World Health Organization

Anti-Microbial Resistance in Leprosy

Report of the virtual consultation

New Delhi, India

14-17 June 2021

Anti-microbial resistance surveillance in leprosy: Report of the virtual meeting

Document no.: SEA/GLP/7

Suggested citation. Anti-microbial resistance surveillance in leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia; 2021. Licence: CC BY-NC-SA 3.0 IGO.

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

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Annexes

1. Inaugural session

The virtual meeting took place from 14-17 June 2021, for 2.5 hours (18:30-21:00 hours Indian Standard Time). Participants included national leprosy programme (NLP) managers, anti-microbial resistance (AMR) focal points partners, representatives from nongovernmental organizations (NGOs), experts and WHO staff from HQ, regional offices, the Global Leprosy Programme (GLP) and country offices.

1.1. Welcome remarks

Dr Erwin Cooreman, Team Leader, GLP welcomed all participants on behalf of the World Health Organization (WHO). This virtual consultation brings together two main communities, both from countries and at the international level: leprosy programme managers and partners; as well as persons in charge of AMR programmes.

The previous time that WHO convened a (face-to-face) meeting on the same subject was in October 2016 (Kathmandu, Nepal) and before that almost every two or three years. Since that time, several innovations have come into place; but progress has been much less than desired. This meeting may look into ways to move the agenda of addressing AMR in leprosy forward.

The main new opportunity that has occurred is the significant increased attention for AMR globally, in WHO as well as in countries. This was prompted by serious threats in several infectious diseases caused by wide and inappropriate use of antibiotics. Based on available data, such threat is not perceived in leprosy, which fortunately can be benefit from its robust first-line regimen in the form of multidrug therapy and the controlled dispensation of leprosy treatment. This may be a reason also why AMR in leprosy is typically treated as having a lower priority.

In WHO, AMR has been elevated to a cross-cutting, top priority. A division was created in HQ which is headed by an Assistant Director General. Regional Offices are also streamlining AMR as a horizontal platform to support multiple disease control programmes. In the South-East Asia Region, both control of neglected tropical diseases (NTDs) – which include leprosy – and AMR are flagship priorities.

1.2. Inaugural address

In her inaugural address, Dr Poonam Khetrapal Singh, Regional Director, WHO South-East Asia Region, highlighted the importance of this meeting for making advances – in spite of COVID-19 related impediments – on several key policy frameworks including the global NTD Roadmap, the Global Leprosy Strategy 2021–2030, and the Global Action Plan on AMR. This meeting also intersects with two of the Region's eight flagship programmes: eliminating NTDs and other diseases on the verge of elimination; and strengthening national capacity to prevent and combat AMR.

She highlighted several key achievements in global leprosy control: a significant reduction in case detection compared to ten years ago, a reduction of new cases with visible deformities at the time of diagnosis to less than 5%, and an important reduction in children diagnosed with leprosy.

The Global Leprosy Strategy 2021–2030 includes a paradigm shift, with a focus on moving towards interruption of transmission and elimination of disease. Achieving zero leprosy will not be easy and requires to overcome existing barriers and anticipate emerging challenges. One such challenge is AMR.

She mentioned the global sentinel network for monitoring AMR in leprosy to which more countries have expressed interest to become part of. Though, resistance to leprosy drugs appears relatively low, this should not be taken for granted and all efforts have to be made to prevent amplification. As the Global Leprosy Strategy highlights, drug-susceptibility patterns must be assessed globally and resistance among both new and retreatment cases must be monitored.

The Regional Director conveyed three messages that are applicable to all stakeholders, whatever a country's current surveillance status.

First, action is everything. Policy frameworks themselves will not drive results unless they are programmatically implemented. She welcomed the development of actional templates, with the aim of providing a clear end-to-end process for surveillance activities and laboratory processes in sentinel centres and reference laboratories.

Second, integration is vital. AMR is a significant threat to health and development globally, and most countries are taking multisectoral action.

Third, partnerships are key. Ample expertise is available in research laboratories across the world, as well as in facilities managed by nongovernmental organizations.

She further remarked that it is by working together, and harnessing all resources at our disposal, that we can achieve the ambitious vision of the Global NTD Roadmap and Global Leprosy Strategy and contribute towards the full implementation of the Global Action Plan on AMR.

1.3. Objectives and expected outcomes

The general objective of the meeting was to contribute to improving surveillance for resistance to antimicrobial drugs used in leprosy.

The specific objectives were:

- To review the status of anti-microbial resistance (AMR) surveillance including inclusion in national AMR plans (where applicable) and magnitude of AMR in leprosy;
- To review and confirm current technical guidance in light of any recent evidence;
- To outline a template for roll-out of AMR surveillance in leprosy endemic countries in line with technical guidance;

- To explore development of a network of reference laboratories and experts to support countries;
- To discuss alternate regimens used in treating patients with *M. leprae* strains resistant to multidrug therapy (MDT) and follow-up actions.

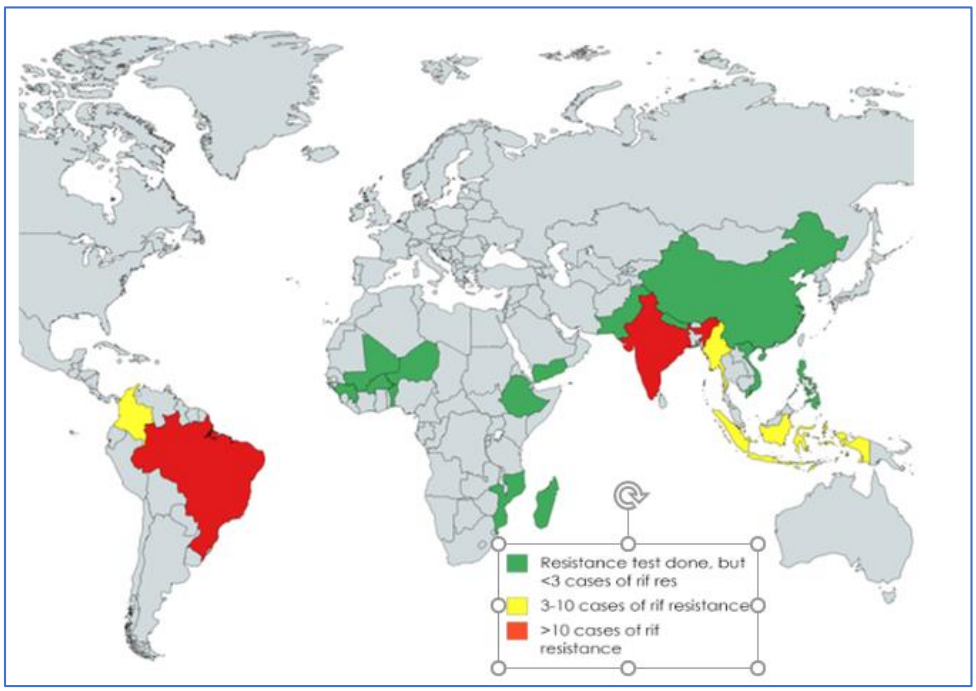
The expected outcomes were:

- ✓ Status of AMR surveillance (including national AMR plans or leprosy AMR plans) and extent of AMR problem in leprosy programmes documented;
- ✓ Confirmation of current technical guidance and advice on any new tools for AMR in leprosy;
- ✓ Draft Template for roll-out of AMR surveillance in leprosy agreed;
- ✓ New leprosy programmes/countries identified interested in developing AMR surveillance for leprosy need for strengthening of existing network identified;
- ✓ List of reference laboratories, experts for potential linkage with designated national laboratories updated.

2. Current status on AMR in countries

Data on AMR surveillance from countries were received through sentinel centres between 2009 and 2015. Data from 19 countries indicated that 5.1% of the tests on relapse patients tested were positive for rifampicin while 2% were positive in new cases (Figure 1). Brazil and India reported more than 10 cases with rifampicin resistance between 2009 and 2015

Fig. 1: ***Map indicating countries as part of sentinel network and test undertaken during 2009-2015***



Resistance to dapsone was observed in greater proportions both in relapses and new cases from the data received from 19 countries covering the period 2009-2015. Resistance to all three drugs are presented in Table 1.

Table 1: *AMR to leprosy drugs, 2009-2015*

Drug tested	Relapse		New cases	
	Number of samples tested	Number (proportion) of resistant samples	Number of samples tested	Number (proportion) of resistant samples
Rifampicin	1,123	57 (5.1%)	802	16 (2.0%)
Dapsone	877	35 (3.9%)	762	52 (6.8%)
Ofloxacin	822	16 (1.9%)	684	13 (1.9%)

From 2016 onwards data on AMR surveillance was collected through annual leprosy statistics. AMR tests were conducted on 1658 retreatment patients. Dapsone resistance was found in more patients. Resistance to more than one drug was found in 4.2% of retreatment cases. Resistance levels in new patients were lower than in retreatment cases for all the three drugs (Table 2).

Table 2: *AMR to leprosy drugs, 2016-2019*

Drug tested	Retreatment cases		New cases	
	Number of samples tested	Number (proportion) of resistant samples	Number of samples tested	Number (proportion) of resistant samples
Rifampicin	1,658	51 (3.1%)	1,665	19 (1.1%)
Dapsone		37 (2.2%)		42 (2.5%)
Ofloxacin		10 (0.6%)		9 (0.5%)
2 or more drugs		70 (4.2%)		6 (0.4%)

3. AMR surveillance in leprosy: current guidance to leprosy programmes

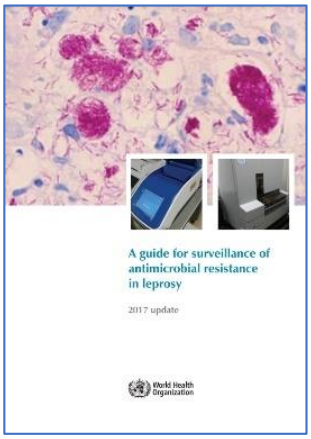
Dr Erwin Cooreman highlighted that in the Global Leprosy Strategy 2021–2030, 'anti-microbial resistance' is featured three times: it is identified as one of the major challenges; monitoring AMR is a key component under the Strategy's first pillar ("Implement integrated, country-owned zero leprosy roadmaps in all endemic countries"); and an indicator on AMR is included in the monitoring framework.

