnson, R. C., Cauchoix, B., … Nanba, Y. (2018). Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009–15. *Clinical Microbiology and Infection*, *24*(12), 1305–1310. https://doi.org/10.1016/j.cmi.2018.02.022

Chandler, D. J., Hansen, K. S., Mahato, B., Darlong, J., John, A., & Lockwood, D. N. J. (2015). Household Costs of Leprosy Reactions (ENL) in Rural India. *PLoS Neglected Tropical Diseases*, *9*(1). https://doi.org/10.1371/journal.pntd.0003431

Christie, C. A., & Barela, E. (2005). The Delphi technique as a method for increasing inclusion in the evaluation process. *Canadian Journal of Program Evaluation*, *20*(1), 105–122.

Costa, L. G., Cortela, D., Soares, R. C. F. R., & Ignotti, E. (2015). Factors associated with the worsening of the disability grade during leprosy treatment in Brazil. *Leprosy Review*, *86*(3), 265–272. http://www.ncbi.nlm.nih.gov/pubmed/26665362

Costa Queiroz, R. H., de Souza, A. M., Sampaio, S. V., & Melchior, E. (2002). Biochemical and hematological side effects of clofazimine in leprosy patients. *Pharmacological Research*, *46*(2), 191–194. https://doi.org/10.1016/s1043-6618(02)00086-5

Courtright, P., Daniel, E., Sundarrao, Ravanes, J., Mengistu, F., Belachew, M., Celloria, R. V, & Ffytche, T. (2002). Eye disease in multibacillary leprosy patients at the time of their leprosy diagnosis: findings from the Longitudinal Study of Ocular Leprosy (LOSOL) in India, the Philippines and Ethiopia. *Leprosy Review*, *73*(3), 225–238. http://www.ncbi.nlm.nih.gov/pubmed/12449887

da Silva Júnior, G. B., & Daher, E. D. F. (2006). Renal involvement in leprosy: retrospective analysis of 461 cases in Brazil. *The Brazilian Journal of Infectious Diseases : An Official Publication of the Brazilian Society of Infectious Diseases*, *10*(2), 107–112. https://doi.org/10.1590/s1413-86702006000200007

Daher, E. F., Silva, G. B., Cezar, L. C., Lima, R. S. A., Gurjão, N. H., Mota, R. M. S., Abreu, K. L. S., Rocha, N. A., Oliveira, M. J. C., & Libório, A. B. (2011). Renal dysfunction in leprosy: a historical cohort of 923 patients in Brazil. *Tropical Doctor*, *41*(3), 148–150. https://doi.org/10.1258/td.2011.100436

De Paula, H. L., De Souza, C. D. F., Silva, S. R., Martins-Filho, P. R. S., Barreto, J. G., Gurgel, R. Q., Cuevas, L. E., & Santos, V. S. (2019). Risk Factors for Physical Disability in Patients with Leprosy: A Systematic Review and Meta-analysis. *JAMA Dermatology*, *155*(10), 1120–1128. https://doi.org/10.1001/jamadermatol.2019.1768

Delbecq, A. L., Van de Ven, A. H., & Gustafson, D. H. (1986). *Group techniques for program planning: a guide to nominal group and Delphi processes*. Green Briar Press.

Department of Health. (2014). *National TB Control Program: Manual of Procedures* (5th ed.). Department of Health. http://www.doh.gov.ph

Department of Health. (2018). *National Leprosy Control Program*. https://www.doh.gov.ph/leprosy-control-program

Department of Health. (2021). *Administrative Order 2021-0004*.

Department of Health Northern Territory [Australia]. (2018). *Guidelines for the control of leprosy in the Northern Territory*. www.health.nt.gov

Department of Health Philippines. (2018). *Manual for Clinical Practice Guideline Development* (1st ed.).

Diório, S. M., Rosa, P. S., Belone, A. de F. F., Sartori, B. G. C., Trino, L. M., Baptista, I. M. F. D., Marcos, E. V. C., Barreto, J. A., & Ura, S. (2009). Relapse Related To Drug. *Hansen Int*, *34*(1), 43–48.

Dogra, S., Kumaran, M. S., Narang, T., Radotra, B. D., & Kumar, B. (2013). Clinical characteristics and outcome in multibacillary (MB) leprosy patients treated with 12 months WHO MDT-MBR: a retrospective analysis of 730 patients from a leprosy clinic at a tertiary care hospital of Northern India. *Leprosy Review*, *84*(1), 65–75. http://www.ncbi.nlm.nih.gov/pubmed/23741883

Dos Santos, A. R., Silva, P. R. D. S., Steinmann, P., & Ignotti, E. (2020). Disability progression among leprosy patients released from treatment: A survival analysis. *Infectious Diseases of Poverty*, *9*(1), 1–7. https://doi.org/10.1186/s40249-020-00669-4

Eichelmann, K., González González, S. E., Salas-Alanis, J. C., & Ocampo-Candiani, J. (2013). Leprosy. An Update: Definition, Pathogenesis, Classification, Diagnosis, and Treatment. *Actas Dermo-Sifiliográficas (English Edition)*, *104*(7), 554–563. https://doi.org/10.1016/j.adengl.2012.03.028

Elias, J., Nogueira-Barbosa, M. H., Feltrin, L. T., Furini, R. B., Foss, N. T., Marques, W., & dos Santos, A. C. (2009). Role of Ulnar Nerve Sonography in Leprosy Neuropathy With Electrophysiologic Correlation. *Journal of Ultrasound in Medicine*, *28*(9), 1201–1209. https://doi.org/10.7863/jum.2009.28.9.1201

Feenstra, S. G., Pahan, D., Moet, F. J., Oskam, L., & Richardus, J. H. (2012). Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. *Leprosy Review*, *83*(3), 292–304. https://pubmed.ncbi.nlm.nih.gov/23356030/

Ferreira, S. M. B., Yonekura, T., Ignotti, E., Oliveira, L. B. de, Takahashi, J., & Soares, C. B. (2017). Effectiveness of rifampicin chemoprophylaxis in preventing leprosy in patient contacts: a systematic review of quantitative and qualitative evidence. *JBI Database of Systematic Reviews and Implementation Reports*, *15*(10), 2555–2584. https://doi.org/10.11124/JBISRIR-2016-003301

Frade, M. A. C., Nogueira-Barbosa, M. H., Lugão, H. B., Furini, R. B., Marques Júnior, W., & Foss, N. T. (2013). New sonographic measures of peripheral nerves: a tool for the diagnosis of peripheral nerve involvement in leprosy. *Memorias Do Instituto Oswaldo Cruz*, *108*(3). https://doi.org/10.1590/S0074-02762013000300001

Gonçalves, S. D., Sampaio, R. F., & Antunes, C. M. de F. (2009). [Predictive factors of disability in patients with leprosy]. *Revista de Saude Publica*, *43*(2), 267–274. https://doi.org/10.1590/s0034-89102009000200007

Goto, M., Nogam, R., Okano, Y., Gidoh, M., Yotsu, R., Ishida, Y., Kitajima, S., Kai, M., Ishii, N., Ozaki, M., Hatano, K., Ad Hoc Committee on Treatment Guideline, & Japanese Leprosy Association. (2013). [Guidelines for the treatment of Hansen's disease in Japan (third edition)]. *Nihon Hansenbyō Gakkai Zasshi = Japanese Journal of Leprosy : Official Organ of the Japanese Leprosy Association*, *82*(3), 143–184. https://doi.org/10.5025/hansen.82.143

Guerrero-Guerrero, M. I., Muvdi-Arenas, S., & León-Franco, C. I. (2012). Relapses in multibacillary leprosy patients: a retrospective cohort of 11 years in Colombia. *Leprosy Review*, *83*(3), 247–260.

http://www.ncbi.nlm.nih.gov/pubmed/23356026

Guragain, S., Upadhayay, N., & Bhattarai, B. M. (2017). Adverse reactions in leprosy patients who underwent dapsone multidrug therapy: a retrospective study. *Clinical Pharmacology : Advances and Applications*, *9*, 73–78. https://doi.org/10.2147/CPAA.S135846

Gurung, P., Gomes, C. M., Vernal, S., & Leeflang, M. M. G. (2019). Diagnostic accuracy of tests for leprosy: a systematic review and meta-analysis. In *Clinical Microbiology and Infection* (Vol. 25, Issue 11, pp. 1315–1327). Elsevier B.V. https://doi.org/10.1016/j.cmi.2019.05.020

Handog, E. B., Gabriel, M. T. G., & Co, C. C. (2011). Leprosy in the Philippines: A review. *International Journal of Dermatology*, *50*(5), 573–581. https://doi.org/10.1111/j.1365-4632.2011.05044.x

Hay, S. I., Abajobir, A. A., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abdulkader, R. S., Abdulle, A. M., Abebo, T. A., Abera, S. F., Aboyans, V., Abu-Raddad, L. J., Ackerman, I. N., Adedeji, I. A., Adetokunboh, O., Afshin, A., Aggarwal, R., Agrawal, S., Agrawal, A., … Murray, C. J. L. (2017). Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *390*(10100), 1260–1344. https://doi.org/10.1016/S0140-6736(17)32130-X

Health Resources & Services Administration [United States]. (2018, September). *Preparation and Examination of Skin Smears*. Official Web Site of the U.S. Health Resources & Services Administration. https://www.hrsa.gov/hansens-disease/diagnosis/skin-smears.html

Hilder, R., & Lockwood, D. (2020). The adverse drug effects of dapsone therapy in leprosy: a systematic review. *Leprosy Review*, *91*(3), 232–243. https://doi.org/10.47276/lr.91.3.232

Holey, E. A., Feeley, J. L., Dixon, J., & Whittaker, V. J. (2007). An exploration of the use of simple statistics to measure consensus and stability in Delphi studies. *BMC Medical Research Methodology*, *7*(February). https://doi.org/10.1186/1471-2288-7-52

Idema, W. J., Majer, I. M., Pahan, D., Oskam, L., Polinder, S., & Richardus, J. H. (2010). Cost-Effectiveness of a Chemoprophylactic Intervention with Single Dose Rifampicin in Contacts of New Leprosy Patients. *PLoS Neglected Tropical Diseases*, *4*(11), e874. https://doi.org/10.1371/journal.pntd.0000874

International Federation of Anti-Leprosy Associations. (2020). *How to do a skin smear examination for leprosy*.

Jamet, P., & Ji, B. (1995). Relapse after long-term follow up of multibacillary patients treated by WHO multidrug regimen. Marchoux Chemotherapy Study Group. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *63*(2), 195–201. http://www.ncbi.nlm.nih.gov/pubmed/7602214

Kaluarachchi, S. I., Fernandopulle, B. M., & Gunawardane, B. P. (2001). Hepatic and haematological adverse reactions associated with the use of multidrug therapy in leprosy--a five year retrospective study. *Indian Journal of Leprosy*, *73*(2), 121–129. http://www.ncbi.nlm.nih.gov/pubmed/11579648

Khambati, F. A., Shetty, V. P., Ghate, S. D., & Capadia, G. D. (2009). Sensitivity and specificity of nerve palpation, monofilament testing and voluntary muscle testing in detecting peripheral nerve abnormality, using nerve conduction studies as gold standard; a study in 357 patients. *Leprosy Review*, *80*(1), 34–50. http://www.ncbi.nlm.nih.gov/pubmed/19472851

Kumar, A., Girdhar, A., & Girdhar, B. K. (2012). Risk of developing disability in pre and post-multidrug therapy treatment among multibacillary leprosy: Agra MB Cohort study. *BMJ Open*, *2*(2), e000361. https://doi.org/10.1136/bmjopen-2011-000361

Kumar, A., Girdhar, A., & Girdhar, B. K. (2013). Twelve months fixed duration WHO multidrug therapy for multibacillary leprosy: incidence of relapses in Agra field based cohort study. *The Indian Journal of Medical Research*, *138*(4), 536–540. http://www.ncbi.nlm.nih.gov/pubmed/24434261

Kyaw, K., Tsoh, T. M., Swe, S. Y. Y., Nagaoka, Y., Takezaki, S., Suzuki, K., & Ishii, N. (2008). Clinical analysis of multibacillary leprosy patients after 1-year fixed World Health Organization recommended multidrug

therapy at Yangon General Hospital, Myanmar. *The Journal of Dermatology*, *35*(5), 264–269. https://doi.org/10.1111/j.1346-8138.2008.00464.x

Kyu, H. H., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, M., Abebe, Z., Abil, O. Z., Aboyans, V., Abrham, A. R., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., … Murray, C. J. L. (2018). Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1859–1922. https://doi.org/10.1016/S0140-6736(18)32335-3

Lambert, S. M., Alembo, D. T., Nigusse, S. D., Yamuah, L. K., Walker, S. L., & Lockwood, D. N. J. (2016). A Randomized Controlled Double Blind Trial of Cyclosporine versus Prednisolone in the Management of Leprosy Patients with New Type 1 Reaction, in Ethiopia. *PLOS Neglected Tropical Diseases*, *10*(4), e0004502. https://doi.org/10.1371/journal.pntd.0004502

Lemes, R. M. R., Silva, C. A. de M. e, Marques, M. Â. de M., Atella, G. C., Nery, J. A. da C., Nogueira, M. R. S., Rosa, P. S., Soares, C. T., De, P., Chatterjee, D., Pessolani, M. C. V., & de Macedo, C. S. (2020). Altered composition and functional profile of high-density lipoprotein in leprosy patients. *PLOS Neglected Tropical Diseases*, *14*(3), e0008138. https://doi.org/10.1371/journal.pntd.0008138

Leonardo, L., Hernandez, L., Magturo, T. C., Palasi, W., Rubite, J. M., de Cadiz, A., Moendeg, K., Fornillos, R. J., Tabios, I. K., Mistica, M., & Fontanilla, I. K. (2020). Current status of neglected tropical diseases (NTDs) in the Philippines. *Acta Tropica*, *203*(July 2019), 105284. https://doi.org/10.1016/j.actatropica.2019.105284

Lockwood, D. N. J., Darlong, J., Govindharaj, P., Kurian, R., Sundarrao, P., & John, A. S. (2017). AZALEP a randomized controlled trial of azathioprine to treat leprosy nerve damage and Type 1 reactions in India: Main findings. *PLOS Neglected Tropical Diseases*, *11*(3), e0005348. https://doi.org/10.1371/journal.pntd.0005348

Lugão, H. B., Frade, M. A. C., Marques-Jr, W., Foss, N. T., & Nogueira-Barbosa, M. H. (2016). Ultrasonography of Leprosy Neuropathy: A Longitudinal Prospective Study. *PLOS Neglected Tropical Diseases*, *10*(11), e0005111. https://doi.org/10.1371/journal.pntd.0005111

Maghanoy, A., Balagon, M., Saunderson, P., & Scheelbeek, P. (2017). A prospective randomised, double-blind, placebo controlled trial on the effect of extended clofazimine on Erythema Nodosum Leprosum (ENL) in multibacillary (MB) leprosy. *Leprosy Review*, *88*(2), 208–2016. https://doi.org/10.47276/lr.88.2.208

Maghanoy, A., Mallari, I., Balagon, M., & Saunderson, P. (2011). Relapse study in smear positive multibacillary (MB) leprosy after 1 year WHO-multi-drug therapy (MDT) in Cebu, Philippines. *Leprosy Review*, *82*(1), 65–69. http://www.ncbi.nlm.nih.gov/pubmed/21644473

Mangum, L., Kilpatrick, D., Stryjewska, B., & Sampath, R. (2018). Tuberculosis and Leprosy Coinfection: A Perspective on Diagnosis and Treatment. *Open Forum Infectious Diseases*, *5*(7). https://doi.org/10.1093/ofid/ofy133

Matsuoka, M. (2010). Drug resistance in leprosy. *Japanese Journal of Infectious Diseases*, *63*(1), 1–7. http://www.ncbi.nlm.nih.gov/pubmed/20093754

Matsuoka, M., Budiawan, T., Aye, K. S., Kyaw, K., Tan, E. V., Cruz, E. Dela, Gelber, R., Saunderson, P., Balagon, V., & Pannikar, V. (2007). The frequency of drug resistance mutations in Mycobacterium leprae isolates in untreated and relapsed leprosy patients from Myanmar, Indonesia and the Philippines. *Leprosy Review*, *78*(4), 343–352. https://doi.org/10.47276/lr.78.4.343

Maymone, M. B. C., Laughter, M., Venkatesh, S., Dacso, M. M., Rao, P. N., Stryjewska, B. M., Hugh, J., Dellavalle, R. P., & Dunnick, C. A. (2020). Leprosy: Clinical aspects and diagnostic techniques. *Journal of the American Academy of Dermatology*, *83*(1), 1–14. https://doi.org/10.1016/j.jaad.2019.12.080

Moet, F. J., Pahan, D., Oskam, L., & Richardus, J. H. (2008). Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ*, *336*(7647), 761–764. https://doi.org/10.1136/bmj.39500.885752.BE

Mowla, M. R., Ara, S., Mizanur Rahman, A. F. M., Tripura, S. P., & Paul, S. (2017). Leprosy reactions in postelimination stage: the Bangladesh experience. *Journal of the European Academy of Dermatology and Venereology*, *31*(4), 705–711. https://doi.org/10.1111/jdv.14049

Murphy, M., Black, N., Lamping, D., McKee, C., Sanderson, C., Askham, J., & Marteau, T. (1998). Consensus development methods, and their use in clinical guideline development. *Health Technology Assessment*, *2*(3). https://doi.org/10.4135/9781848608344.n24

Naafs, B., & van Hees, C. L. M. (2016). Leprosy type 1 reaction (formerly reversal reaction). *Clinics in Dermatology*, *34*(1), 37–50. https://doi.org/10.1016/j.clindermatol.2015.10.006

Nair, S. P. (2018). A 19-Year Retrospective Study of Adverse Drug Reactions to Multidrug Therapy in Leprosy Requiring a Change in Regime. *Indian Dermatology Online Journal*, *9*(1), 33–36. https://doi.org/10.4103/idoj.IDOJ_116_17

National Institute for Health and Care Excellence. (2014). *Developing NICE guidelines: the manual*. www.nice.org.uk/process/pmg20

National Leprosy Control Program. (2018a). *National Leprosy Control Program (NLCP) Manual of Procedures*.

National Leprosy Control Program. (2018b). *National Leprosy Control Program Medium Term Plan 2017-2022*.

Negera, E., Tilahun, M., Bobosha, K., Lambert, S. M., Walker, S. L., Spencer, J. S., Aseffa, A., Dockrell, H. M., & Lockwood, D. N. (2018). The effects of prednisolone treatment on serological responses and lipid profiles in Ethiopian leprosy patients with Erythema Nodosum Leprosum reactions. *PLoS Neglected Tropical Diseases*, *12*(12), e0007035. https://doi.org/10.1371/journal.pntd.0007035

Nery, J. A. da C., Bernardes Filho, F., Quintanilha, J., Machado, A. M., Oliveira, S. de S. C., & Sales, A. M. (2013). Understanding the type 1 reactional state for early diagnosis and treatment: a way to avoid disability in leprosy. *Anais Brasileiros de Dermatologia*, *88*(5), 787–792. https://doi.org/10.1590/abd1806-4841.20132004

Nunes, M. I. (2001). The relationship between quality of life and adherence to treatment. *Current Hypertension Reports*, *3*(6), 462–465. https://doi.org/10.1007/s11906-001-0007-9

Oliveira, D. T. de, Sherlock, J., Melo, E. V. de, Rollemberg, K. C. V., Paixao, T. R. S. da, Abuawad, Y. G., Simon, M. do V., Duthie, M., & Jesus, A. R. de. (2013). Clinical variables associated with leprosy reactions and persistence of physical impairment. *Revista Da Sociedade Brasileira de Medicina Tropical*, *46*(5), 600–604. https://doi.org/10.1590/0037-8682-0100-2013

Oliveira, R. A., Silva, G. B., Souza, C. J., Vieira, E. F., Mota, R. M. S., Martins, A. M. C., Libório, A. B., & Daher, E. F. (2008). Evaluation of renal function in leprosy: a study of 59 consecutive patients. *Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *23*(1), 256–262. https://doi.org/10.1093/ndt/gfm568

Oxman, A. D. (2004). Grading quality of evidence and strength of recommendations. In *British Medical Journal* (Vol. 328, Issue 7454, pp. 1490–1494). BMJ Publishing Group. https://doi.org/10.1136/bmj.328.7454.1490

Pamba, A., Richardson, N. D., Carter, N., Duparc, S., Premji, Z., Tiono, A. B., & Luzzatto, L. (2012). Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. *Blood*, *120*(20), 4123–4133. https://doi.org/10.1182/blood-2012-03-416032

Pavezzi, P. D., do Prado, R. B., Boin Filho, P. Â., Gon, A. dos S., Tuma, B., Fornazieri, M. A., Scalone, F. de M., Alves, L. R. M., Montero, R. H., & Casella, A. M. B. (2020). Evaluation of ocular involvement in patients with Hansen's disease. *PLOS Neglected Tropical Diseases*, *14*(9), e0008585. https://doi.org/10.1371/journal.pntd.0008585

Pepito, V. C. F., Amit, A. M. L., Samontina, R. E. D., Abdon, S. J. A., Fuentes, D. N. L., & Saniel, O. P. (2018). Variations in the clinical management of multibacillary leprosy patients in selected hospitals in Metro Manila. *Acta Medica Philippina*, *52*(3), 268–276. https://doi.org/10.47895/amp.v52i3.409

Pfyffer, G. E., & Inderlied, C. B. (2010). Mycobacteria. In *Infectious Diseases: Third Edition* (Vol. 2, pp. 1777–1800). Elsevier Inc. https://doi.org/10.1016/B978-0-323-04579-7.00174-X

Philippine Health Insurance Corporation. (2017). *PhilHealth Circular 2017-0019* (Vol. 6). https://www.philhealth.gov.ph/circulars/2017/circ2017-0019.pdf.

Polito, M. G., Moreira, S. R., Nishida, S. K., & Mastroianni Kirsztajn, G. (2015). It is time to review concepts on renal involvement in leprosy: pre- and post-treatment evaluation of 189 patients. *Renal Failure*, *37*(7), 1171–1174. https://doi.org/10.3109/0886022X.2015.1057470

Poojabylaiah, M., Marne, R. B., Varikkodan, R., Bala, N., Dandakeri, S., & Martis, J. (2008). Relapses in multibacillary leprosy patients after multidrug therapy. *Leprosy Review*, *79*(3), 320–324. http://www.ncbi.nlm.nih.gov/pubmed/19009982

Prabu, R., Manickam, P., Mahalingam, V. N., Jayasree, P., Selvaraj, V., & Mehendale, S. M. (2015). Relapse and deformity among 2177 leprosy patients released from treatment with MDT between 2005 and 2010 in South India: A retrospective cohort study. *Leprosy Review*, *86*(4), 345–355. http://www.ncbi.nlm.nih.gov/pubmed/26964430

Rao, P. S. S. S., Sugamaran, D. S. T., Richard, J., & Smith, W. C. S. (2006). Multi-centre, double blind, randomized trial of three steroid regimens in the treatment of type-1 reactions in leprosy. *Leprosy Review*, *77*(1), 25–33. http://www.ncbi.nlm.nih.gov/pubmed/16715687

Rathod, S. P., Jagati, A., & Chowdhary, P. (2020). Disabilities in leprosy: an open, retrospective analyses of institutional records. *Anais Brasileiros de Dermatologia*, *95*(1), 52–56. https://doi.org/10.1016/j.abd.2019.07.001

Ravanes, J. M., Cellona, R. V, Balagon, M., Abalos, R. M., Walsh, G. P., & Walsh, D. S. (2011). Longitudinal ocular survey of 202 Filipino patients with multi-bacillary (MB) leprosy treated with 2 year WHO-multiple drug therapy. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *42*(2), 323–330. http://www.ncbi.nlm.nih.gov/pubmed/21710853

Reed, N. K., van Brakel, W. H., & Reed, D. S. (1997). Progress of impairment scores following commencement of chemotherapy in multibacillary leprosy patients. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *65*(3), 328–336. http://www.ncbi.nlm.nih.gov/pubmed/9401485

Renault, C. A., & Ernst, J. D. (2015). Mycobacterium leprae (Leprosy). In *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* (Vol. 2, pp. 2819-2831.e2). Elsevier. https://doi.org/10.1016/B978-1-4557-4801-3.00252-6

Reveiz, L., Buendía, J. A., & Téllez, D. (2009). Chemoprophylaxis in contacts of patients with leprosy: Systematic review and meta-analysis. In *Revista Panamericana de Salud Publica/Pan American Journal of Public Health* (Vol. 26, Issue 4, pp. 341–349). Pan American Health Organization. https://doi.org/10.1590/S1020-49892009001000009

Richardus, Jan H, Nicholls, P. G., Croft, R. P., Withington, S. G., & Smith, W. C. S. (2004). Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up. *International Journal of Epidemiology*, *33*(2), 337–343. https://doi.org/10.1093/ije/dyg225