He recalled that drug resistance was rampant in the 1970ies, when dapsone monotherapy was the mainstay of leprosy treatment. The introduction of MDT could reverse this and since the 1980ies, rifampicin has been the backbone of leprosy treatment. Rifampicin resistance does occur as well as

resistance to ofloxacin (second-line drug); resistance to the latter drug likely emerged due to the widespread use of quinolones for indications other than leprosy.

He gave an overview of activities undertaken at the international level to address drug resistance surveillance.

He recapitulated the key elements described in the *Guide for surveillance of antimicrobial resistance in leprosy (2017 Update)*.



The objectives of the surveillance system are: (i) To determine primarily resistance to rifampicin among new and retreatment cases (mono- or poly-resistance); (ii) to monitor resistance rates over time; and (iii) based on disaggregated data, identify associations, e.g. with sex, age or geographical location.

The aim is to assess all retreatment cases and 10% of new cases for drug resistance. The guide describes how collection and testing centres can be identified. For new cases, the system can be designed as (one time or periodic) cross-sectional surveys, through sentinel sites or in a continuous fashion. Obtaining consent from the patient is required. Specific records are to be maintained at collection centres, in testing laboratories and by NLP through a National Leprosy AMR Register.

He elaborated the different steps that are described in the technical guidance document and that encompass topics mentioned below. Where relevant, he highlighted the responsibilities of each actor.

- Setting up or expanding a surveillance system at the national level;
- Selection of a laboratory for quality control
- Identification of sample collection centres
- Calculating the sample size (for new cases)
- Sample collection
- Laboratory test
- Recording of information

He referred to the annexes included in the Guide which includes model examples for different types of forms and registers.

He ended his presentation with linking the guidance with the agenda of this meeting.

4. Recent advances in the diagnosis of AMR to anti-leprosy drugs

This topic was presented by Professor Emmanuelle Cambau of the National Reference Centre for Mycobacteria and Drug Resistance, Paris, France.

She highlighted the change in leprosy treatment as it occurred throughout the years. MDT was mainly introduced as an answer to resistance to anti-leprosy drugs when used as monotherapy. Till date, MDT has proven to be robust to minimize drug resistance.

There are two main ways of assessing drug resistance: phenotypic and genotypic. The phenotypic assessment is performed through inoculation of the mouse footpad, a technique which is still performed in only few countries.

Molecular detection of resistance focus on detecting mutations that are associated with resistance. There are three main approaches in this: (i) DNA extraction, PCR and Sanger sequencing; (ii) line probe assay with a commercial kit; or (iii) whole genome sequencing.

There is a large (though not complete) overlap between genotype and phenotype: all *M. leprae* resistant strains identified through the mouse footpad were genotypically confirmed but not all mutations described in the *M. leprae* genome confer resistance in the mouse footpad test. Not all mutations conferring resistance lead to clinical failure (due to the use of multiple drugs in MDT). Not all strains with resistance in the mouse footpad test harbor mutations. Treatment failure or relapse is not always due to resistance.

A new development is the automated matching of mutations detected with those known to confer resistance to anti-leprosy drugs. The tool is called "HARP" (Hansen's disease Anti-microbial Resistance Profiles) and constitutes a database of structural impacts of systematic missense mutations in drug targets of *M. leprae*.

A second innovation is Deeplex Myc-Lep (Genoscreen), which is a kit for amplicon sequencing using next-generation sequencing. From DNA contained in the skin smears or biopsy it can amplify in a multiplex specific format nine genes involved in resistance as well as 18 other genomic markers specific of the *M. leprae* strain used for comparing strains.

She made the following conclusions:

- AMR detection in leprosy can be done through molecular analysis and mouse footpad testing;
- New mechanisms or new mutations are and will be detected, hence the need for further research and exchange of information;
- Clinical information should be kept together with the molecular one to evaluate of the impact of resistance.

5. Integrated anti-microbial resistance surveillance

5.1. Global Anti-microbial Resistance and Use Surveillance System

Dr Eremin Sergey, Medical Officer, WHO-HQ, presented the Global Anti-microbial Resistance and Use Surveillance System (GLASS). This system provides a standardized approach to the collection, analysis, interpretation and sharing of data by countries and seeks to actively support capacity building and monitoring of the status of national surveillance systems.

The objective of GLASS is to foster national AMR and antimicrobial consumption and use (AMC/AMU) surveillance systems through harmonized global standards to: (i) monitor AMR and AMC/AMU trends; (ii) detect emerging resistance; (iii) identify patterns of use of antimicrobials; and (iv) inform estimates of extent of AMR.

The following steps have been taken as part of global AMR surveillance:

- 2014: status report on AMR;
- 2015: development of global standards for surveillance;
- 2016: establishment of a global surveillance system;
- 2017: reporting and data collection;
- 2019: development of AMC and focused surveillance activities; undertake studies and surveys;
- 2020: revision of GLASS;
- 2021: Third high level technical consultation and meeting on surveillance of anti-microbial resistance and use for concerted actions.

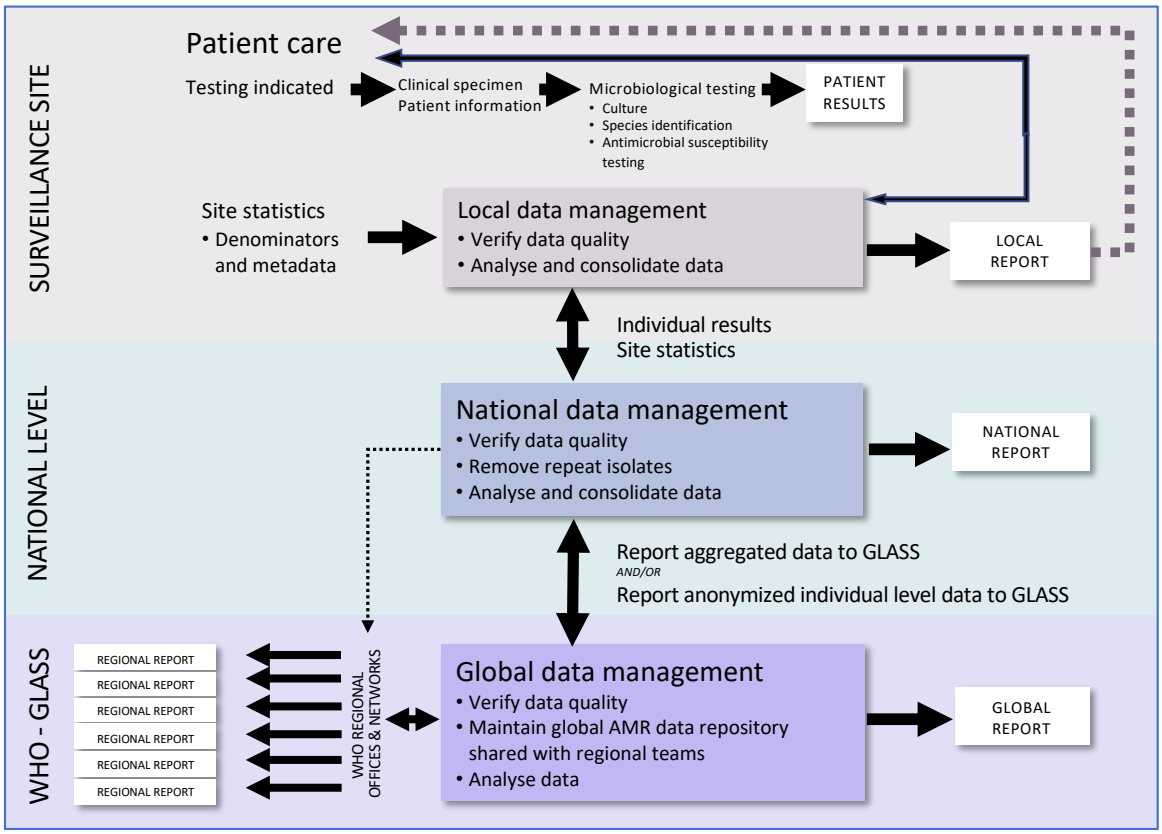
The current GLASS environment consists of: (i) routine data surveillance which includes anti-microbial resistance surveillance (GLASS-AMR) and anti-microbial consumption surveillance (GLASS-AMC); (ii) reporting (GLASS-EAR); (iii) focused surveillance which includes enhanced gonococcal anti-microbial surveillance programme (EGASP) and *Candida* spp. AMR surveillance (GLASS-Fungi); (iv) survey and studies which includes one health AMR surveillance (One Health), point prevalence survey methodology for antibiotic use in hospital and GLASS methodology for estimating attributable mortality due to AMR.

GLASS-AMR surveillance approach. The population coverage of GLASS-AMR surveillance is patients seeking care in healthcare facilities for whom clinical samples are collected for routine microbiological investigations. Data for AMR are collected through a surveillance system which gathers results from susceptibility testing for targeted human bacterial pathogens isolated from clinical specimens routinely sent to laboratories for diagnostic purposes. Together with patients' microbiological results (species identification and AST), countries are also invited to report demographic and epidemiological variables, either in aggregated or individual-level format.

GLASS covers common bacterial infections associated with facility- as well as community-acquired infections. They are selected based on public health burden (especially in case of resistance). Some pathogens (e.g. *Salmonella* spp., *Shigella* spp.) were selected because of the significant morbidity and/or mortality they cause in low- and middle-income countries. Some pathogens affect vulnerable populations (e.g. *H. influenzae* which can cause severe infections in children). Several of the GLASS target pathogens are included in the *WHO Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics (2017)*. Local and national surveillance may include other organisms and antimicrobial agents that should be addressed properly. The typical specimen types are blood, cerebro-spinal fluid, urine, stool and swabs from the lower respiratory track, urethra, cervix, rectum and pharynx.

Figure 2 shows the flow of data through the GLASS network.

Fig. 2: ***GLASS-AMR data flow scheme***



The **GLASS-AMR manual** summarizes the WHO methodology for a global programme on surveillance of AMC, and guides countries on how to use the GLASS-AMC template to prepare the national AMC surveillance data; produce national AMC data files to foster AMC data analysis at national level; and facilitate the preparation of the AMC national data for submission to GLASS-AMC.

The system includes:

- An option for submission of anonymized individual patient-level data providing additional opportunities for AMR surveillance data validation and analysis;
- An option for submission of data generated by molecular AMR diagnostics to complement phenotypic AMR diagnostics data and improve understanding of the underlying mechanisms responsible for resistance.
- An approach to assessing and improving the validity and representativeness of surveillance data to guide interpretation of the data reported by countries and guide and monitor development of the national surveillance systems and their quality.