Richardus, Jan H, Withington, S. G., Anderson, A. M., Croft, R. P., Nicholls, P. G., Van Brakel, W. H., & Smith, W. C. S. (2003). Adverse events of standardized regimens of corticosteroids for prophylaxis and treatment of nerve function impairment in leprosy: results from the "TRIPOD" trials. *Leprosy Review*, *74*(4), 319–327. http://www.ncbi.nlm.nih.gov/pubmed/14750577

Richardus, Jan Hendrik. (2013). Leprosy remains an important public health challenge in India. In *The Indian journal of medical research* (Vol. 137, Issue 5, pp. 878–879). Wolters Kluwer -- Medknow Publications. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3734677/

Robertson, J. (2016). Leprosy, Historical. In *International Encyclopedia of Public Health* (Second Edi, Vol. 4). Elsevier. https://doi.org/10.1016/B978-0-12-803678-5.00252-6

Rosa, P. S., D'Espindula, H. R. S., Melo, A. C. L., Fontes, A. N. B., Finardi, A. J., Belone, A. F. F., Sartori, B. G. C., Pires, C. A. A., Soares, C. T., Marques, F. B., Branco, F. J. D., Baptista, I. M. F. D., Trino, L. M., Fachin, L. R. V, Xavier, M. B., Floriano, M. C., Ura, S., Diório, S. M., Delanina, W. F. B., … Mira, M. T. (2020). Emergence and Transmission of Drug-/Multidrug-resistant Mycobacterium leprae in a Former Leprosy Colony in the Brazilian Amazon. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *70*(10), 2054–2061. https://doi.org/10.1093/cid/ciz570

Sabin, T. D., & Swift, T. R. (2014). Neurologic Complications of Leprosy. In *Aminoff's Neurology and General Medicine* (pp. 845–856). Elsevier. https://doi.org/10.1016/B978-0-12-407710-2.00042-4

Sales, A. M., Sabroza, P. C., Nery, J. A. da C., Dupprè, N. C., & Sarno, E. N. (2007). No difference in leprosy treatment outcomes comparing 12- and 24-dose multidrug regimens: a preliminary study. *Cadernos de Saúde Pública*, *23*(4), 815–822. https://doi.org/10.1590/S0102-311X2007000400009

Schively, C. (2007). A quantitative analysis of consensus building in local environmental review. *Journal of Planning Education and Research*, *27*(1), 82–98. https://doi.org/10.1177/0739456X07305794

Schreuder, P. A. (1998). The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in northeastern Thailand, 1987-1995 [correction of 1978-1995]. I. Overview of the study. *International Journal of Leprosy and Other Mycobacterial Diseases : Official Organ of the International Leprosy Association*, *66*(2), 149–158. http://www.ncbi.nlm.nih.gov/pubmed/9728447

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013, October). *GRADE Handbook*. https://gdt.gradepro.org/app/handbook/handbook.html

Schünemann, H., Wiercioch, W., Brozek, J., Etxeandia-Ikobaltzeta, I., Mustafa, R. A., Manja, V., Brignardello-Petersen, R., Neumann, I., Falavigna, M., Alhazzani, W., Santesso, N., Zhang, Y., Meerpohl, J. J., Morgan, R. L., Rochwerg, B., Darzi, A., Rojas, M. X., Carrasco-Labra, A., Adi, Y., … Akl, E. A. (2017). GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *Journal of Clinical Epidemiology*, *81*, 101–110. https://doi.org/10.1016/j.jclinepi.2016.09.009

Scollard, D. M., Martelli, C. M. T., Stefani, M. M. A., De Fatima Maroja, M., Villahermosa, L., Pardillo, F., & Tamang, K. B. (2015). Risk factors for leprosy reactions in three endemic countries. *American Journal of Tropical Medicine and Hygiene*, *92*(1), 108–114. https://doi.org/10.4269/ajtmh.13-0221

Scottish Intercollegiate Guidelines Network (SIGN). (2015). *SIGN 50 Guideline Developer's Handbook*. *November*. http://www.sign.ac.uk/guidelines/fulltext/50/section1.html,

Sharma, P., Kar, H. K., Beena, K. R., Kaur, H., & Narayan, R. (1996). Disabilities in multibacillary leprosy patients: before, during and after multidrug therapy. *Indian Journal of Leprosy*, *68*(2), 127–136. http://www.ncbi.nlm.nih.gov/pubmed/8835580

Smith, C. M., & Smith, W. C. (2000). Chemoprophylaxis is effective in the prevention of leprosy in endemic countries: a systematic review and meta-analysis. MILEP2 Study Group. Mucosal Immunology of Leprosy. *The Journal of Infection*, *41*(2), 137–142. https://doi.org/10.1053/jinf.2000.0698

Solanki, J., Thesia, A., Mehta, H., Shah, C., & Mehta, H. (2016). Evaluation of cardiac autonomic status using QTc interval in patients with leprosy. *Asia Pacific Clinical and Translational Nervous System Diseases*, *1*(3), 144. https://doi.org/10.4103/2468-5577.187081

Somar, P., Waltz, M., & van Brakel, W. (2020). The impact of leprosy on the mental wellbeing of leprosy-affected persons and their family members – a systematic review. *Global Mental Health*, *7*. https://doi.org/10.1017/gmh.2020.3

Srinivas, G., Muthuvel, T., Lal, V., Vaikundanathan, K., Schwienhorst-Stich, E.-M., & Kasang, C. (2019). Risk of disability among adult leprosy cases and determinants of delay in diagnosis in five states of India: A case-control study. *PLoS Neglected Tropical Diseases*, *13*(6), e0007495. https://doi.org/10.1371/journal.pntd.0007495

Suchonwanit, P., Triamchaisri, S., Wittayakornrerk, S., & Rattanakaemakorn, P. (2015). Leprosy Reaction in Thai Population: A 20-Year Retrospective Study. *Dermatology Research and Practice*, *2015*, 253154.

https://doi.org/10.1155/2015/253154

Tabri, F., Maskur, Z., Amiruddin, M. D., & Makalew, H. L. (2017). Analysis of SGOT, SGPT, and IgM anti PGL-1 in Multibacillary Leprosy Patient after Multi Drug Therapy. *Global Journal of Health Science*, *9*(9), 36. https://doi.org/10.5539/gjhs.v9n9p36

Tamez-Pérez, H. E. (2015). Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World Journal of Diabetes*, *6*(8), 1073. https://doi.org/10.4239/wjd.v6.i8.1073

Tapinos, N., & Rambukkana, A. (2005). Insights into regulation of human Schwann cell proliferation by Erk1/2 via a MEK-independent and p56Lck-dependent pathway from leprosy bacilli. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(26), 9188–9193. https://doi.org/10.1073/pnas.0501196102

The James Lind Alliance. (2020). *The James Lind Alliance Guidebook* (9th ed.). http://www.jla.nihr.ac.uk/jla-guidebook/

Thompson, K. J., Allardice, G. M., Babu, G. R., Roberts, H., Kerketta, W., & Kerketta, A. (2006). Patterns of ocular morbidity and blindness in leprosy--a three centre study in Eastern India. *Leprosy Review*, *77*(2), 130–140. http://www.ncbi.nlm.nih.gov/pubmed/16895069

Tiwary, P. K., Kar, H. K., Sharma, P. K., Gautam, R. K., Arora, T. C., Naik, H., & Dhir, V. (2011). Epidemiological trends of leprosy in an urban leprosy centre of Delhi: A retrospective study of 16 years. *Indian Journal of Leprosy*, *83*(4), 201–208. http://europepmc.org/article/med/22783754

Umpierrez, G. E., Murphy, M. B., & Kitabchi, A. E. (2002). Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome. *Diabetes Spectrum*, *15*(1), 28–36. https://doi.org/10.2337/diaspect.15.1.28

Van Brakel, W. H., Anderson, A. M., Withington, S. G., Croft, R. P., Nicholls, P. G., Richardus, J. H., & Smith, W. C. S. (2003). The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2). *Leprosy Review*, *74*(4), 300–310. http://www.ncbi.nlm.nih.gov/pubmed/14750575

van Brakel, W. H., Nicholls, P. G., Wilder-Smith, E. P., Das, L., Barkataki, P., & Lockwood, D. N. J. (2008). Early Diagnosis of Neuropathy in Leprosy—Comparing Diagnostic Tests in a Large Prospective Study (the INFIR Cohort Study). *PLoS Neglected Tropical Diseases*, *2*(4), e212. https://doi.org/10.1371/journal.pntd.0000212

Van Veen, N. H., Nicholls, P. G., Smith, W. C. S., & Richardus, J. H. (2016). Corticosteroids for treating nerve damage in leprosy. In N. H. Van Veen (Ed.), *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd. https://doi.org/10.1002/14651858.CD005491.pub3

Voorend, C. G. N., & Post, E. B. (2013). A Systematic Review on the Epidemiological Data of Erythema Nodosum Leprosum, a Type 2 Leprosy Reaction. *PLoS Neglected Tropical Diseases*, *7*(10), e2440. https://doi.org/10.1371/journal.pntd.0002440

Wagenaar, I., Post, E., Brandsma, W., Bowers, B., Alam, K., Shetty, V., Pai, V., Husain, S., Sigit Prakoeswa, C. R., Astari, L., Hagge, D., Shah, M., Neupane, K., Tamang, K. B., Nicholls, P., & Richardus, J. H. (2017). Effectiveness of 32 versus 20 weeks of prednisolone in leprosy patients with recent nerve function impairment: A randomized controlled trial. *PLOS Neglected Tropical Diseases*, *11*(10), e0005952. https://doi.org/10.1371/journal.pntd.0005952

Walker, S. L., Sales, A. M., Butlin, C. R., Shah, M., Maghanoy, A., Lambert, S. M., Darlong, J., Rozario, B. J., Pai, V. V., Balagon, M., Doni, S. N., Hagge, D. A., Nery, J. A. C., Neupane, K. D., Baral, S., Sangma, B. A., Alembo, D. T., Yetaye, A. M., Hassan, B. A., … Lockwood, D. N. J. (2017). A leprosy clinical severity scale for erythema nodosum leprosum: An international, multicentre validation study of the ENLIST ENL Severity Scale. *PLOS Neglected Tropical Diseases*, *11*(7), e0005716. https://doi.org/10.1371/journal.pntd.0005716

Wang, Z., Norris, S. L., & Bero, L. (2018). The advantages and limitations of guideline adaptation frameworks. *Implementation Science*, *13*(1), 72. https://doi.org/10.1186/s13012-018-0763-4

World Health Organization. (1950). *WHA3.71 Adjustment of Operating Programme for 1951 The Third World Health Assembly*.

World Health Organization. (2014). *Handbook for guideline development* (2nd ed.). http://www.who.int/kms/handbook_2nd_ed.pdf (accessed 15 May 2015)

World Health Organization. (2016a). *Classification of leprosy*. https://www.who.int/lep/classification/en/

World Health Organization. (2016b). Global Leprosy Strategy 2016-2020: accelerating towards a leprosy-free world. In *Weekly Epidemiological record* (Vol. 1, Issue 35). http://apps.who.int/iris/bitstream/10665/205149/1/B5233.pdf?ua=1

World Health Organization. (2016c). *MDT: relapse after treatment FAQ*. https://www.who.int/lep/mdt/relapse/en/

World Health Organization. (2016d). *Microbiology of M. leprae*. https://www.who.int/lep/microbiology/en/

World Health Organization. (2016e). *WHO recommended MDT regimens*. https://www.who.int/lep/mdt/regimens/en/

World Health Organization. (2017). *A guide for surveillance of antimicrobial resistance in leprosy: 2017 update*. World Health Organization, Regional Office for South-East Asia.

World Health Organization. (2018a). Global leprosy update, 2017: reducing the disease burden due to leprosy. *Weekly Epidemiological Record*, *93*(35), 445–456. http://apps.who.int/iris/bitstream/hand%0Ahttp://www.who.int/wer/2009/wer8440.pdf?ua=1

World Health Organization. (2018b). *Guidelines for the diagnosis, treatment and prevention of leprosy*. World Health Organization, Regional Office for South-East Asia.

World Health Organization. (2019a). *Leprosy - Number of new G2D cases*. The Global Health Observatory. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/leprosy---number-of-new-g2d-cases

World Health Organization. (2019b). *Leprosy (Hansen's disease)*. The Global Health Observatory. https://www.who.int/data/gho/data/themes/topics/leprosy-hansens-disease

World Health Organization. (2019c, September 10). *Leprosy*. https://www.who.int/news-room/fact-sheets/detail/leprosy

World Health Organization. (2020a). Global leprosy (Hansen disease) update, 2019: time to step-up prevention initiatives. *Weekly Epidemiological Record*, *95*(36), 417–440. http://www.who.int/wer

World Health Organization. (2020b). *Leprosy/Hansen Disease: Management of reactions and prevention of disabilities*.

Youngster, I., Arcavi, L., Schechmaster, R., Akayzen, Y., Popliski, H., Shimonov, J., Beig, S., & Berkovitch, M. (2010). Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety*, *33*(9), 713–726. https://doi.org/10.2165/11536520-000000000-00000

Annexes

Annex A. Summary of conflicts of interest of working groups.

Technical Advisory Group

Name	Qualifications	Conflict of Interest
Dr. Leda M. Hernandez	Chairperson, Department of Health–Disease Prevention and Control Bureau	No Conflict of Interest
Dr. Francesca Gajete	Co-chairperson, International Leprosy Association Philippines	No Conflict of Interest
Ms. Rouselle Gajete	International Leprosy Association Philippines	No Conflict of Interest
Dr. Ma. Luisa Abad-Venida	Honorary Advisor, Philippine Dermatological Society Leprosy Specialty Group Chairman Emeritus, Department of Dermatology, Jose R. Reyes Memorial Medical Center	No Conflict of Interest
Dr. Rajendra Prasad Huraj Yadav	World Health Organization Regional Office of the Western Pacific	No Conflict of Interest
Dr. Gloria Nenita Velasco	Department of Health–Health Policy Development and Planning Bureau	No Conflict of Interest

Steering Committee

Name	Qualifications	Conflict of Interest
Dr. Julie Mart Rubite	Program Manager, Department of Health–National Leprosy Control Program	No Conflict of Interest
Dr. Anna Melissa Guerrero	Member, Department of Health–Pharmaceutical Division	No Conflict of Interest
Ms. Joyce Ceria-Perena	Alternate Member, Department of Health–Pharmaceutical Division	No Conflict of Interest
Dr. Hyacinth Balderama	Pathologist Department of Health–Health Facilities Development Bureau	No Conflict of Interest

Name	Qualifications	Conflict of Interest
Dr. Marc Anthony Cepeda	Technical Staff, Philippine Health Insurance Corporation–Standards and Monitoring Department	No Conflict of Interest
Engr. Emerito L. Rojas	National Council on Disability Affairs	No Conflict of Interest
Dr. Kalpeshinh Rahevar	Leprosy Focal Person, World Health Organization Regional Office of the Western Pacific	No Conflict of Interest
Dr. Teresita G. Gabriel	Chairman, Research Institute at the Tropical Medicine–Department of Dermatology Immediate Past Head, Philippine Dermatological Society Subspecialty Core Group on Leprosy	No Conflict of Interest
Dr. Teresita R. Castillo	Ophthalmologist, Philippine Academy of Ophthalmology	No Conflict of Interest
Dr. Maylene Agrimano	Pediatric Infectious Disease Specialist	No Conflict of Interest
Dr. Maria Mercedes S. Cauilan	Head, Southern Philippines Medical Center–Leprosy Subspecialty Clinic Member, Philippine Dermatological Society Leprosy Specialty Group	No Conflict of Interest
Dr. Malaya P. Santos	Member, Philippine Dermatological Society Leprosy Specialty Group Saint Luke's Medical Center College of Medicine Medical Education Unit	Consultant for the DOH Novartis foundation leprosy task force from 2012-2017
Dr. Irene Florentino Farinas	Head, Department of Health–Policy Program Development and Research Unit of the Pharmaceutical Division, Health Regulation	No Conflict of Interest

Consensus Panel

Name	Qualifications	Conflict of Interest
Ms. Pacita Alano	Senior Health Program Officer, Department of Health	No Conflict of Interest
Dr. Annabelle Pabiona-De Guzman	Director-General, Philippine Institute of Traditional Alternative Health Care	No Conflict of Interest
Dr. Arturo Cunanan, Jr.	Medical Center Chief, Culion Sanitarium and General Hospital	A descendant of persons affected by leprosy, working for leprosy for almost 35 years
Dr. Frederica Veronica Marquez Protacio	Member, Philippine Dermatological Society Leprosy Specialty Group Head, Dr. Jose N. Rodriguez Memorial Hospital and Sanitarium–Department of Dermatology, Leprosy Unit	No Conflict of Interest
Dr. Angela M. Lavadia	Member, Philippine Dermatological Society Leprosy Specialty Group Chairman, East Avenue Medical Center–Department of Dermatology	No Conflict of Interest
Dr. Jessica Mae C. Cruz	Family Medicine Member, Philippine Academy of Family Physicians	No Conflict of Interest
Dr. Franz Marie Cruz	Member, Philippine Academy of Ophthalmology	No Conflict of Interest
Dr. Sinamar Ann C. Dela Cruz–Abando	Municipal Health Officer	No Conflict of Interest
Dr. Dimpna Cecilia D. Sare	Member, Association of Municipal Health Officers	No Conflict of Interest
Ms. Corazon L. Paras	Member, Integrated Midwives Association of the Philippines	No Conflict of Interest
Mr. Michael P. Gabilo	Member, Philippine Physical Therapy Association	No Conflict of Interest
Ms. Catherine Joy Escuarda	Treasurer, Philippine Physical Therapy Association	No Conflict of Interest
Mr. Eugene Caccam	Executive Director, Culion Foundation	No Conflict of Interest

Annex B. CPG Questions in PICO Framework

1. How are leprosy cases best defined? What clinical parameters should be considered when suspecting leprosy?

Population	Intervention	Comparison	Outcome
Adult patients with leprosy Adult patients suspected to have leprosy Pediatric patients with leprosy Pediatric patients suspected to have leprosy	Number of lesions Bacillary index according to slit-skin smear Number of hypoesthetic or neuritic skin lesions, degree of hypoesthesia or neuritis		Sensitivity, specificity, predictive values

2. Among patients for treatment of leprosy, what initial clinical and laboratory evaluation should be done?

Population	Intervention	Comparison	Outcome
Adult patients with leprosy to undergo treatment Pediatric patients with leprosy to undergo treatment	Clinical and laboratory evaluation	No laboratory or additional clinical evaluation	Early recognition of adverse drug reactions or side effects, cost-benefit

3. Among patients with diagnosed PB/MB leprosy, what is the dose and duration of treatment?

Population	Intervention	Comparison	Outcome
Patients with leprosy	Alternative regimen	WHO-MDT antibiotic regimen Rifampicin/dapsone/clofazimine	Cure, clinical improvement, decreased infectivity, treatment, completion, cost-benefit, safety

4. Among patients with MB leprosy, can MDT be extended to 24 months versus 12 months and what are the indications for extension?

Population	Intervention	Comparison	Outcome
Adult patients with multibacillary leprosy Pediatric patients with multibacillary leprosy	Extension of WHO-MDT regimen to 24 months	12 month WHO-MDT regimen	Cure, clinical improvement, decreased infectivity, treatment, completion, cost-benefit, safety

5. What is the recommended monitoring interval post-treatment?

Population	Intervention	Comparison	Outcome
Adult patients with leprosy who are undergoing or who have completed the appropriate treatment regimen Pediatric patients with leprosy who are undergoing or who have completed the appropriate regimen	Monitoring interval	No monitoring	Relapse detection, reaction detection, adverse drug effect detection and drug complications, drug resistance detection, detection of nerve function impairments

6. What is the treatment of complicated/refractory cases of lepra reactions?

Population	Intervention	Comparison	Outcome
Adult patients with leprosy who are undergoing or who have completed the appropriate treatment regimen Pediatric patients with leprosy who are undergoing or who have completed the appropriate regimen	Monitoring interval	No monitoring	Relapse detection, reaction detection, adverse drug effect detection and drug complications, drug resistance detection, detection of nerve function impairments

7. What is the treatment regimen for drug-resistant leprosy?

Population	Intervention	Comparison	Outcome
Adult patients with drug-resistant leprosy Pediatric patients with drug-resistant leprosy	Drug treatment regimen	WHO drug treatment regimen	Cure, clinical improvement, treatment completion, cost-benefit

8. How is drug resistance evaluated among leprosy patients?

Population	Intervention	Comparison	Outcome
Adult patients with leprosy Pediatric patients with leprosy	Diagnostic tests Clinical symptoms		Specificity, sensitivity, cost-effectiveness

9. Should contacts exposed to a patient with leprosy be offered chemoprophylaxis versus followed with observation alone?

Population	Intervention	Comparison	Outcome
Adult contacts of patients with confirmed leprosy Pediatric contacts of patients with confirmed leprosy	Chemoprophylaxis	Observation and no chemoprophylaxis	Infection rate, drug resistance, cost-effectiveness

10. What is an effective and safe chemoprophylaxis among contacts of leprosy with patients and high-risk populations?

Population	Intervention	Comparison	Outcome
Adult contacts of patients with confirmed leprosy Pediatric contacts of patients with confirmed leprosy	Alternative regimen for chemoprophylaxis	Single-dose rifampicin as recommended by WHO	Infection rate, drug resistance, cost-effectiveness, adverse drug reactions, drug safety

Annex C. Summary of ADAPTE evidence

During the development of the Philippine Leprosy Clinical Practice Guideline, ADAPTE methodology was used to take advantage of the existing high-quality guidelines that can be modified or customized to suit the local context while addressing relevant health questions. This is based on the developed a systematic approach to aid in the adaptation of guidelines by the ADAPTE collaboration using the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument which provides a framework for assessing the quality of clinical practice guidelines ensuring that high quality guidelines are used for adaptation.

Annex C.1 CPG questions in PIPOH framework

- **P**opulation: Adult and pediatric patients with leprosy
- **I**nterventions of interest: Screening, diagnostics, treatment and prevention
- **P**rofessionals to whom the Guideline will be targeted: Health care workers
- **O**utcomes: Sensitivity and specificity, cure rate, treatment completion rate, transmission rate
- **H**ealth care setting and context: Primary care

Annex C.2 Search strategy

The four previously identified databases were systematically searched for guidelines on leprosy. The following were the inclusion criteria used for selection of applicable guidelines:

1. The guideline must be about leprosy in the primary care setting.
2. The guideline must have been published.
3. There were no restrictions on language of publication.
4. There were no restrictions to the year of publication.

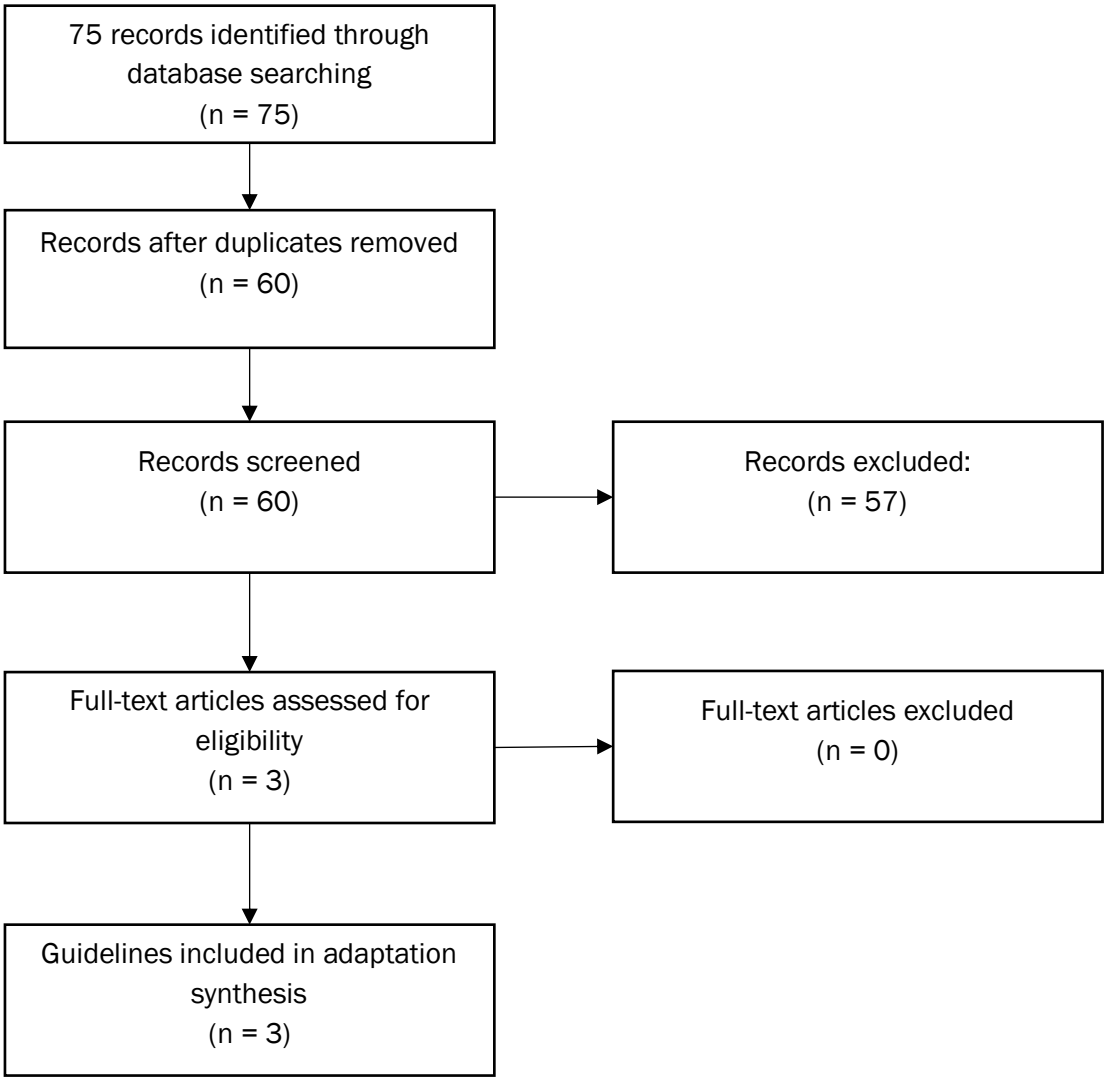
Guidelines were excluded based on the following exclusion criteria:

1. The guideline was a duplicate of existing guidelines.
2. The guideline was written by a single author or published without any multidisciplinary input.