The SDG framework includes, under SDG 3 (ensure healthy lives and promote the well-being for all at all ages), target 3.d (strengthen the capacity of all countries for early warning, risk reduction and management of national and global health risk) an indicator on AMR.

In order to move forward while maintaining the GLASS objectives, global and national surveillance systems should be fostered and AMR and AMU should be globally monitored:

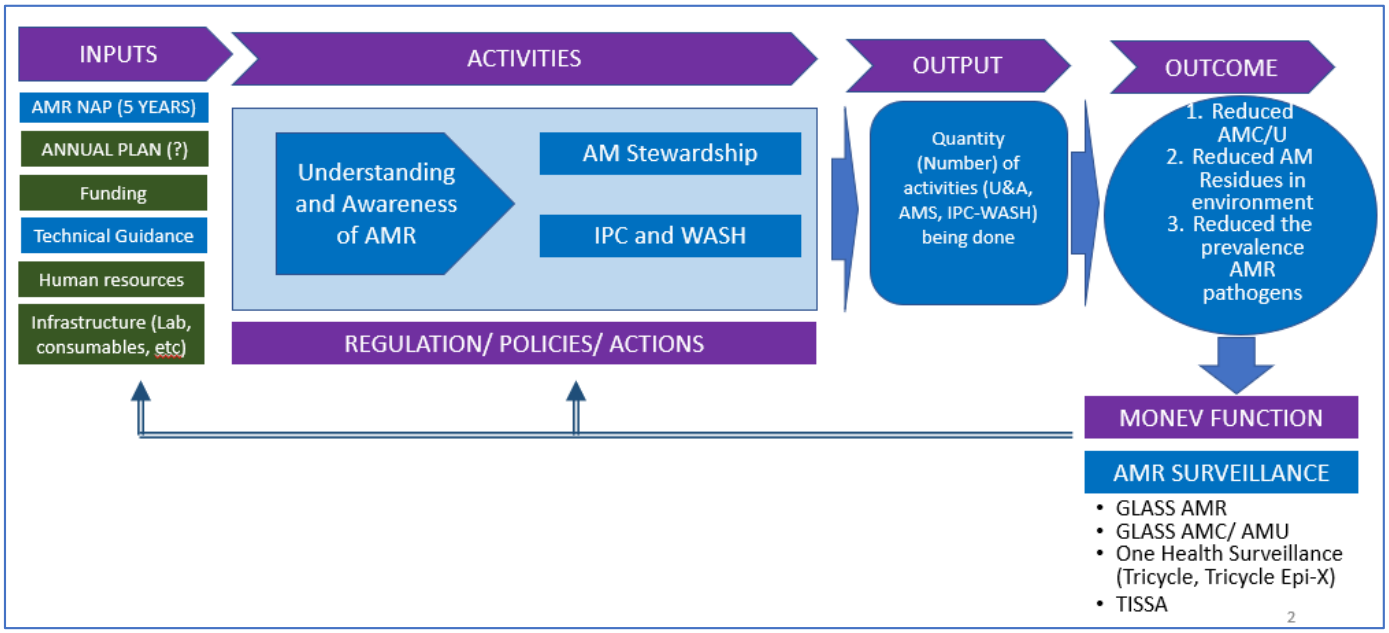
- Two-pronged approach for surveillance: (i) Continue data collection based on routine clinical sampling of patients; and (ii) application of complementary strategies (e.g. surveys) to improve quality, completeness and representativeness of data.
- Assessment of impact on human health of selected types of AMR causing bloodstream infections.
- Application of new technologies, including new and more agile IT tools and incorporation of molecular markers of AMR to the reporting.
- Fostering the use of AMR/AMU data for policy making, and integration with other health information and data from other sectors.
- Collaborating with the Food and Agriculture Organization and the World Organization for Animal Health for the development of a *Tripartite Integrated Surveillance System*.

5.2. Regional (SEARO)

Dr Siswanto, Senior Adviser for Science, Research and Innovation, presented the AMR Surveillance System for Better Policies and Actions.

National AMR plans are prepared to reduce antimicrobial consumption or use and reduction in prevalence of AMR pathogens. The activities include understanding and awareness of AMR. The structure of activities involved in developing AMR surveillance is presented in Figure 3. implementation is measured by continuous monitoring and evaluation (MONEV).

Fig. 3: ***Structure of activities in AMR (IPOO perspective)***



The focus is on people behaviour model, which includes changing people's behaviour with regard to: (i) effectively killing of bacteria (effective use of antimicrobials and WASH); reducing exposure to microbes with antimicrobials so that there are less mutants selected; and (iii) preventing the spread of AMR pathogens (IPC, WASH).

Guidance into real actions can be brought by:

- ✓ Improving the governance of (three) levels of organizations, specifically at country level;
- ✓ Presence of a strong AMR Focal Point in the WHO Country Office who has the capacity of conducting advocacy, communication and coordination, leadership, management in a multi-sectoral environment;
- ✓ Translating the NAP, supported by WHO technical guidance, into real governance and practices in order to obtain deliverable outputs (incorporating NAP into Midterm National Development Plan, strategic plans of the Ministry of Health and Ministry of Agriculture, incorporating NAP into performance indicators of hospitals, of primary care, incorporating NAP into accreditation tools, Incorporating AMR into diseases control programmes (including leprosy), etc.

6. Country experiences

6.1. Malaysia

A presentation was made by Dr Amrish Shah Osman, Microbiologist, National Public Health Laboratory.

While leprosy control comes under the Communicable Disease Control Section, testing for drug resistance is undertaken at the Leprosy Unit of the National Public Health Laboratory, requiring a close coordination between NLP and the laboratory.

The laboratory has capacity for both mouse footpad testing as well as line probe assay molecular testing. The turn-around-time for mouse footpad testing is 12 to 15 months while for line probe assay it is 7 days. The cost for mouse footpad testing comes to US$ 426 per patient while it is around US$ 30 for line probe assay. The laboratory has acquired the equipment for performing whole genome sequencing, though is in need for technical assistance to operationalize this.

Results of the last five years are shown in Table 3 for retreatment cases and Table 4 for new cases.

Table 3: *Results of drug-susceptibility testing in retreatment leprosy cases, Malaysia, 2015-2019*

Indicator	2015	2016	2017	2018	2019
Relapse after MB treatment	4	6	13	16	9
Relapse after PB treatment	1	5	2	5	3
Total relapses	**5**	**11**	**15**	**21**	**12**
Relapses tested with line probe assay PCR			**1**	**7**	**7**
Rifampicin mono-resistance				1	1

Indicator	2015	2016	2017	2018	2019
Dapsone and clofazimine resistance					1
No resistance			1	6	5
Relapses tested with mouse footpad test	**6**	**4**	**2**	**2**	**1**
Dapsone mono-resistance	1		2		
No resistance	5	4		2	1

Table 4: *Results of drug-susceptibility testing in new leprosy cases, Malaysia, 2015-2019*

Indicator	2015	2016	2017	2018	2019
Total new cases	176	191	194	182	195
New MB cases	143	136	140	132	149
MB tested for resistance	29 (20%)	17 (12%)	21 (15%)	34 (26%)	23 (15%)
New cases tested with line probe assay PCR			**1**	**12**	**17**
Rifampicin mono-resistance				1	
Dapsone mon-resistance					2
Dapsone and rifampicin resistance					2
No resistance			1	11	13
Relapses tested with mouse footpad test	**29**	**17**	**20**	**22**	**6**
Dapsone mono-resistance	5	4	9	3	
Dapsone and clofazimine resistance				2	
No resistance	24	13	11	17	6

6.2. Benin, Guinea, Madagascar, Mali, Niger, Senegal

On behalf of the drug resistance surveillance network of the *Fondation Raoul Follereau*, Dr Ronald Gnimavo, xxx from Guinea, presented the experience from francophone countries in Africa with regard to AMR surveillance. The NGO has supported AMR surveillance in six African countries since 2011. As of now, biopsy samples are collected in the countries and shipped to Lausanne, Switzerland (till 2017) and Paris, France.

The main objectives of the network are:

- To detect and confirm suspected relapse cases;
- To detect secondary resistance to anti-leprosy drugs, especially rifampicin, and check its trend;
- To genotype *M. leprae* strains in samples sent to laboratories.

Relapse is defined as the re-occurrence of the disease at any time after the completion of a full course of MDT. It is diagnosed by the appearance of definite new skin lesions and/or an increase in the bacteriological index of two or more units at any single site.

Table 5 shows the case detection while Table 6 shows the results of AMR surveillance in the six countries.

Table 5: *Epidemiological information, francophone Africa, 2011-2019*

Country	Type of cases	2011	2012	2013	2014	2015	2016	2017	2018	2019
Benin	All cases	246	243	254	192	194	167	150	154	109
	MB cases	192	192	170	142	159	140	131	139	92
Guinea	All cases	998	438	378	241	184	280	239	279	272
	MB cases	389	320	287	183	142	216	206	223	215
Madagascar	All cases	1,577	1,474	1,569	1,617	1,494	1,889	1,550	1,421	1,700
	MB cases	1,277	1,312	1,381	1,423	1,315	1,606	1,349	1,236	1,445
Mali	All cases	226	288	176	259	222	148	174	162	182
	MB cases	158	181	155	220	191	129	150	143	164
Niger	All cases	405	433	424	403	378	350	278	317	333
	MB cases	340	346	348	330	306	280	220	244	256
Senegal	All cases		224	247	233	248	332	235	204	189
	MB cases		186	217	193	236	203	139	175	183
All countries	All cases	3,452	3,100	3,048	2,945	2,720	3,166	2,626	2,537	2,785
	MB cases	2,356	2,537	2,558	2,491	2,349	2,574	2,195	2,160	2,355
	All cases	26,379								
	MB cases	21,575								

Table 6: *Results of AMR testing, francophone Africa, 2011-2019*

Indicator	Benin	Guinea	Madagascar	Mali	Niger	Senegal	Total
Patients tested	97	24	42	101	63	2	**329**
New cases tested							**297**
Relapse cases tested							**32**
Dapsone mono-resistance	4	3	0	2	1	0	**10 (3.0%)**
Rifampicin mono-resistance	1	1	0	0	1	0	**3 (0.9%)**
Ofloxacin mono-resistance	0	0	0	0	0	0	**0**

6.3. India

India accounts for 57% of the global new case burden. The new case detection showed a gradual decline from 135 485 new cases in 2016 to 114 451 in 2019. In 2020, the COVID-19 pandemic affected leprosy programmes (with cancellation of active case detection campaigns and reduced access to health services) resulting in a significant dip in case detection: only 65 147 new cases were reported during the year. Relapses are defined as per the WHO guidance, i.e. a patient who has completed a full course of treatment and returns with signs and symptoms of leprosy that are not deemed to be due to a reaction. In 2019, 896 relapses were reported while this number was 498 in 2020 (of whom 455 after MB treatment and 50 after PB treatment). Most relapses were reported from two states: Maharashtra and Uttar Pradesh.