Database	Search terms
Google Scholar (title search)	("leprosy" OR "Hansen disease" OR "Hansen's disease") AND ("guidelines" OR "CPG" OR "guidance")
Google Scholar (keyword search)	("leprosy" OR "Hansen disease" OR "Hansen's disease") AND ("guidelines" OR "CPG" OR "guidance")
PubMed	("leprosy" OR "Hansen disease" OR "Hansen's disease") AND ("guidelines" OR "CPG" OR "guidance")
SCOPUS	(TITLE("leprosy" OR "Hansen disease" OR "Hansen's disease") OR KEY("leprosy" OR "Hansen disease" OR "Hansen's disease")) AND (TITLE("guidelines" OR "CPG" OR "guidance") OR KEY("guidelines" OR "CPG" OR "guidance"))

Database	Search terms
DOAJ	leprosy guidelines
	leprosy CPG
	leprosy guidance
	Hansen disease guidelines
	Hansen disease CPG
	Hansen disease guidance
	Hansen's disease guidelines
	Hansen's disease CPG
	Hansen's disease guidance

Annex C.3. PRISMA flow diagram for guidelines included in the ADAPTE methodology



Annex C.4. Characteristics of screened guidelines

Three guidelines were reviewed and evaluated by 2 members of the technical review team in duplicate using the AGREE II reporting checklist. The PIPOH components of the guidelines are shown in the table below.

SCOPE	CPG #1 (WHO 2018)	CPG #2 NORTHERN TERRITORY, 2018)	CPG #3 (GOTO ET.AL., 2013)
POPULATION	Adult and children with leprosy	Adult and children with leprosy	Adult and children with leprosy
INTERVENTIONS	Screening, diagnostics, treatment and prophylaxis	Screening, diagnostics, treatment and prophylaxis	Screening, diagnostics, treatment and prophylaxis
PROFESSIONAL/PATIENTS	Primary care healthcare workers/physicians	Primary care healthcare workers/physicians	Primary care healthcare workers/physicians
OUTCOME	Cure Prevention (Primary)	Cure Prevention (Primary, secondary and tertiary)	Cure Prevention (Primary, secondary and tertiary)
HEALTHCARE SETTING	Primary healthcare	Primary healthcare	Primary healthcare

Annex C.5. Assessment and selection of the guidelines

The tables below show the summary of guideline characteristics of the included guidelines that were assessed to be considered for adaptation. Two appraisers who were part of the Evidence Reviewers completed the rigor dimension of the AGREE II instrument for the three guidelines. Upon review with the consensus panel, only the WHO Leprosy Guidelines was considered based on the rigor score. The two guidelines were considered in the initial assessment because they could still address the scope set for the CPG.

TITLE	PUBLISHER	COUNTRY/ LANGUAGE	PUBLICATION DATE	END OF SEARCH DATE	COMMENTS
GUIDELINES FOR THE DIAGNOSIS, TREATMENT, AND PREVENTION OF LEPROSY	WHO, Regional Office for South-East Asia	International/ English	2018	For laboratory tests inclusion was limited to studies published after 1996	Discusses both clinical and programmatic issues in the management of leprosy in low

TITLE	PUBLISHER	COUNTRY/ LANGUAGE	PUBLICATION DATE	END OF SEARCH DATE	COMMENTS
					resource setting
GUIDELINES FOR THE CONTROL OF LEPROSY IN THE NORTHERN TERRITORY	Department of Health, Northern Territory (Australia)	Australia/ English	2018	Not mentioned	Third updated version originally published 1996. Systematic review of existing literature was not documented
GUIDELINES FOR THE TREATMENT OF HANSEN'S DISEASE IN JAPAN	Japanese Journal of Leprosy (official journal of the Japanese Leprosy Association)	Japan/ Japanese	2013	Not mentioned	Intended as treatment guideline for clinicians

Annex C.6 Comparison of contents across leprosy management guidelines identified in literature review

CPG questions in the Philippine leprosy CPG	Content of guidelines (CPG) A check (✓) indicates inclusion of the relevant discussion in the guideline		
	CPG #1 (WHO 2018)	**CPG #2 Northern Territory, 2018)**	**CPG #3 (Goto et.al, 2013)**
How are leprosy cases best defined? Or what clinical parameters should be considered when suspecting leprosy?	✓	✓	✓
Among patients for treatment of leprosy, what initial clinical and laboratory evaluation should be done?		✓	✓
Among patients with diagnosed pb/mb leprosy, what is the dose and duration of treatment?	✓	✓	✓

CPG questions in the Philippine leprosy CPG	Content of guidelines (CPG) A check (✓) indicates inclusion of the relevant discussion in the guideline		
	CPG #1 (WHO 2018)	CPG #2 Northern Territory, 2018)	CPG #3 (Goto et.al, 2013)
Among patients with mb leprosy, can MDT be extended to 24 months versus 12 months and what are the indications of extension?		✓	✓
What is the recommended monitoring interval post treatment?		✓	✓
What is the treatment of complicated/refractory cases of lepra reactions?		✓	✓
What is the treatment regimen for drug-resistant leprosy?	✓		
How is drug resistance evaluated among leprosy patients?			
Should contacts exposed to a patient with leprosy be offered chemoprophylaxis vs. Followed with observation alone?	✓	✓	✓
What is effective and safe chemoprophylaxis among contacts of patients with leprosy and high-risk populations?	✓	✓	

Annex C.7. Overall quality assessment and summary of included recommendations

AGREE II rigor scores	Guidelines		
	WHO 2018	NT 2018*	Goto, et.al., 2013*
	50/56	8/56	8/56
Overall Quality Assessment	Strongly recommended with some modifications (2)	Recommended with some modifications (2)	Not recommended (2)
Diagnosis			
The diagnosis of leprosy may be based on clinical examination, with or without slit-skin smears or pathological examination of biopsies.	Conditional, low	-	-
There is currently no test recommended to diagnose leprosy infection (latent leprosy) among asymptomatic contacts.	Conditional, low	-	-
Treatment			
The same 3-drug regimen of rifampicin, dapsone and clofazimine may be used for	Conditional, low	-	-

AGREE II rigor scores	Guidelines		
	WHO 2018	NT 2018*	Goto, et.al., 2013*
	50/56	8/56	8/56
all leprosy patients, with a duration of treatment of 6 months for PB leprosy and of 12 months for MB 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)	-	-
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	-	-

Annex C.8. Adaptation and customization

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Guide questions	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Overall, was the search for evidence comprehensive?									
The authors had a clearly focused question (population, intervention and outcome).	✓					✓			✓
Appropriate databases were searched as source guidelines	✓				✓			✓	
Years covered in search	✓				✓			✓	

Guide questions	WHO 2018			NT 2018*			Goto et.al., 2013*		
	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Languages covered in search		✓			✓			✓	
Keywords used	✓					✓			✓
Combinations of keywords	✓					✓			✓
Detailed search strategies are provided with the guideline	✓					✓			✓
Snowball methods were used		✓			✓			✓	
A hand search of the reference lists was completed		✓			✓			✓	
Local experts and/or societies were asked for guideline recommendation	✓				✓			✓	
Overall, was bias in the selection of articles avoided?									
Inclusion and exclusion criteria reported		✓				✓			✓
The number of persons who selected and analyzed the data is documented		✓				✓			✓
The procedure to solve disagreement is described	✓					✓			✓
The number of excluded references is documented		✓			✓			✓	
The reasons for excluding references are given		✓			✓			✓	
The criteria for inclusion and exclusion are clinically and methodologically valid		✓			✓			✓	
The reasons for exclusion conform to the selection and exclusion criteria		✓			✓			✓	
The process for selection of evidence is adequately described.		✓				✓			✓

The following tables present the customization evaluation for each clinical question included in the CPG. Where a question is not included in the results tables below, none of the three guidelines located in the systematic search addressed the clinical question of concern.

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Health Question No. 1: How are leprosy cases best defined? or What clinical parameters should be considered when suspecting leprosy?	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Coherence between the evidence and recommendations									
The evidence was direct. Patients and interventions included in the studies were comparable to those targeted by the recommendation	✓					✓			✓
Conclusions were supported by data and/or the analysis; results were consistent from study to study. When inconsistencies existed in the data, considered judgement was applied and reported	✓					✓			✓
The conclusions are clinically relevant. (Statistical significance is not always equal to clinical significance)	✓					✓			✓
The conclusions derived from data point to effectiveness/ineffectiveness of the intervention and the recommendation is written accordingly	✓					✓			✓
There is some justification to recommend/not recommend the intervention even though the evidence is weak	✓				✓			✓	
The hierarchy of strength of evidence is adequately described	✓					✓			✓
Overall, the scientific quality of this recommendation does not present risks of bias									
The strength of evidence attributed to the recommendation is adequately described and justified	✓					✓			✓
Risks and benefits have been weighed	✓					✓			✓

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Health Question No. 3: Among patients with diagnosed PB/MB leprosy, what is the dose and duration of treatment?	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Coherence between the evidence and recommendations									
The evidence was direct. Patients and interventions included in the studies were comparable to those targeted by the recommendation	✓					✓			✓
Conclusions were supported by data and/or the analysis; results were consistent from study to study. When inconsistencies existed in the data, considered judgement was applied and reported	✓					✓			✓
The conclusions are clinically relevant. (Statistical significance is not always equal to clinical significance)	✓					✓			✓
The conclusions derived from data point to effectiveness/ineffectiveness of the intervention and the recommendation is written accordingly	✓					✓			✓
There is some justification to recommend/not recommend the intervention even though the evidence is weak	✓				✓			✓	
The hierarchy of strength of evidence is adequately described	✓					✓			✓
Overall, the scientific quality of this recommendation does not present risks of bias									
The strength of evidence attributed to the recommendation is adequately described and justified	✓					✓			✓
Risks and benefits have been weighed	✓					✓			✓

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Health Question No. 4: Among patients with MB leprosy, can MDT be extended to 24 months versus 12 months and what are the indications of extension?	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Coherence between the evidence and recommendations									
The evidence was direct. Patients and interventions included in the studies were comparable to those targeted by the recommendation						✓			✓
Conclusions were supported by data and/or the analysis; results were consistent from study to study. When inconsistencies existed in the data, considered judgement was applied and reported						✓			✓
The conclusions are clinically relevant. (Statistical significance is not always equal to clinical significance)						✓			✓
The conclusions derived from data point to effectiveness/ineffectiveness of the intervention and the recommendation is written accordingly						✓			✓
There is some justification to recommend/not recommend the intervention even though the evidence is weak					✓			✓	
The hierarchy of strength of evidence is adequately described						✓			✓
Overall, the scientific quality of this recommendation does not present risks of bias									
The strength of evidence attributed to the recommendation is adequately described and justified						✓			✓
Risks and benefits have been weighed						✓			✓

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Health Question No. 5: What is the recommended monitoring interval post treatment?	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Coherence between the evidence and recommendations									
The evidence was direct. Patients and interventions included in the studies were comparable to those targeted by the recommendation						✓			✓
Conclusions were supported by data and/or the analysis; results were consistent from study to study. When inconsistencies existed in the data, considered judgement was applied and reported						✓			✓
The conclusions are clinically relevant. (Statistical significance is not always equal to clinical significance)						✓			✓
The conclusions derived from data point to effectiveness/ineffectiveness of the intervention and the recommendation is written accordingly						✓			✓
There is some justification to recommend/not recommend the intervention even though the evidence is weak					✓			✓	
The hierarchy of strength of evidence is adequately described						✓			✓
Overall, the scientific quality of this recommendation does not present risks of bias									
The strength of evidence attributed to the recommendation is adequately described and justified						✓			✓
Risks and benefits have been weighed						✓			✓

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Health Question No. 6: What is the treatment of complicated/refractory cases of lepra reactions?	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Coherence between the evidence and recommendations									
The evidence was direct. Patients and interventions included in the studies were comparable to those targeted by the recommendation						✓			✓
Conclusions were supported by data and/or the analysis; results were consistent from study to study. When inconsistencies existed in the data, considered judgement was applied and reported						✓			✓
The conclusions are clinically relevant. (Statistical significance is not always equal to clinical significance)						✓			✓
The conclusions derived from data point to effectiveness/ineffectiveness of the intervention and the recommendation is written accordingly						✓			✓
There is some justification to recommend/not recommend the intervention even though the evidence is weak					✓			✓	
The hierarchy of strength of evidence is adequately described						✓			✓
Overall, the scientific quality of this recommendation does not present risks of bias									
The strength of evidence attributed to the recommendation is adequately described and justified						✓			✓
Risks and benefits have been weighed						✓			✓

Note: Treatment for Leprae Reaction was not addressed as a health question in WHO CPG. The 2 treatment guidelines outlined the management of the leprae reaction but presentation between evidence and recommendation was not done.

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Health Question No. 7: What is the treatment regimen for drug-resistant leprosy?	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Coherence between the evidence and recommendations									
The evidence was direct. Patients and interventions included in the studies were comparable to those targeted by the recommendation	✓								
Conclusions were supported by data and/or the analysis; results were consistent from study to study. When inconsistencies existed in the data, considered judgement was applied and reported	✓								
The conclusions are clinically relevant. (Statistical significance is not always equal to clinical significance)	✓								
The conclusions derived from data point to effectiveness/ineffectiveness of the intervention and the recommendation is written accordingly	✓								
There is some justification to recommend/not recommend the intervention even though the evidence is weak	✓								
The hierarchy of strength of evidence is adequately described	✓								
Overall, the scientific quality of this recommendation does not present risks of bias									
The strength of evidence attributed to the recommendation is adequately described and justified	✓								
Risks and benefits have been weighed	✓								

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Health Question No. 9: Should contacts exposed to a patient with leprosy be offered chemoprophylaxis vs. followed with observation alone?	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Coherence between the evidence and recommendations									
The evidence was direct. Patients and interventions included in the studies were comparable to those targeted by the recommendation	✓					✓			✓
Conclusions were supported by data and/or the analysis; results were consistent from study to study. When inconsistencies existed in the data, considered judgement was applied and reported	✓					✓			✓
The conclusions are clinically relevant. (Statistical significance is not always equal to clinical significance)	✓					✓			✓
The conclusions derived from data point to effectiveness/ineffectiveness of the intervention and the recommendation is written accordingly	✓					✓			✓
There is some justification to recommend/not recommend the intervention even though the evidence is weak	✓				✓			✓	
The hierarchy of strength of evidence is adequately described	✓					✓			✓
Overall, the scientific quality of this recommendation does not present risks of bias									
The strength of evidence attributed to the recommendation is adequately described and justified	✓					✓			✓
Risks and benefits have been weighed	✓					✓			✓

	WHO 2018			NT 2018*			Goto et.al., 2013*		
Health Question No. 10: What is effective and safe chemoprophylaxis among contacts of patients with leprosy and high-risk populations?	Yes	Unsure	No	Yes	Unsure	No	Yes	Unsure	No
Coherence between the evidence and recommendations									
The evidence was direct. Patients and interventions included in the studies were comparable to those targeted by the recommendation	✓					✓			✓
Conclusions were supported by data and/or the analysis; results were consistent from study to study. When inconsistencies existed in the data, considered judgement was applied and reported	✓					✓			✓
The conclusions are clinically relevant. (Statistical significance is not always equal to clinical significance)	✓					✓			✓
The conclusions derived from data point to effectiveness/ineffectiveness of the intervention and the recommendation is written accordingly	✓					✓			✓
There is some justification to recommend/not recommend the intervention even though the evidence is weak	✓				✓			✓	
The hierarchy of strength of evidence is adequately described	✓					✓			✓
Overall, the scientific quality of this recommendation does not present risks of bias									
The strength of evidence attributed to the recommendation is adequately described and justified	✓					✓			✓
Risks and benefits have been weighed	✓					✓			✓

Annex D. AGREE reporting checklist

TITLE OF CPG: _____

EVALUATOR: _____ DATE: _____

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
DOMAIN 1. SCOPE AND PURPOSE			
1. THE OVERALL OBJECTIVE(S) OF THE GUIDELINES IS (ARE) SPECIFICALLY DESCRIBED.	□ Health intent □ Expected benefit or outcome □ Target		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
2. THE HEALTH QUESTION(S) COVERED BY THE GUIDELINE IS (ARE) SPECIFICALLY DESCRIBED)	□ Target population □ Intervention or exposure □ Comparisons □ Outcomes □ Health care setting or context		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
3. THE POPULATION (PATIENT, PUBLIC, ETC.) TO WHOM THE GUIDELINE IS MEANT TO APPLY IS SPECIFICALLY DESCRIBED.	□ Target population □ Clinical condition □ Severity/stage □ Comorbidities □ Excluded populations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 2. STAKEHOLDER INVOLVEMENT			
4. THE GUIDELINE DEVELOPMENT GROUP INCLUDES INDIVIDUALS FROM ALL RELEVANT PROFESSIONAL GROUPS.	□ Name of participant □ Discipline/content expertise □ Institution □ Geographical location □ A description of the member's role in the guideline development		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
5. THE VIEWS AND PREFERENCES OF THE TARGET POPULATION (PATIENTS, PUBLIC, ETC.) HAVE BEEN SOUGHT.	□ Statement of type of strategy used to capture patient/public views and preferences □ Methods by which preferences and views were sought		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Outcomes/ information gathered on patient/public information □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations		
6. THE TARGET USERS OF THE GUIDELINE ARE CLEARLY DEFINED.	□ The intended guideline audience □ How the guideline may be used by its target audience		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 3. RIGOUR OF DEVELOPMENT			
7. SYSTEMATIC METHODS WERE USED TO SEARCH FOR EVIDENCE.	□ Named electronic databases or evidence source where the search was performed □ Time periods searched □ Search terms used □ Full search strategy included		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
8. THE CRITERIA FOR SELECTING THE EVIDENCE ARE CLEARLY DESCRIBED.	□ Target population □ Study design □ Comparisons □ Outcomes □ Language □ Context		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
9. THE STRENGTHS AND LIMITATIONS OF THE BODY OF EVIDENCE ARE CLEARLY DESCRIBED. TOOLS EXIST THAT CAN FACILITATE THE REPORTING OF THIS CONCEPT.	□ Study design included in body of evidence □ Study methodology limitations □ Appropriateness/ relevance of primary and secondary outcomes considered □ Consistency of results across studies		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Direction of results across studies □ Magnitude of benefit vs magnitude of harm □ Applicability to practice context.		
10, THE METHODS FOR FORMULATING THE RECOMMENDATIONS ARE CLEARLY DESCRIBED. SPECIFY AREAS OF DISAGREEMENTS AND METHODS USED TO RESOLVE THEM.	□ Recommendation development process □ Outcomes of the recommendation development process □ How the process influenced the recommendations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
11. THE HEALTH BENEFITS, SIDE EFFECTS, AND RISKS HAVE BEEN CONSIDERED IN FORMULATING THE RECOMMENDATIONS.	□ Supporting data and report of benefits □ Supporting data and report of harms/side effects/ risks □ Reporting of the balance/trade-off between benefits and harms/side effects/risks □ Recommendations reflect considerations of both benefits and harms/side effects/risks		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
12. THERE IS AN EXPLICIT LINK BETWEEN THE RECOMMENDATIONS AND THE SUPPORTING EVIDENCE.	□ How the guideline development group linked and used the evidence to inform recommendations. □ Link between each recommendation and key evidence □ Link between recommendations and evidence summaries/or evidence tables in the results section of the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
13. THE GUIDELINE HAS BEEN EXTERNALLY REVIEWED BY EXPERTS PRIOR TO ITS PUBLICATION.	□ Purpose and intent of the external review □ Methods taken to undertake the external review		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Description of the external reviewers □ Outcomes/information gathered from the external review □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations.		Comments:
14. A PROCEDURE FOR UPDATING THE GUIDELINE IS PROVIDED.	□ A statement that the guideline will be updated □ Explicit time interval or explicit criteria to guide decisions about when an update will occur □ Methodology for the updating procedure		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 4. CLARITY OF PRESENTATION			
15. THE RECOMMENDATIONS ARE SPECIFIC AND UNAMBIGUOUS.	□ A statement of the recommended action □ Intent or purpose of the recommended action □ Relevant population □ Caveats or qualifying statements, if relevant □ If there is uncertainty about the best care option, the uncertainty should be stated in the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
16. THE DIFFERENT OPTIONS FOR MANAGEMENT OF THE CONDITION OR HEALTH ISSUE ARE CLEARLY PRESENTED.	□ Description of management options □ Population or clinical situation most appropriate to each option		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
17. KEY RECOMMENDATIONS ARE EASILY IDENTIFIABLE.	□ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms □ Specific recommendations grouped together in one section		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 5. APPLICABILITY			
18. THE GUIDELINE DESCRIBES FACILITATORS AND BARRIERS TO ITS APPLICATION.	□ Types of facilitators and barriers that were considered □ Method by which information regarding the facilitators and barriers to implementing recommendations were sought. □ Information/ description of the types of facilitators and barriers that emerged from the injury □ How the information influenced the guideline development process and/or formation of the recommendations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
19. THE GUIDELINE PROVIDES ADVICE AND/OR TOOLS ON HOW THE RECOMMENDATIONS CAN BE PUT INTO PRACTICE.	□ Additional materials to support the implementation		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
20. THE POTENTIAL SOURCE IMPLICATIONS OF APPLYING THE RECOMMENDATIONS HAVE BEEN CONSIDERED.	□ Types of cost information that were considered □ Methods by which the cost information was sought		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Information/ description of the cost information that emerged from the inquiry □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations.		
21. THE GUIDELINE PRESENTS MONITORING AND/OR AUDITING CRITERIA.	□ Criteria to assess guideline implementation or adherence to recommendations □ Criteria for assessing impact of implementing the recommendations □ Advice on the frequency and interval of measurement □ Operational definitions of how the criteria should be measured.		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 6. EDITORIAL INDEPENDENCE			
22. THE VIEWS OF THE FUNDING BODY HAVE NOT INFLUENCED THE CONTENT OF THE GUIDELINE.	□ The name of the funding body or source of funding □ A statement that the funding body did not influence the content of the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
23. COMPETING INTERESTS OF GUIDELINE DEVELOPMENT GROUP MEMBERS HAVE BEEN RECORDED AND ADDRESSESD.	□ Types of competing interests considered □ Methods by which potential competing interests were sought □ a description of the competing interests □ How the competing interests influenced the guideline process and		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	development of recommendations		
OVERALL GUIDELINE ASSESSMENT			
1. RATE THE OVERALL QUALITY OF THIS GUIDELINE			1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
2. I WOULD RECOMMEND THIS GUIDELINE FOR USE.			YES YES WITH MODIFICATTION NO