Data on AMR were only available from 2010 to 2015 (Table 7).

Table 7: *Leprosy case notification and AMR data, India, 2011-2020*

Indicator	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
New cases	127,295	134,752	126,913	125,785	127,334	135,485	126,164	120,334	114,451	65,164
Other retreatments	5,945	5,831	5,359	5,199	5,311	5,893	5,040	5,158	5,332	3,376
Relapse after MB	557	595	664	587	459	536	457	436	455	464
Relapse after PB									50	34
New cases tested	**311**									
Rifampicin resistant	3.5%									
Dapsone resistant	2.3%									
Ofloxacin resistant	2.3%									
Retreatments tested	**355**									
Rifampicin resistant	8.2%									
Dapsone resistant	4.8%									
Ofloxacin resistant	2.3%									

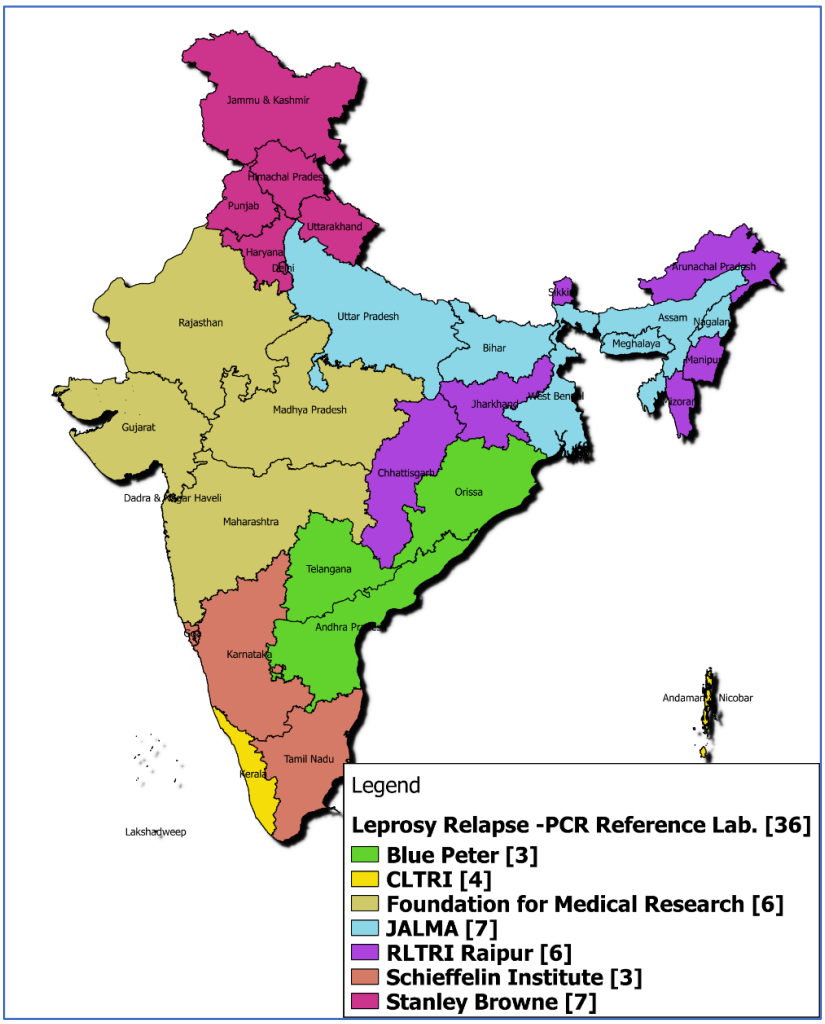
National guidelines were developed through a series of consultations between 2017 and 2020 and a feasibility study. AMR surveillance was included as one area of work under the National Leprosy Eradication Programme with the following objectives:

- ✓ To establish a nationwide robust surveillance system for AMR in leprosy;
- ✓ To estimate the burden and monitor trends of AMR in leprosy among new cases and relapses.
- ✓ To provide evidence-based inputs for programme intervention.

The AMR surveillance plan includes identifying of six apex laboratories to which all states and union territories were linked (Figure 4).

Roll-out of AMR surveillance was planned in three phases: preparatory, appraisal and implementation phases. Health facilities were divided into three levels: in Level 1, patients are diagnosed and treated; in Level 2, laboratory technicians who can perform skin smear examinations and collect specimens for AMR are available; while in Level 3, facilities for skin biopsy are available. All relapses and a proportion of new patients will be referred to Level 2 for skin smear. Patients with a negative PCR would be referred to Level 3 for skin biopsy. The apex laboratories receive specimens for PCR and resistance testing.

Fig. 4: ***Map of India showing states and union territories, based on designated apex laboratory***



The plans further included:

- Training of Medical Officer (In-charge) on referral; and laboratory technicians;
- Procurement of laboratory reagents, equipment and logistics for transport of specimens;
- Arrangements for delivery of specimens;
- Logistics for recording and reporting;
- Appraisal of preparedness of the levels 1, 2 and 3 by experts;
- Roll-out of surveillance; and
- Gradual expansion to more districts.

An appraisal was carried out reviewing the data. Capacity was planned for 6718 tests per year (505 relapses and 6213 new MB cases) (Table 8).

Table 8: *Planned capacity for AMR testing, by apex laboratory, 2019*

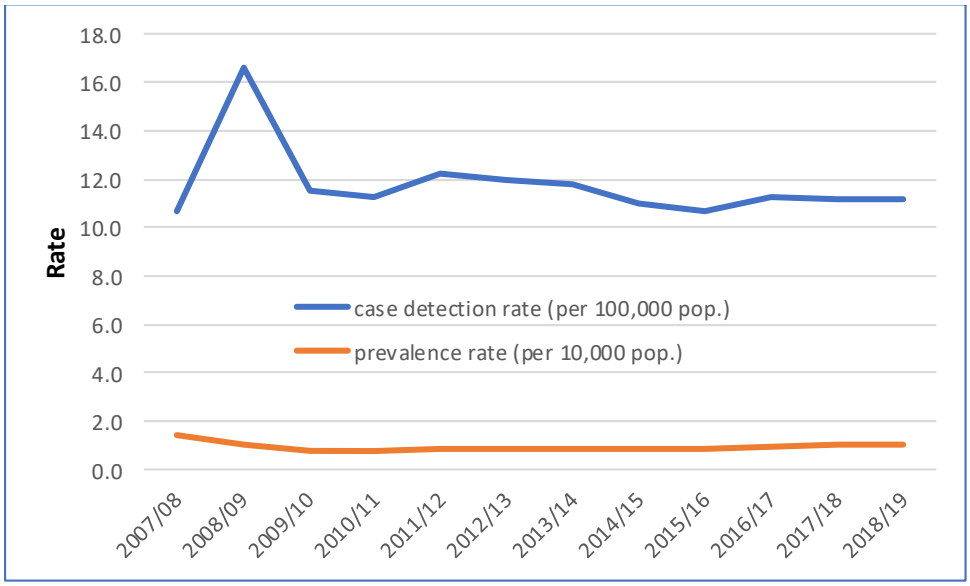
Apex laboratory	Number of new MB cases in 2019	Number of relapse cases	Estimated number of specimens
Blue Peter, Hyderabad	9,413	26	967
Central Leprosy Teaching and Research Institute, Chengalpattu	512	26	77
Foundation Research, Mumbai	17,596	72	1,832
JALMA, Agra	19,776	146	2,124
Regional Leprosy Training and Research Institute, Raipur	7,946	38	833
Schieffelin Institute for Health Research and Leprosy Centre, Karigiri	3,899	177	567
Stanley Brown, New Delhi	2,977	20	318
Total	**62,119**	**505**	**6,718**

6.4. Nepal

Dr Krishna Paudel, Director of the Epidemiology and Disease Control Division, Ministry of Health and Population, Nepal, presented on the implementation of AMR surveillance in Nepal.

Leprosy elimination as a public health problem was achieved at the national level in 2009 (prevalence of 0.8 per 10 000 population). Elimination status at national level has been sustained since then (Figure 5). However, further reducing the disease burden and eliminating leprosy at the sub-national level remains a major challenge. Of the country's 77 districts, 17 reported a prevalence above one per 10 000 population in the financial year 2075/76 (2018/19).

Fig. 5: ***Trends in annual new case detection rate and prevalence rate, Nepal, 2007/08-2018/19***



Though the prevalence rate at the national level remained below 1 per 10 000 since 2009, there is almost no decline in the occurrence of new cases. New child cases even show an increasing trend. The occurrence of new MB cases almost remains same in the last nine years. Relapse cases and other retreatment cases have shown an increasing trend in the last six years (Table 9).

Table 9: *Trends in new cases detected, Nepal, 2010/11-2018/19*

Indicator	2011	2012	2013	2014	2015	2016	2017	2018	2019
New cases detected	3,142	3,481	3,253	3,223	3,053	3,054	3,215	3,249	3,282
New child cases	163	218	136	204	236	220	220	202	260
New MB cases	1,644	1,817	1,709	1,666	1,631	1,678	1,806	1,819	1,785
Relapse cases	20	25	5	11	8	12	15	15	36
Relapse after MB MDT	20	25	5	11	8	12	15	15	36
Relapse after PB MDT	0	0	0	0	0	0	0	0	0
Relapse after DDS mono	0	0	0	0	0	0	0	0	0
Other retreatment cases	42	37	61	53	72	59	84	55	88

AMR surveillance in Nepal encompasses the following:

- Identification of patients (criteria): all leprosy patients suspected of relapse. Only recently, new leprosy cases are also covered as part of the surveillance;
- Collection of specimens: suspected relapse patients are referred to AMR surveillance sentinel site;
- The samples taken are slit skin smears and skin biopsy;
- Sentinel site: AMR surveillance for leprosy is being conducted through one sentinel surveillance site: Anandaban Hospital (run by an international NGO)
- Testing laboratory: the testing laboratory is Anandaban Hospital; this service is not integrated with surveillance for resistance in other pathogens.
- Testing method: PCR and mouse footpad techniques.
- At present the AMR testing is done for relapse cases. The following tables shows the results by carrying out PCR and mouse footpad techniques

Table 10 shows the results of the AMR tests in relapses using PCR technique.