Annex E. Search terms and limits for de novo synthesis

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
How are leprosy cases best defined? or What clinical parameters should be considered when suspecting leprosy?	Sensitivity Specificity Positive predictive value Negative predictive value	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (signs OR symptoms OR assessment OR examination OR diagnosis OR "clinical evaluation") AND (sensitivity OR specificity OR "predictive value")	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (signs OR symptoms OR assessment OR examination OR diagnosis OR "clinical evaluation") AND ALL (sensitivity OR specificity OR "predictive value")	(leprosy OR (Hansen disease) OR (Hansen's disease)) AND (signs OR symptoms OR assessment OR examination OR diagnosis OR (clinical evaluation)) AND (sensitivity OR specificity OR (predictive value))	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (signs OR symptoms OR assessment OR examination OR diagnosis OR "clinical evaluation") AND (sensitivity OR specificity OR "predictive value")
Among patients for treatment of leprosy, what initial clinical and laboratory evaluation should be done?	Detection of adverse drug events	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((pre-treatment OR "before treatment" OR baseline)) AND (evaluation OR assessment OR (physical examination) OR (laboratory)) AND ("adverse drug reaction" OR "adverse reaction" OR "side-effect" OR "side effect" OR "adverse drug event" OR "adverse outcome")	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((pre-treatment OR "before treatment" OR baseline)) AND (evaluation OR assessment OR (physical examination) OR (laboratory)) AND ALL ("adverse drug reaction" OR "adverse reaction" OR "side-effect" OR "side effect" OR "adverse drug event" OR "adverse outcome")	(leprosy OR (Hansen disease) OR (Hansen's disease)) AND ((pre-treatment OR (before treatment) OR baseline)) AND (evaluation OR assessment OR (physical examination) OR (laboratory)) AND ((adverse drug reaction) OR (adverse reaction) OR (side-effect) OR (side effect) OR (adverse drug event) OR (adverse outcome))	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((pre-treatment OR "before treatment" OR baseline)) AND (evaluation OR assessment OR (physical examination) OR (laboratory)) AND ("adverse drug reaction" OR "adverse reaction" OR "side-effect" OR "side effect" OR "adverse drug event" OR "adverse outcome")
	Cost-effectiveness	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((pre-treatment OR "before treatment" OR baseline)) AND (evaluation OR assessment OR (physical	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((pre-treatment OR "before treatment" OR baseline))	(leprosy OR (Hansen disease) OR (Hansen's disease)) AND ((pre-treatment OR (before treatment) OR baseline))	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((pre-treatment OR "before treatment" OR baseline))

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
		examination) OR (laboratory)) AND (cost-effectiveness OR "cost benefit" OR "economic evaluation")	AND (evaluation OR assessment OR (physical examination) OR (laboratory)) AND ALL (cost-effectiveness OR "cost benefit" OR "economic evaluation")	AND (evaluation OR assessment OR (physical examination) OR (laboratory)) AND (cost-effectiveness OR (cost benefit) OR (economic evaluation))	AND (evaluation OR assessment OR (physical examination) OR (laboratory)) AND (cost-effectiveness OR "cost benefit" OR "economic evaluation")
Among patients with diagnosed PB/MB leprosy, what is the dose and duration of treatment?	Cure rate	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND (cure OR remission OR convalescence)	ALL (leprosy OR "Hansen's disease" OR "Hansen disease") AND ALL ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ALL ("alternative" OR "shorter course") AND ALL (cure OR remission OR convalescence)	(leprosy OR (Hansen's disease) OR (Hansen disease)) AND ((WHO-MDT) OR (WHO MDT) OR (multi-drug treatment) OR (multi-drug therapy) OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ((alternative) OR (shorter course)) AND (cure OR remission OR convalescence)	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND (cure OR remission OR convalescence)
	Clinical improvement	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND ("clinical improvement" OR improvement OR "patient-important outcomes" OR "patient-relevant	ALL (leprosy OR "Hansen's disease" OR "Hansen disease") AND ALL ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ALL ("alternative" OR "shorter course") AND ALL ("clinical improvement" OR	(leprosy OR (Hansen's disease) OR (Hansen disease)) AND ((WHO-MDT) OR (WHO MDT) OR (multi-drug treatment) OR (multi-drug therapy) OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ((alternative) OR (shorter course)) AND ((clinical improvement) OR	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND ("clinical improvement" OR

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
		outcomes" OR "lesion clearance" OR "lesion resolution")	improvement OR "patient-important outcomes" OR "patient-relevant outcomes" OR "lesion clearance" OR "lesion resolution")	improvement OR (patient-important outcomes) OR (patient-relevant outcomes) OR (lesion clearance) OR (lesion resolution))	improvement OR "patient-important outcomes" OR "patient-relevant outcomes" OR "lesion clearance" OR "lesion resolution")
	Infectivity	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND (infectivity OR transmission)	ALL (leprosy OR "Hansen's disease" OR "Hansen disease") AND ALL ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ALL ("alternative" OR "shorter course") AND ALL (infectivity OR transmission)	(leprosy OR (Hansen's disease) OR (Hansen disease)) AND ((WHO-MDT) OR (WHO MDT) OR (multi-drug treatment) OR (multi-drug therapy) OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ((alternative) OR (shorter course)) AND (infectivity OR transmission)	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND (infectivity OR transmission)
	Cost-effectiveness	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND (cost-effectiveness OR "cost effectiveness" OR cost-benefit OR "economic evaluation")	ALL (leprosy OR "Hansen's disease" OR "Hansen disease") AND ALL ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ALL ("alternative" OR "shorter course") AND ALL (cost-effectiveness OR "cost effectiveness" OR cost-	(leprosy OR (Hansen's disease) OR (Hansen disease)) AND ((WHO-MDT) OR (WHO MDT) OR (multi-drug treatment) OR (multi-drug therapy) OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ((alternative) OR (shorter course)) AND (cost-effectiveness OR (cost effectiveness) OR cost-	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND (cost-effectiveness OR "cost effectiveness" OR cost-

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
			benefit OR "economic evaluation")	benefit OR (economic evaluation))	benefit OR "economic evaluation")
	Treatment completion rate	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND ("treatment completion" OR "completion rate")	ALL (leprosy OR "Hansen's disease" OR "Hansen disease") AND ALL ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ALL ("alternative" OR "shorter course") AND ALL ("treatment completion" OR "completion rate")	(leprosy OR (Hansen's disease) OR (Hansen disease)) AND ((WHO-MDT) OR (WHO MDT) OR (multi-drug treatment) OR (multi-drug therapy) OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ((alternative) OR (shorter course)) AND ((treatment completion) OR (completion rate))	(leprosy OR "Hansen's disease" OR "Hansen disease") AND ("WHO-MDT" OR "WHO MDT" OR "multi-drug treatment" OR "multi-drug therapy" OR ((rifampicin OR rifampin) AND dapsone AND clofazimine) AND ("alternative" OR "shorter course") AND ("treatment completion" OR "completion rate")
Among patients with MB leprosy, can MDT be extended to 24 months versus 12 months and what are the indications of extension?	Cure	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (cure OR remission OR convalescence)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((therapy OR treatment) AND (duration OR period OR schedule) AND ALL (extension OR prolongation OR protraction OR protracted OR extended) AND ALL (cure OR remission OR convalescence)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (cure OR remission OR convalescence)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (cure OR remission OR convalescence)
	Clinical improvement	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((therapy OR treatment) AND	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
		OR prolongation OR protraction OR protracted OR extended) AND (“clinical improvement” OR improvement OR “patient-important outcomes” OR “patient-relevant outcomes” OR “lesion clearance” OR “lesion resolution”)	(duration OR period OR schedule) AND ALL (extension OR prolongation OR protraction OR protracted OR extended) AND ALL (“clinical improvement” OR improvement OR “patient-important outcomes” OR “patient-relevant outcomes” OR “lesion clearance” OR “lesion resolution”)	(duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND ((clinical improvement) OR improvement OR (patient-important outcomes) OR (patient-relevant outcomes) OR (lesion clearance) OR (lesion resolution))	(duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (“clinical improvement” OR improvement OR “patient-important outcomes” OR “patient-relevant outcomes” OR “lesion clearance” OR “lesion resolution”)
	Decreased infectivity or transmission	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (infectivity OR transmission)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((therapy OR treatment) AND (duration OR period OR schedule) AND ALL (extension OR prolongation OR protraction OR protracted OR extended) AND ALL (infectivity OR transmission)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (infectivity OR transmission)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (infectivity OR transmission)
	Treatment completion rate	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((therapy OR treatment) AND (duration OR period OR schedule) AND ALL (extension OR prolongation OR protraction OR	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
		(“treatment completion” OR “completion rate”)	protracted OR extended) AND ALL (“treatment completion” OR “completion rate”)	OR extended) AND ((treatment completion) OR (completion rate))	OR extended) AND (“treatment completion” OR “completion rate”)
	Cost-effectiveness	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((therapy OR treatment) AND (duration OR period OR schedule) AND ALL (extension OR prolongation OR protraction OR protracted OR extended) AND ALL (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (cost-effectiveness OR (cost effectiveness) OR cost-benefit OR (economic evaluation))	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((therapy OR treatment) AND (duration OR period OR schedule) AND (extension OR prolongation OR protraction OR protracted OR extended) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)
What is the recommended monitoring interval post treatment?	Better and earlier detection of relapse	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (relapse OR recurrence OR recrudescence)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND ALL (relapse OR recurrence OR recrudescence)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR (clinic visit) OR consultation OR outpatient) AND (interval OR schedule)) AND (relapse OR recurrence OR recrudescence)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (relapse OR recurrence OR recrudescence)
	Better and earlier detection	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL	(leprosy OR "Hansen disease" OR "Hansen's disease") AND	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
	of leprae reactions	consultation OR outpatient) AND (interval OR schedule)) AND (“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 2 reaction” OR “type 1 reaction” OR “reversal reaction”)	((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND ALL (“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 2 reaction” OR “type 1 reaction” OR “reversal reaction”)	((monitoring OR follow-up OR (clinic visit) OR consultation OR outpatient) AND (interval OR schedule)) AND ((leprae reaction) OR (erythema nodosum leprosum) OR ENL OR (type 2 reaction) OR (type 1 reaction) OR (reversal reaction))	OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 2 reaction” OR “type 1 reaction” OR “reversal reaction”)
	Better and earlier detection of adverse drug events and drug complications	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (“adverse drug event” OR “adverse drug reaction” OR “side-effect” OR “side effect” OR “drug complication” OR “toxicity”)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND ALL (“adverse drug event” OR “adverse drug reaction” OR “side-effect” OR “side effect” OR “drug complication” OR “toxicity”)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR (clinic visit) OR consultation OR outpatient) AND (interval OR schedule)) AND ((adverse drug event) OR (adverse drug reaction) OR (side-effect) OR (side effect) OR (drug complication) OR (toxicity))	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (“adverse drug event” OR “adverse drug reaction” OR “side-effect” OR “side effect” OR “drug complication” OR “toxicity”)
	Better and earlier detection of drug-resistant leprosy	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (“drug resistance” OR “drug-resistant”)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule))	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR (clinic visit) OR consultation OR outpatient) AND (interval OR schedule)) AND ((drug	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (“drug

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
			AND ALL (“drug resistance” OR “drug-resistant”)	resistance) OR (drug-resistant))	resistance” OR “drug-resistant”)
	Earlier detection of nerve function impairment	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (“nerve function impairment” OR disability OR neuritis)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND ALL (“nerve function impairment” OR disability OR neuritis)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR (clinic visit) OR consultation OR outpatient) AND (interval OR schedule)) AND ((nerve function impairment) OR disability OR neuritis)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((monitoring OR follow-up OR “clinic visit” OR consultation OR outpatient) AND (interval OR schedule)) AND (“nerve function impairment” OR disability OR neuritis)
What is the treatment of complicated/refractory cases of lepra reactions?	Better cure rate	(“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND (alternative OR “steroid sparing” OR “steroid-sparing”) AND (corticosteroid OR steroid) AND (cure OR remission OR convalescence)	ALL (“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND ALL (alternative OR “steroid sparing” OR “steroid-sparing”) AND ALL (corticosteroid OR steroid) AND ALL (cure OR remission OR convalescence)	((leprae reaction) OR (erythema nodosum leprosum) OR ENL OR (type 1 reaction) OR (type 2 reaction) OR (reversal reaction)) AND (alternative OR (steroid sparing) OR (steroid-sparing)) AND (corticosteroid OR steroid) AND (cure OR remission OR convalescence)	(“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND (alternative OR “steroid sparing” OR “steroid-sparing”) AND (corticosteroid OR steroid) AND (cure OR remission OR convalescence)
	Low relapse rate	(“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND (alternative OR “steroid sparing” OR “steroid-sparing”) AND	ALL (“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND ALL	((leprae reaction) OR (erythema nodosum leprosum) OR ENL OR (type 1 reaction) OR (type 2 reaction) OR (reversal reaction)) AND (alternative	(“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND (alternative