Table 10: *Results of AMR testing in leprosy relapse cases, Nepal, 2014/15-2018/19*

Criterion	2014/15	2015/16	2016/17	2017/18	2018/19
PCR testing					
Patients tested	14	7	ND	ND	ND
Rifampicin resistance	0	0	ND	ND	ND
Dapsone resistance	0	1	ND	ND	ND
Ofloxacin resistance	0	0	ND	ND	ND
Resistance to >1 drug	0	0	ND	ND	ND
Not resistant	14	6	ND	ND	ND
Mouse footpad test					
Patients tested		15	15	16	26
Rifampicin resistance		0	0	0	0
Dapsone resistance		0	1	1	0
Ofloxacin resistance		ND	ND	ND	ND
Resistance to >1 drug		0	0	0	0
Not resistant		15	14	15	26

Nepal is planning the following activities in future:

- To strengthen AMR surveillance for both new cases and retreatment cases;
- To develop and implement a national guideline for AMR surveillance in leprosy;
- Set up of a reference laboratory.
- Capacity building of the national team for strengthening AMR surveillance.

6.5. Brazil

Professor Ciro Gomez, Head of the Department of Dermatologist, University of Brasilia, made a presentation on AMR surveillance in leprosy in Brazil.

There was a significant reduction in leprosy case detection in 2020, compared to 2019: 37% for all new cases, 49% for child cases and 32% for relapses. This is due to COVID-19 and may not reflect a true decline in leprosy incidence. Since 2021, the NLP has adopted the three-drug MDT regimen for PB patients.

With regard to AMR surveillance, the following milestones were achieved:

- 2008: integration in the WHO sentinel surveillance network; testing for secondary resistance;
- 2010: Focus on former leprosy colonies - investigation of retreatment cases due to the possibility of resistance (Ordinance No. 3.125: Guidelines for the Surveillance, Attention and Control of Hansen's Disease);

- 2015: New definitions of relapse cases; flow diagram for sample collection and analysis (Information Note 51/2015);
- 2016: Guidelines for surveillance, attention and elimination as a public health problem
- 2018: Adoption of national sentinel surveillance system; testing for secondary and primary resistance (Information Note 31/2018; National Strategy to Fight Hansen's Disease; Technical Note 8/2020).
- 2021: Hansen's Disease clinical protocol and therapeutic guidelines: Recommendations

Since 2018, screening for AMR is systematically undertaken for all relapse cases and cases that do not respond adequate to the standard MDT regimen from 83 sentinel centres across the country. Testing is done in three national reference laboratories (*Fundaçao Alfredo da Matta* in Manaus, *Instituto Lauro de Souza Lima* in Bauru and *Fundaçao Oswaldo Cruz* in Rio de Janeiro). Tests include genomic DNA extraction, PCR and gene sequencing.

The turn-around-time typically is less than two months (seven days between the treatment centre and the sentinel collection centre; two weeks between the sentinel collection centre and the testing laboratory; and one month to perform the test and return the results to the treatment centre).

Results of the drug-susceptibility testing performed during 2018-2020 are presented in Table 11.

Table 11: *Results of Hansen's Disease drug-susceptibility testing, Brazil, 2018-2020*

Indicator	2018	2019	2020
New cases tested	14	237	82
Relapse cases tested	16	227	69
Suspected treatment failure tested	25	398	126
Total patients tested	55	862	277
	1,194		
Rifampicin mono-resistance	1 (<0.1%)		
Dapsone mono-resistance	12 (1.0%)		
Ofloxacin mono-resistance	1 (<0.1%)		
Resistance to rifampicin and dapsone	2 (<0.1%)		
Total resistance (any type)	**16 (1.3%)**		

As next steps, the country plans to increase the number of sentinel sites and improve the data management system.

7. Role of sentinel centres and of reference laboratories

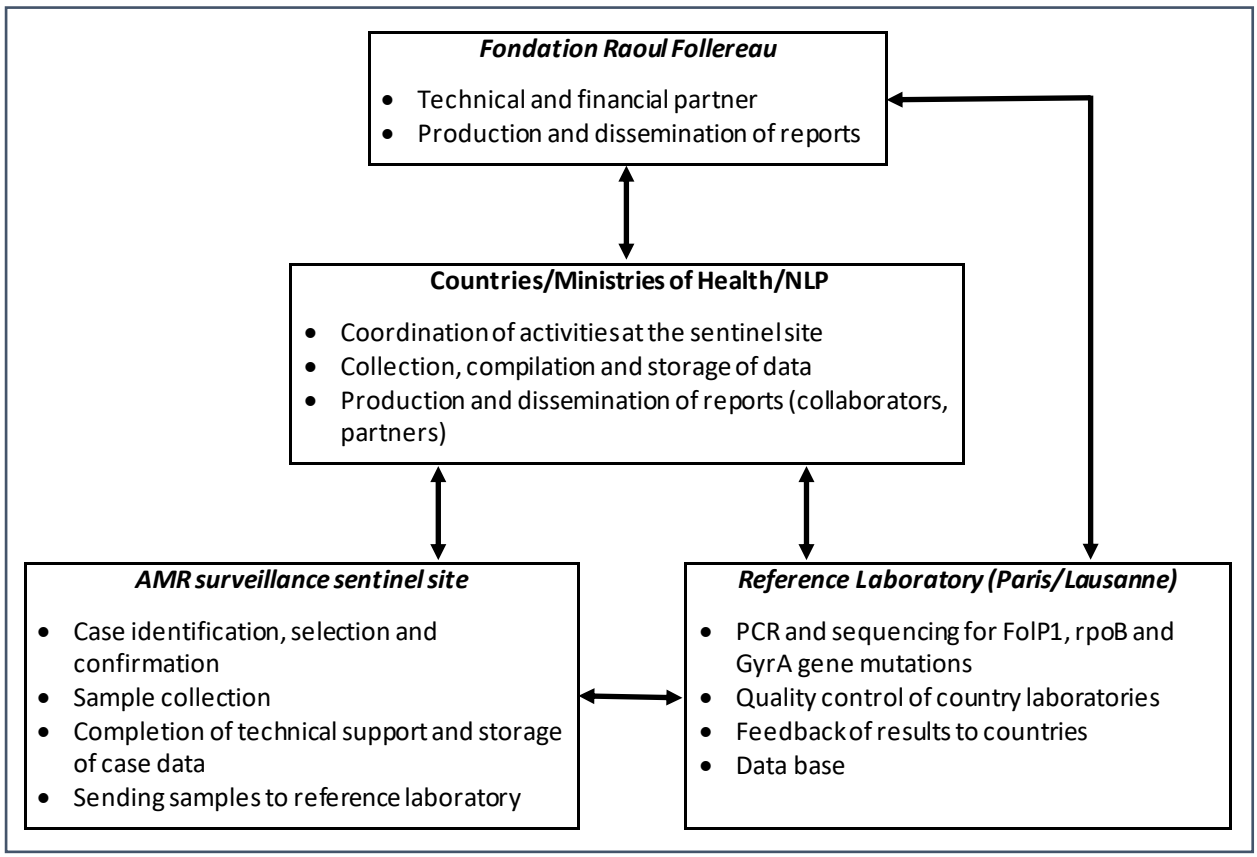
7.1. Role of sentinel centres

Sentinel centres provide support to leprosy programmes and in certain situations, to independent clinicians in carrying out PCR testing, sequencing for gene mutations (folP1, rpoB and gyrA) to detect

bacilli with resistance to drugs used in leprosy treatment. They report results to sample collection site, to NLP and to the reference laboratory. Most sentinel centres are supported by NGOs. Dr Aparna Srikantam from LEPRA Blue Peter Public Health Research Centre, Hyderabad and Dr Roch Christian Johnson from *Fondation Raoul Follearau* made presentations on the role of sentinel centres in implementing AMR surveillance. The sentinel centres cater for patients referred by the leprosy programme treatment facilities and the walk-in patients.

In addition to providing the testing services under AMR surveillance, the sentinel centres also supported NLPs in enhancing skills for skin smear microscopy and collection of samples for the tests. Standardized procedures are in place for DNA extraction, PCR and sequencing to identify gene mutations. The sentinel centres of the *Fondation Raoul Follearau* support AMR surveillance by providing both technical and financial support to NLPs. Its sentinel centre covers leprosy programmes in several African countries, coordinates collection of samples from NLP facilities, and sends the samples to referral centres. The conceptual framework is presented Fig. 6.

Fig. 6: ***Framework AMS surveillance, Fondation Raoul Follereau***



The challenges faced by sentinel centres in supporting AMR surveillance ranged from inadequate skills in collecting skin smear samples, getting clear clinical information pertaining to the samples referred. On the laboratory front the sentinel centre finds difficulty in identifying skilled work force and quality facilities for DNA sequencing. Sentinel centres invest in developing testing facilities and use in-house funding for carrying out tests. National strategic plans need to include funding for the services provided by the sentinel centres in AMR surveillance.

During discussions, it was proposed to name the centres depending on the role it plays in AMR surveillance rather than "sentinel centres". Instead such facilities would be called "designated testing facility", "reference laboratory", etc.

7.2. Role of reference laboratories

Dr Yuji Miyamoto from the Leprosy Research Centre, National Institute of Infectious Diseases, Japan, elaborated on the role of (international) reference laboratories in AMR surveillance for leprosy. The Leprosy Research Centre has eight laboratories of which the following are linked to AMR surveillance: molecular bacteriology, therapeutic research and drug resistance, molecular epidemiology and molecular diagnostics. The centre provides state-of-the-art diagnosis and also concentrates on training of doctors and scientists from endemic countries (especially in Asia).

The reference laboratory was involved in three different ways:

- Analysis of mutations in samples. Between 2016 and 2020, around 120 samples were checked from Myanmar, Sri Lanka and Viet Nam. This involves extraction of DNA, PCR and sequencing.
- Provision of technical assistance through exchange of information (bi-directional visits);
- Quality control through provision of samples with known normal or mutant strains of *M. leprae* to other laboratories and check on the level of concordance.

WHO can play an important role in facilitate the linkage between the reference laboratory and the the country.

The Leprosy Research Centre can provide financial support for sample transportation as well as training of relevant country staff.

8. Flowcharts

Flowcharts for different processes in AMR surveillance were presented. These were drafted by staff from the Schieffelin Institute for Health Research and Leprosy Centre, Karigiri, India. They are largely based on the WHO Technical Guide for AMR Surveillance in Leprosy (2017 Update).

Antimicrobial resistance to *M. leprae* is being reported in several countries and could become more prevalent in the future. It was felt necessary to strengthen AMR surveillance and its reporting. In most countries, characterized by a decrease in leprosy cases, the knowledge and experience in dealing with leprosy and AMR surveillance is also decreasing. Hence there was a need to adapt the protocols in line with global antimicrobial resistance strategies, if possible, in an integrated approach.

To achieve elimination of leprosy disease, it is vital to monitor AMR in order to strengthen research on new drug regimens. It would be desirable to have easy-to-understand templates that depict a plan or method to roll out (operationalize) AMR surveillance. The flow charts will make it easier for

understanding each step in AMR surveillance. Such flow charts will also help the programme managers to see exactly how each job is meant to be performed, and accordingly build the capacity of health staff. It should also be straightforward to translate flowcharts into other local languages.

The WHO Guide for surveillance of antimicrobial resistance in leprosy (2017 update); National antimicrobial resistance surveillance systems and participation in the Global Antimicrobial Resistance Surveillance System (GLASS) – A guide to planning, implementation, and monitoring and evaluation and AMR guidelines of the countries were taken as reference documents to prepare the flowcharts. The flow charts are listed in Table xx.

Table: *List of flow charts describing various steps in AMR surveillance*

Sl No.	Content
1	Scheme for surveillance of AMR in leprosy Situation analysis for establishing a National surveillance system
2	Selection of patients for AMR
3	Specimen collection and storage
4	Packaging and transportation of specimens to designated testing facility
5	Testing at designated testing facility
6	Reference laboratories – Quality control of Designated testing facility
7	Capacity of health staff at various levels

It was concluded that the proposed templates could be used for initiating AMR surveillance in countries as it is easy to understand. They can also act as checklists. The templates refer to 'functions' rather than to 'facilities', e.g. specimen collection, PCR testing, gene sequencing.

For the sake of testing AMR, two categories of leprosy patients are distinguished: (i) patients who have never received treatment, i.e. new cases; and (ii) patients who have received treatment, i.e. re-treatment cases. A baseline assessment in each country could be carried out to decide the percentage of new MB cases to be taken for AMR surveillance.

In case of outsourcing to private companies, only companies with evidence of providing quality assured services should be selected. Data pertaining to AMR surveillance should be integrated with national health information system. Services of health information specialist or a biostatistician can be used wherever available. Bioinformatics expert could be included at the reference laboratories wherever feasible. Innovative technologies for drug resistance screening could be allowed.

The flowcharts are shown in Annexes xx to xx.

9. Clinical aspects for AMR testing

This subject was introduced by Dr Paul Saunderson, American Leprosy Missions.

The purpose in collecting clinical data on patients undergoing tests for AMR are two-fold:

- To gain insight into factors which may be linked to the emergence of AMR – e.g. previous treatment with MDT, post-exposure prophylaxis, tuberculosis treatment, etc. It is only practical to collect clinical information on those testing positive for AMR. These clinical notes should be compiled and forwarded to NLP. The patient's status as a new or retreatment case should be confirmed and any decision about further treatment can be made.
- To improve the management of resistant cases through comprehensive information on the outcomes of current treatment, for all cases. This would include patients treated with standard MDT as well as those treated with second-line drugs. These clinical notes can also be forwarded to NLP.

National leprosy programmes should authorize the analysis and publication of the findings.

Because of the need to extract DNA, only MB cases can be studied. PB patients could, theoretically, be at risk of primary resistance, if it starts to become more widespread. Rifampicin resistance is still rare, so most cases of relapse or treatment failure do not have AMR; this means that the retreatment regimen should never be used without laboratory proof that resistance is present, as it is burdensome for patients. Retreatment should always start with standard MDT, while the results of AMR testing are awaited. If good progress occurs, it may not be necessary to switch to the retreatment regimen.

At present, there is no strict definition of treatment failure, but any case thought to need additional antibiotic treatment should be considered for AMR testing. If testing is easy to do, clinicians would have a lower threshold for requesting it, which will lead to better surveillance.

The following information is to be taken from all patients for who AMR will be tested:

- Registration number and informed consent
- Demographic data (age, sex, place of residence)
- Clinical signs of MB disease; bacteriological index
- Clinical history of the presenting symptoms; time since first symptoms were noted
- History of contact with a known case of leprosy (family or other)
- History of ingestion of rifampicin (oral history and medical records, if available): timing and dosage should be recorded. This includes rifampicin taken as chemoprophylaxis for leprosy or TB; rifampicin taken as treatment for TB; rifampicin taken for any other reason.

Treatment outcomes of patient diagnosed with drug-resistant leprosy should be collected. This includes resistant patients treated with either standard MDT or another regimen. As the number of patients treated with second-line drugs is very low, NLP could authorize a referral centre to analyze and publish the results, from time to time. The reporting form should include the following information:

- Registration number and informed consent;
- Demographic data (age, sex, place of residence)

- Type of case
- Date and details of positive test for AMR;
- Date and details of current treatment regimen;
- Outcome: Completed, Died, Lost, Transferred, Poor response

For the treatment of drug-resistant cases, reference is made to the *WHO Guidelines for the diagnosis, treatment and prevention of leprosy (2018)* (Table 12).

Table 12: *Recommended treatment regimens for drug-resistant leprosy*

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

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

Proven dapsone resistance can be treated with rifampicin/clofazimine, but many clinicians like to add a third drug (either ofloxacin, minocycline or clarithromycin), which would also be given once a month, not daily as in the regimen for rifampicin resistance.

10. Conclusions and recommendations

10.1. Conclusions

- Participants concluded that AMR surveillance is an important component of leprosy control.
- Progress in implementing AMR surveillance by several countries is acknowledged.
- Expression of interest in developing or expanding AMR surveillance by several countries was welcomed.
- Support from partners and reference laboratories to sustain AMR surveillance in some countries is acknowledged.
- Participants appreciated WHO for coordinating AMR surveillance in leprosy with national programmes, partners and reference laboratories.
- Limitations in AMR testing are recognized particularly in PB leprosy.
- Data on existing techniques including real-time PCR and hybridization need to be correlated with epidemiological behaviour of the disease.

10.2. Recommendations

1. Countries are encouraged to implement AMR surveillance in leprosy and include this in their AMR National Action Plans.

2. The following steps are recommended in implementing AMR surveillance in leprosy

   2.1. Templates consisting of flow charts based on '*A guide for surveillance of antimicrobial resistance in leprosy, 2017 update*' to be used for initiating AMR surveillance in countries.

   2.2. Countries especially with very few cases to consider sending specimens for AMR testing to a laboratory in another country instead of establishing a testing facility.

   2.3. Introduce or re-introduce skin smear examination in selected health facilities to make it possible to test for AMR.

   2.4. Quality control needs to be introduced for each step involved in AMR surveillance.

   2.5. In case of outsourcing to private companies, only companies with evidence of providing quality assured service should be selected.

3. Mouse foot pad testing to be continued in selected laboratories as it constitutes the gold standard for resistance testing.

4. For the sake of testing AMR, the following two categories of leprosy patients are distinguished:

   4.1. Patients who have never received anti-leprotic treatment, i.e. new cases

   4.2. Patients who have received anti-leprotic treatment, i.e. re-treatment cases (including relapses, treatment after interruption of treatment, treatment after loss to follow up, suspected treatment failure cases) and patients who are on treatment (including not responding to treatment, reclassification from PB to MB during the course of treatment).

5. Steps involved in AMR to be identified by function rather than facility, e.g. specimen collection, PCR testing, gene sequencing.

   5.1. Referral centre could provide specimen collection, testing, quality control

   5.2. Testing laboratory could include specimen collection and some or all of the laboratory tests (e.g. PCR testing, gene sequencing, mouse footpad testing)

6. All positive laboratory test results should be reported to the national leprosy programme and AMR surveillance.

7. Laboratory results should be correlated with clinical history and findings to guide individual patient management.

8. Clinical outcome of all patients with resistance to leprosy antimicrobials should be recorded for further analysis.

9. Evidence-based guidance on managing the treatment of patients with inconclusive AMR surveillance tests but unresponsive to the standard MDT regimen should be developed.

10. AMR surveillance being a public health function, governments are advised to pay for the services provided for this purpose by designated private or NGO laboratories.

11. Partners supporting national leprosy programmes should include AMR surveillance in their agenda.

12. WHO to facilitate a formal network of reference laboratories to:

    12.1. Enhance capacity of countries for implementing AMR surveillance;

    12.2. develop external quality assurance systems for AMR surveillance.