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
		(corticosteroid OR steroid) AND (relapse OR recurrence OR recrudescence)	(alternative OR "steroid sparing" OR "steroid-sparing") AND ALL (corticosteroid OR steroid) AND ALL (relapse OR recurrence OR recrudescence)	OR (steroid sparing) OR (steroid-sparing)) AND (corticosteroid OR steroid) AND (relapse OR recurrence OR recrudescence)	OR "steroid sparing" OR "steroid-sparing") AND (corticosteroid OR steroid) AND (relapse OR recurrence OR recrudescence)
	Lower rate of adverse drug events	("leprae reaction" OR "erythema nodosum leprosum" OR ENL OR "type 1 reaction" OR "type 2 reaction" OR "reversal reaction") AND (alternative OR "steroid sparing" OR "steroid-sparing") AND (corticosteroid OR steroid) AND ("adverse drug event" OR "adverse drug reaction" OR "side-effect" OR "side effect" OR "drug complication" OR "toxicity")	ALL ("leprae reaction" OR "erythema nodosum leprosum" OR ENL OR "type 1 reaction" OR "type 2 reaction" OR "reversal reaction") AND ALL (alternative OR "steroid sparing" OR "steroid-sparing") AND ALL (corticosteroid OR steroid) AND ALL ("adverse drug event" OR "adverse drug reaction" OR "side-effect" OR "side effect" OR "drug complication" OR "toxicity")	((leprae reaction) OR (erythema nodosum leprosum) OR ENL OR (type 1 reaction) OR (type 2 reaction) OR (reversal reaction)) AND (alternative OR (steroid sparing) OR (steroid-sparing)) AND (corticosteroid OR steroid) AND ((adverse drug event) OR (adverse drug reaction) OR (side-effect) OR (side effect) OR (drug complication) OR (toxicity))	("leprae reaction" OR "erythema nodosum leprosum" OR ENL OR "type 1 reaction" OR "type 2 reaction" OR "reversal reaction") AND (alternative OR "steroid sparing" OR "steroid-sparing") AND (corticosteroid OR steroid) AND ("adverse drug event" OR "adverse drug reaction" OR "side-effect" OR "side effect" OR "drug complication" OR "toxicity")
	Prevention of nerve function impairment	("leprae reaction" OR "erythema nodosum leprosum" OR ENL OR "type 1 reaction" OR "type 2 reaction" OR "reversal reaction") AND (alternative OR "steroid sparing" OR "steroid-sparing") AND (corticosteroid OR steroid) AND ("nerve function impairment" OR disability OR neuritis)	ALL ("leprae reaction" OR "erythema nodosum leprosum" OR ENL OR "type 1 reaction" OR "type 2 reaction" OR "reversal reaction") AND ALL (alternative OR "steroid sparing" OR "steroid-sparing") AND ALL (corticosteroid OR steroid)	((leprae reaction) OR (erythema nodosum leprosum) OR ENL OR (type 1 reaction) OR (type 2 reaction) OR (reversal reaction)) AND (alternative OR (steroid sparing) OR (steroid-sparing)) AND (corticosteroid OR steroid) AND ((nerve function	("leprae reaction" OR "erythema nodosum leprosum" OR ENL OR "type 1 reaction" OR "type 2 reaction" OR "reversal reaction") AND (alternative OR "steroid sparing" OR "steroid-sparing") AND (corticosteroid OR steroid) AND ("nerve function

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
			AND ALL (“nerve function impairment” OR disability OR neuritis)	impairment) OR disability OR neuritis)	impairment” OR disability OR neuritis)
	Cost-effectiveness	(“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND (alternative OR “steroid sparing” OR “steroid-sparing”) AND (corticosteroid OR steroid) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	ALL (“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND ALL (alternative OR “steroid sparing” OR “steroid-sparing”) AND ALL (corticosteroid OR steroid) AND ALL (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	((leprae reaction) OR (erythema nodosum leprosum) OR ENL OR (type 1 reaction) OR (type 2 reaction) OR (reversal reaction)) AND (alternative OR (steroid sparing) OR (steroid-sparing)) AND (corticosteroid OR steroid) AND (cost-effectiveness OR (cost effectiveness) OR cost-benefit OR (economic evaluation))	(“leprae reaction” OR “erythema nodosum leprosum” OR ENL OR “type 1 reaction” OR “type 2 reaction” OR “reversal reaction”) AND (alternative OR “steroid sparing” OR “steroid-sparing”) AND (corticosteroid OR steroid) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)
Should contacts exposed to a patient with leprosy be offered chemoprophylaxis vs. observation alone?	Lower infectivity and transmission rate	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (observation OR “non-pharmacological”) AND (infectivity OR transmission)	ALL (Leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (contacts OR exposure) AND ALL (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND ALL (observation OR “non-pharmacological”) AND ALL (infectivity OR transmission)	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR (post-exposure prophylaxis) OR prophylaxis) AND (observation OR (non-pharmacological)) AND (infectivity OR transmission)	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (observation OR “non-pharmacological”) AND (infectivity OR transmission)

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
	Lower drug resistance	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (observation OR “non-pharmacological”) AND (“drug resistance” OR “drug-resistant”)	ALL (Leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (contacts OR exposure) AND ALL (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND ALL (observation OR “non-pharmacological”) AND ALL (“drug resistance” OR “drug-resistant”)	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR (post-exposure prophylaxis) OR prophylaxis) AND (observation OR (non-pharmacological)) AND ((drug resistance) OR (drug-resistant))	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (observation OR “non-pharmacological”) AND (“drug resistance” OR “drug-resistant”)
	Cost-effectiveness	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (observation OR “non-pharmacological”) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	ALL (Leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (contacts OR exposure) AND ALL (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND ALL (observation OR “non-pharmacological”) AND ALL (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR (post-exposure prophylaxis) OR prophylaxis) AND (observation OR (non-pharmacological)) AND (cost-effectiveness OR (cost effectiveness) OR cost-benefit OR (economic evaluation))	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (observation OR “non-pharmacological”) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)
What is effective and safe chemoprophylaxis among contacts of patients with	Lower infectivity and	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR	ALL (Leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (contacts OR exposure)	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
leprosy and high-risk populations?	transmission rate	rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (infectivity OR transmission)	AND ALL (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND ALL (infectivity OR transmission)	(chemoprophylaxis OR rifampicin OR rifampin OR (post-exposure prophylaxis) OR prophylaxis) AND (infectivity OR transmission)	(chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (infectivity OR transmission)
	Lower drug resistance	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (“drug resistance” OR “drug-resistant”)	ALL (Leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (contacts OR exposure) AND ALL (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND ALL (“drug resistance” OR “drug-resistant”)	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR (post-exposure prophylaxis) OR prophylaxis) AND ((drug resistance) OR (drug-resistant))	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (“drug resistance” OR “drug-resistant”)
	Cost-effectiveness	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	ALL (Leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (contacts OR exposure) AND ALL (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND ALL (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR (post-exposure prophylaxis) OR prophylaxis) AND (cost-effectiveness OR (cost effectiveness) OR cost-benefit OR (economic evaluation))	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
	Lower incidence of adverse drug events	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (“adverse drug event” OR “adverse drug reaction” OR “side-effect” OR “side effect” OR “drug complication” OR “toxicity”)	ALL (Leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (contacts OR exposure) AND ALL (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND ALL (“adverse drug event” OR “adverse drug reaction” OR “side-effect” OR “side effect” OR “drug complication” OR “toxicity”)	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR (post-exposure prophylaxis) OR prophylaxis) AND ((adverse drug event) OR (adverse drug reaction) OR (side-effect) OR (side effect) OR (drug complication) OR (toxicity))	(Leprosy OR "Hansen disease" OR "Hansen's disease") AND (contacts OR exposure) AND (chemoprophylaxis OR rifampicin OR rifampin OR “post-exposure prophylaxis” OR prophylaxis) AND (“adverse drug event” OR “adverse drug reaction” OR “side-effect” OR “side effect” OR “drug complication” OR “toxicity”)
How is drug resistance evaluated among leprosy patients?	Sensitivity Specificity Positive predictive value Negative predictive value	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (signs OR symptoms OR diagnosis OR assessment OR evaluation OR examination) AND (sensitivity OR specificity OR “predictive value”)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (“drug-resistant” OR “drug resistance”) AND ALL (signs OR symptoms OR diagnosis OR assessment OR evaluation OR examination) AND ALL (sensitivity OR specificity OR “predictive value”)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((drug-resistant) OR (drug resistance)) AND (signs OR symptoms OR diagnosis OR assessment OR evaluation OR examination) AND (sensitivity OR specificity OR (predictive value))	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (signs OR symptoms OR diagnosis OR assessment OR evaluation OR examination) AND (sensitivity OR specificity OR “predictive value”)
	Cost-effectiveness	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (signs OR symptoms OR diagnosis OR assessment OR evaluation OR examination) AND (cost-effectiveness	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (“drug-resistant” OR “drug resistance”) AND ALL (signs OR symptoms OR diagnosis OR assessment OR	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((drug-resistant) OR (drug resistance)) AND (signs OR symptoms OR diagnosis OR assessment	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (signs OR symptoms OR diagnosis OR assessment OR

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
		OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	evaluation OR examination) AND ALL (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	OR evaluation OR examination) AND (cost-effectiveness OR (cost effectiveness) OR cost-benefit OR (economic evaluation))	evaluation OR examination) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)
What is the treatment regimen for drug-resistant leprosy?	Cure rate	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR (“drug therapy” AND (regimen or schedule”)) AND (cure OR remission OR convalescence)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (“drug-resistant” OR “drug resistance”) AND ALL (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR ALL (“drug therapy” AND ALL (regimen or schedule”)) AND ALL (cure OR remission OR convalescence)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((drug-resistant) OR (drug resistance)) AND ((treatment regimen) OR (pharmacological treatment) OR (pharmacological therapy) OR (treatment schedule) OR ((drug therapy) AND (regimen or schedule))) AND (cure OR remission OR convalescence)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR (“drug therapy” AND (regimen or schedule”)) AND (cure OR remission OR convalescence)
	Clinical improvement	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR (“drug therapy” AND (regimen or schedule”)) AND (“clinical improvement” OR improvement OR “patient-important outcomes” OR	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (“drug-resistant” OR “drug resistance”) AND ALL (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR ALL (“drug therapy”	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((drug-resistant) OR (drug resistance)) AND ((treatment regimen) OR (pharmacological treatment) OR (pharmacological therapy) OR (treatment schedule) OR ((drug therapy) AND	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR (“drug therapy” AND

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
		“patient-relevant outcomes” OR “lesion clearance” OR “lesion resolution”)	AND ALL (regimen or schedule”)) AND ALL (“clinical improvement” OR improvement OR “patient-important outcomes” OR “patient-relevant outcomes” OR “lesion clearance” OR “lesion resolution”)	(regimen or schedule))) AND ((clinical improvement) OR improvement OR (patient-important outcomes) OR (patient-relevant outcomes) OR (lesion clearance) OR (lesion resolution))	(regimen or schedule”)) AND (“clinical improvement” OR improvement OR “patient-important outcomes” OR “patient-relevant outcomes” OR “lesion clearance” OR “lesion resolution”)
	Cost-effectiveness	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR (“drug therapy” AND (regimen or schedule”)) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (“drug-resistant” OR “drug resistance”) AND ALL (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR ALL (“drug therapy” AND ALL (regimen or schedule”)) AND ALL (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((drug-resistant) OR (drug resistance)) AND ((treatment regimen) OR (pharmacological treatment) OR (pharmacological therapy) OR (treatment schedule) OR ((drug therapy) AND (regimen or schedule))) AND (cost-effectiveness OR (cost effectiveness) OR cost-benefit OR (economic evaluation))	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR “treatment schedule” OR (“drug therapy” AND (regimen or schedule”)) AND (cost-effectiveness OR “cost effectiveness” OR cost-benefit OR “economic evaluation”)
	Treatment completion rate	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (“treatment regimen” OR “pharmacological treatment” OR “pharmacological therapy” OR	ALL (leprosy OR "Hansen disease" OR "Hansen's disease") AND ALL (“drug-resistant” OR “drug resistance”) AND ALL (“treatment regimen” OR	(leprosy OR "Hansen disease" OR "Hansen's disease") AND ((drug-resistant) OR (drug resistance)) AND ((treatment regimen) OR	(leprosy OR "Hansen disease" OR "Hansen's disease") AND (“drug-resistant” OR “drug resistance”) AND (“treatment regimen” OR

CPG QUESTION	OUTCOMES	PUBMED	SCOPUS®	DOAJ	GOOGLE SCHOLAR (First 1000 results only)
		"treatment schedule" OR ("drug therapy" AND (regimen or schedule")) AND ("treatment completion" OR "completion rate")	"pharmacological treatment" OR "pharmacological therapy" OR "treatment schedule" OR ALL ("drug therapy" AND ALL (regimen or schedule")) AND ALL ("treatment completion" OR "completion rate")	(pharmacological treatment) OR (pharmacological therapy) OR (treatment schedule) OR ((drug therapy) AND (regimen or schedule))) AND ((treatment completion) OR (completion rate))	"pharmacological treatment" OR "pharmacological therapy" OR "treatment schedule" OR ("drug therapy" AND (regimen or schedule")) AND ("treatment completion" OR "completion rate")

DISEASE PREVENTION AND CONTROL BUREAU
INFECTIOUS DISEASE OFFICE
NATIONAL LEPROSY CONTROL PROGRAM

2021