13. WHO to continue to collect data on AMR testing as part of annual leprosy statistics from countries.

14. WHO should include leprosy AMR surveillance in Global AMR surveillance system.

Annex 1: Programme

IST	Virtual meeting sessions
Monday 14 June 2021	
18:30-18:45	Welcome – Dr Erwin Cooreman Inaugural address – Dr Poonam Khetrapal Singh, Regional Director Objectives and expected outcomes; Current status from reports from WHO data base – Dr V R R Pemmaraju
18:45-19:00	AMR surveillance in leprosy: current guidance to leprosy programmes – Dr Erwin Cooreman
19:00-19:15	Diagnosis of anti-microbial resistance to anti-leprosy drugs: recent advances – Professor Emmanuelle Cambau
19:15-19:30	Discussions – Questions and comments
19:30-19:40	***Break***
19:40-20:00	Global Antimicrobial Resistance Surveillance System – Dr Sergey Eremin
20:00-20:30	National AMR Surveillance System – example from a country – Dr Siswanto
Tuesday 15 June 2021	
18:30-19:00	Country experience: Malaysia – Dr Amrish Shah Osman
19:00-19:30	Country experience: Francophone Africa – Dr Ronald Gnimavo
19:30-19:40	***Break***
19:40-19:55	Country experience: India – Dr Sunil Gitte
19:55-20:10	Country experience: Nepal – Dr Krishna Paudel
20:00-20:30	Country experience: Brazil – Professor Ciro Gomez
Wednesday 16 June 2021	
18:30-18:55	Role of sentinel centres – Dr Roch Christian Johnson, FRF
18:55-19:20	Role of reference laboratories – Dr Yuji Miyamoto
19:20-19:30	***Break***
19:30-20:00	Template - rolling out AMR surveillance – SIHRLC Karigiri
20:00-20:30	Discussion and suggestions on templates
Thursday 17 June 2021	
18:30-18:45	Clinical aspects for AMR testing – Dr Paul Saunderson
18:45-19:00	Final draft of Global Template – rolling out AMR Surveillance
19:00-19:30	Partner support in developing AMR surveillance
19:30-19:40	***Break***
19:40-20:00	Statement by partners
20:00-20:30	Conclusions and Recommendations

Annex 2: List of participants

Government representatives

Dr Md. Enamul Haque, **Bangladesh**
Dr Elaine Andrade, **Brazil**
Ms Leticia Barroso, Brazil
Dr Alexandre Casimiro, Brazil
Ms Carmelita Ribeiro Filha, Brazil
Professor Ciro Gomes, Brazil
Ms Cynthia de Oliveira Ferreira, Brazil
Dr Renata Peral, Brazil
Dr Patricia Rosa, Brazil
Ms Juliana Silva, Brazil
Ms Maria Luiza Tepedino Martins, Brazil
Dr Lay Sambath, **Cambodia**
Dr Yesenia Castro Espinosa, **Colombia**
Dr Ingrid Garcia, Colombia
Dr Claudia Llerena, Colombia
Dr Claudia Colorado, Colombia
Marcela Pilar Rojas Diaz, Colombia
Dr DC Assie, **Côte d'Ivoire**
Dr Raisa Rumbaut, **Cuba**
Dr Ahmed Nabil, **Egypt**
Dr Benedict Quao, **Ghana**
Dr Sunil Gitte, **India**
Dr Pushpendra Singh, India
Dr Agus Handito, **Indonesia**
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Dr Hana Krismawati, Indonesia
Dr Azkiya Zulfa, Indonesia
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Dr Yuji Miyamoto, Japan
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Dr Noorliza Noordin, **Malaysia**
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Dr Thilaka, Malaysia
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Dr Patricia Guadarrama, Mexico
Dr Lizbeth Rodríguez, Mexico
Dr Uttam Ghimire, **Nepal**
Dr Krishan Paudel, Nepal
Dr Abdul Wali Khan, **Pakistan**
Dr Chris Schmötzer, Pakistan
Dr Ada Brizuela, **Paraguay**
Dr José Pereira Brunelli, Paraguay
Dr Olga Aldama, Paraguay
Dr Viviana De Egea, Paraguay
Dr Mara Muñoz, Paraguay
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Dr Ma Angeles Leon, The Philippines
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Dr Dushani Jayawardhana, Sri Lanka
Ms Toungborn Auitpol, **Thailand**
Dr Boosbun Chua-Intra, Thailand
Mr Thirasak Hoonchaiyaphum, Thailand
Ms Darunee Khajondecha, Thailand
Mr Booncherd Kladphuang, Thailand
Dr Surakameth Mahasirimongkol, Thailand
Dr Krisada Mahotarn, Thailand
Mr Sutthisak Ngamwachiraporn, Thailand
Dr Nisa Pairayayutakul, Thailand
Dr Benjawan Phetsuksiri, Thailand
Ms Rujira Phoemthanyakam, Thailand
Dr Shutiwan Ponladech, Thailand
Ms Nutcha Prompunjai, Thailand
Ms Siramas Rodchan, Thailand
Ms Janisara Rudeeaneksin, Thailand
Mr Wisut Saelim, Thailand
Dr Silatham Sermrittirong, Thailand
Dr Thaverit Sittiwakin, Thailand
Ms Manee Sukprasert, Thailand
Dr Surirat Suwantrit, Thailand
Dr Jumpol Tantivongsakij, Thailand
Ms Pojana Thanyakittikul , Thailand
Dr Sukanya Wattanapokayakit, Thailand
Ms Napaporn Wiboonyanon, Thailand
Dr Saranjit Wimoolchart, Thailand
Dr Vu Tuan-Anh, **Viet Nam**
Dr Absulsamid Al-Kubati, **Yemen**

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Dr Joydeepa Darlong, The Leprosy Mission Trust India, India
Dr Madhusmita Das, Schieffelin Institute for Health Research and Leprosy Centre, India
Dr William Gallo, Global Partnership for Zero Leprosy, United States of America
Dr Deanna Hagge, The Leprosy Mission, Nepal
Dr Ilse Horo Paul, Schieffelin Institute for Health Research and Leprosy Centre, India
Dr Roch Christian Johnson, International Leprosy Association, Benin
Dr Jerry Joshua, Schieffelin Institute for Health Research and Leprosy Centre, India
Dr Christa Kasang, German Leprosy and Tuberculosis Relief Association, Germany
Dr Vivek Lal, Sasakawa India Leprosy Foundation, India

Dr Paul Saunderson, American Leprosy Missions, Norway
Dr Aparna Srikantam, LEPRA, India
Ms Aya Tobiki, Sasakawa Health Foundation, Japan

Others

Dr Charlotte Avanzi, Colorado State University, United States of America
Dr Rajan Babu, Karigiri, India
Professor Emmanuelle Cambau, Hôpital Lariboisière / Université Paris Diderot, France
Dr Stewart Cole, Institut Pasteur, France
Dr David Coulibaly N'Golo, Institut Pasteur, Côte d'Ivoire
Dr Masanori Matsuoka, Tokyo, Japan
Dr Krisada Mahotarn, Bangkok, Thailand
Ms Padma Nataranjan, Alliance française de Delhi, India
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Dr Roderick Poblete, DOH-Novartis Leprosy Task Force, Manila, The Philippines
Dr P. Narasimha Rao, Indian Association of Dermatologists, Venereologists and Leprologists, India
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Dr Rie Yotsu, Nagasaki, Japan
Professor Furen Zhang, Shandong Provincial Institute of Dermatology and Venereology, China

World Health Organization

Mr Subhash Chand, Global Leprosy Programme, Regional Office for South-East Asia
Dr Erwin Cooreman, Global Leprosy Programme, Regional Office for South-East Asia
Dr VRR Pemmaraju, Global Leprosy Programme, Regional Office for South-East Asia
Dr Augustin Kadima Ebeja, Regional Office for Africa
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Dr Joel Keravec, Pan-American Health Organization/Country Office for Brazil
Dr Rogério Lima, Pan-American Health Organization/Country Office for Brazil
Dr Mona Osman, Regional Office for the Eastern Mediterranean
Dr Supriya Warusavithana, Regional Office for the Eastern Mediterranean
Dr Qutbuddin Kakar, Pakistan
Dr Elkhan Gasimov, Regional Office for Europe
Mr Samiran Sarker, Regional Office for South-East Asia
Dr Siswanto, Regional Office for South-East Asia
Dr Zaw Lin, Regional Office for South-East Asia
Dr Rashmi Shukla, Country Office for India
Dr Achmad Naufal Azhari, Country Office for Indonesia
Dr Serene Joseph, Country Office for Indonesia
Dr Usha Kiran, Country Office for Nepal
Dr Khin Pa Pa Naing, Country Office for Nepal
Dr Mizaya Cader, Country Office for Sri Lanka
Dr Preshila Samaraweera, Country Office for Sri Lanka
Ms Kalayanee Laempo, Country Office for Thailand
Dr Kalpeshsinh Rahevar, Regional Office for the Western Pacific
Dr Sergey Eremin, Headquarters

Annex 3: Opening address by Dr Poonam Khetrapal Singh, Regional Director, WHO South-East Asia Region

"Respected representatives from ministries of health, distinguished experts, dear colleagues, ladies and gentlemen,

Warm greetings and welcome to this meeting, which even amid the COVID-19 pandemic, will enable us to advance progress on several key policy frameworks, including the Global NTD Roadmap, the Global Leprosy Strategy 2021–2030, and the Global Action Plan on Antimicrobial Resistance (AMR).

For participants in the WHO South-East Asia Region, it will also help accelerate progress on two of the Region's eight Flagship Priorities: first, eliminating neglected tropical diseases and other diseases on the verge of elimination; and second, strengthening national capacity to prevent and combat AMR.

The Global Leprosy Programme has in recent years made tremendous progress, driven by the hard work and steely resolve of leprosy-affected countries from across the world.

In 2019 more than 200 000 cases of leprosy were detected, which is around 30 000 fewer than 11 years ago.

Less than 5% of cases had grade-2 disability (G2D) at the time of diagnosis, equating to a G2D rate of 1.4 per million population – a 40% reduction on the 2014 figure.

Globally, the new case detection rate for those aged 0 to 14 years was 7.9 per million children, marking a significant improvement on the 2014 rate of 10.1.

The world is no longer focused only on eliminating leprosy as a public health problem, but rather on eliminating it altogether – a paradigm shift highlighted in the new Global Leprosy Strategy.

Achieving zero leprosy will not be easy, but it is possible, and requires us to overcome existing barriers and anticipate emerging challenges.

One such challenge is AMR.

Recent data submitted to WHO indicates sub-optimal cure rates in more than 50 countries. Relapses were reported from 62 countries.

Twenty countries are part of a global sentinel surveillance network to monitor AMR against leprosy drugs, while several others have expressed their desire to implement similar systems.

In 2019, 446 leprosy patients globally were tested for AMR, and mono-resistance was detected in 15. Three patients showed resistance to more than one drug.

At present, resistance to leprosy drugs appears to be relatively low; however, we must not take that for granted, and must vigorously guard against amplification.

As the Global Leprosy Strategy highlights, we must continue to assess drug-susceptibility patterns globally and continue to monitor resistance among both new and retreatment cases.

We must gain a complete and accurate picture of the situation, for which key WHO guidance on surveillance of AMR in leprosy, updated in 2017, must be fully implemented.

Today, I have three messages that are applicable to all stakeholders, whatever a country's current surveillance status.

First, action is everything. Policy frameworks themselves will not drive results unless they are programmatically implemented.

I welcome the development of actional templates during this meeting, with the aim of providing a clear end-to-end process for surveillance activities and laboratory processes in sentinel centres and reference laboratories. I look forward to the progress they will achieve.

Second, integration is vital. AMR is a significant threat to health and development globally, and most countries are taking multisectoral action.

To achieve our targets and goals in both areas of work, leprosy stakeholders must take advantage of and feed into this momentum, not only at the global level, but also at the national and sub-national levels.

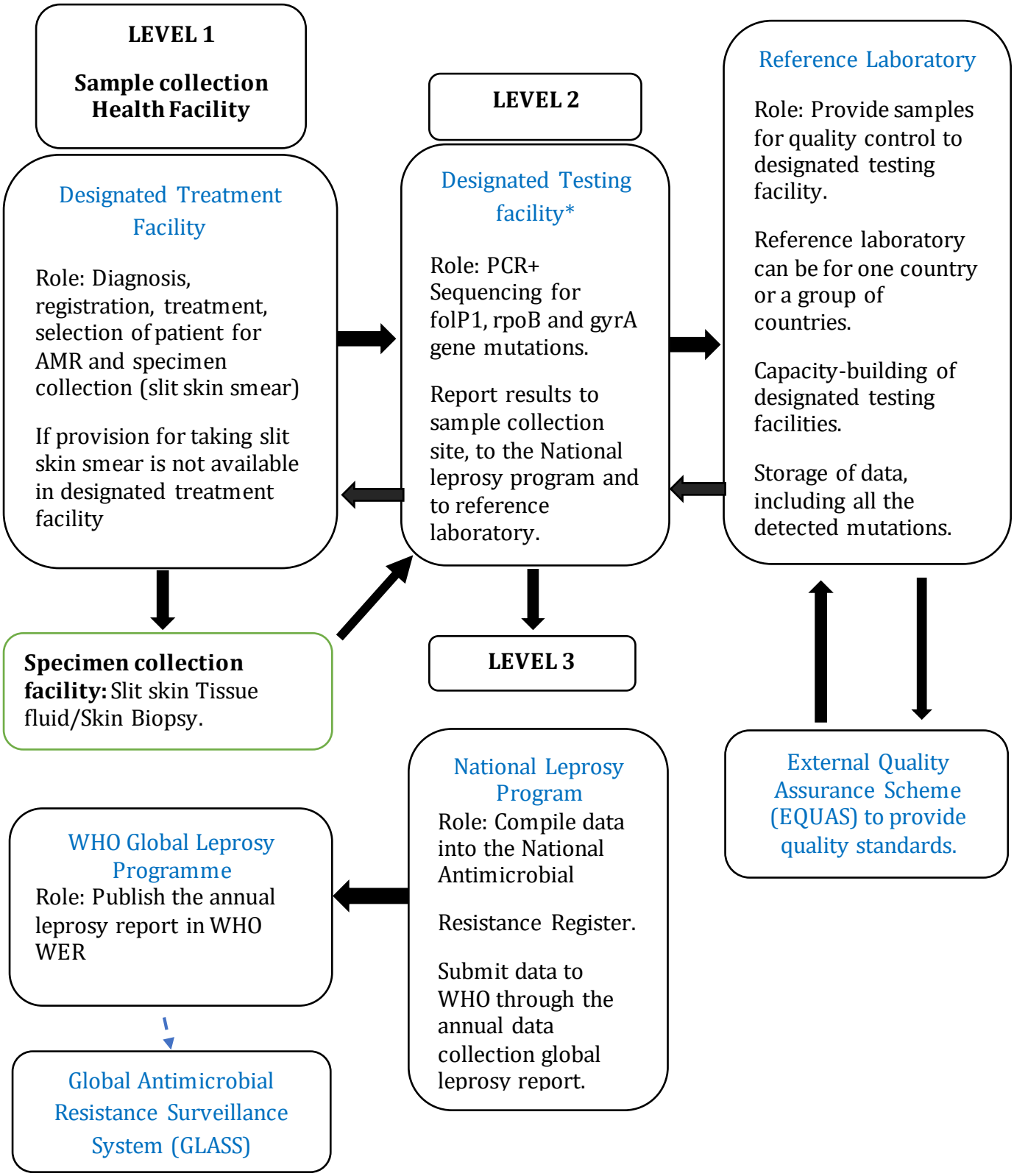
Third, partnerships are key. Ample expertise is available in research laboratories across the world, as well as in facilities managed by nongovernmental organizations. But unless we tap into it, and strengthen existing collaborations, we will not realize its full potential.

It is only by working together, and harnessing all resources at our disposal, that we can achieve the ambitious vision of the Global NTD Roadmap and Global Leprosy Strategy, and contribute towards the full implementation of the Global Action Plan on AMR.

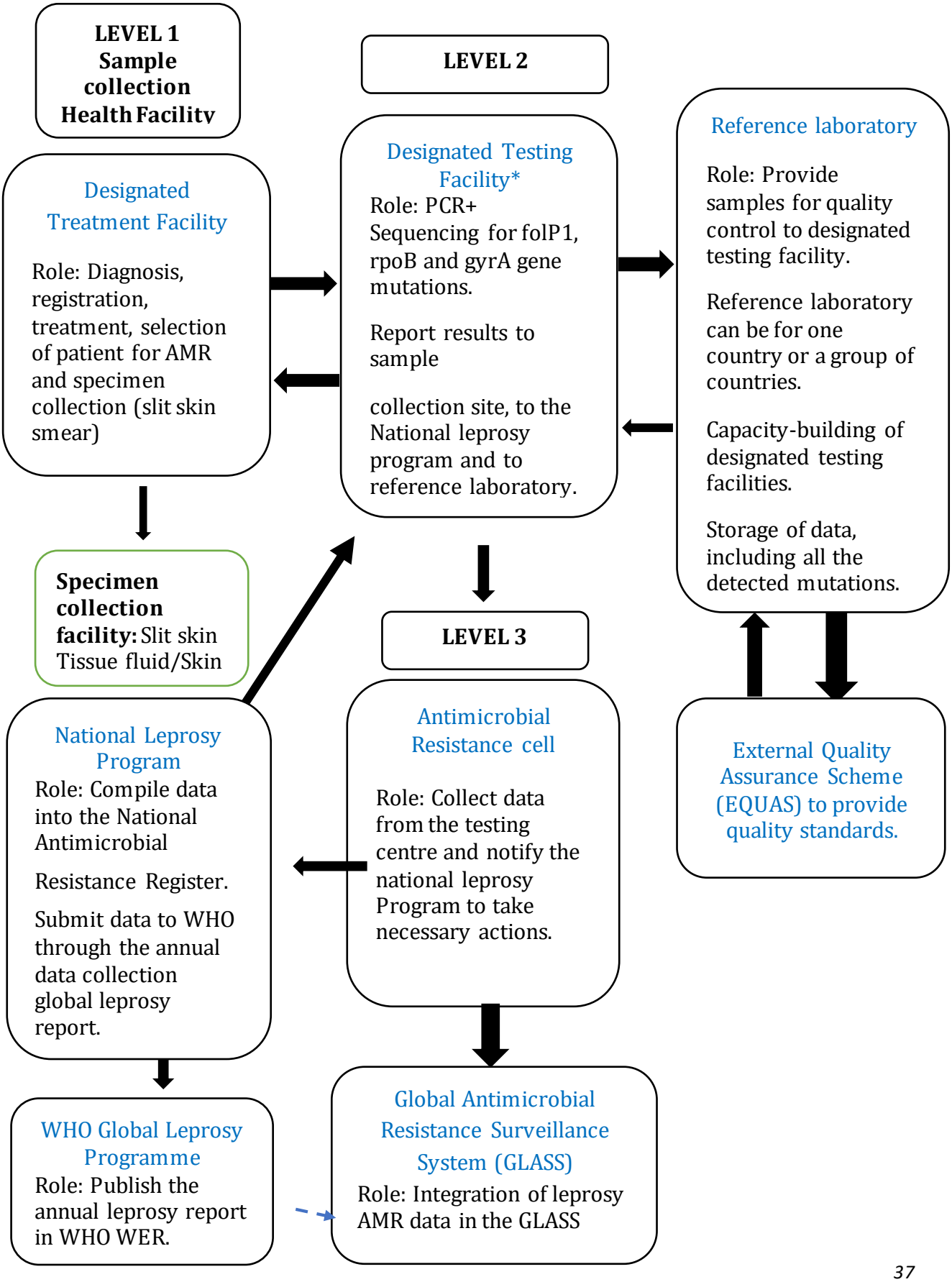
I wish you productive and engaging deliberations, urge you to continue to maintain leprosy programmes amid the COVID-19 response, and look forward to our onward journey together, towards zero leprosy infection and disease, zero disability, and zero leprosy-related stigma and discrimination.

Thank you."

Annex 4: Flowchart 1 – Scheme for surveillance of AMR in leprosy (Scenario 1)



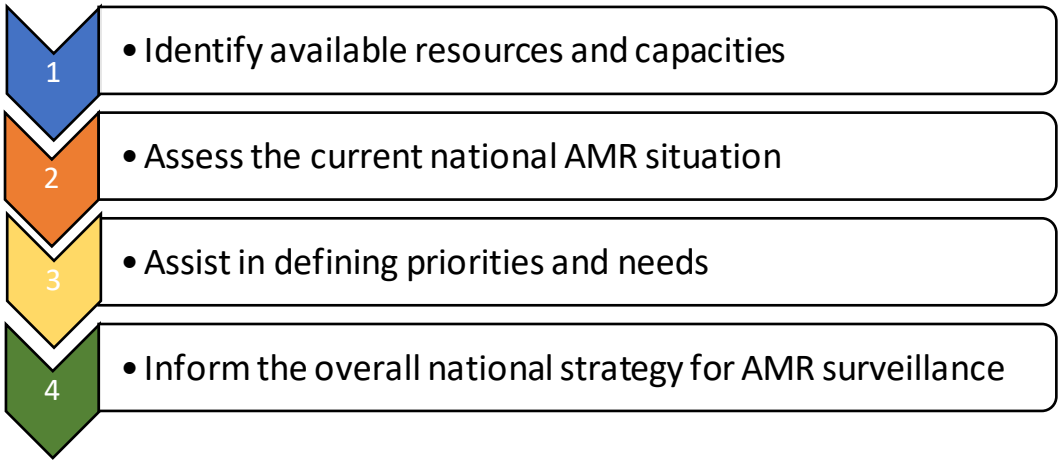
Annex 5: Flowchart 2 – Scheme for surveillance of AMR in leprosy (Scenario 2)



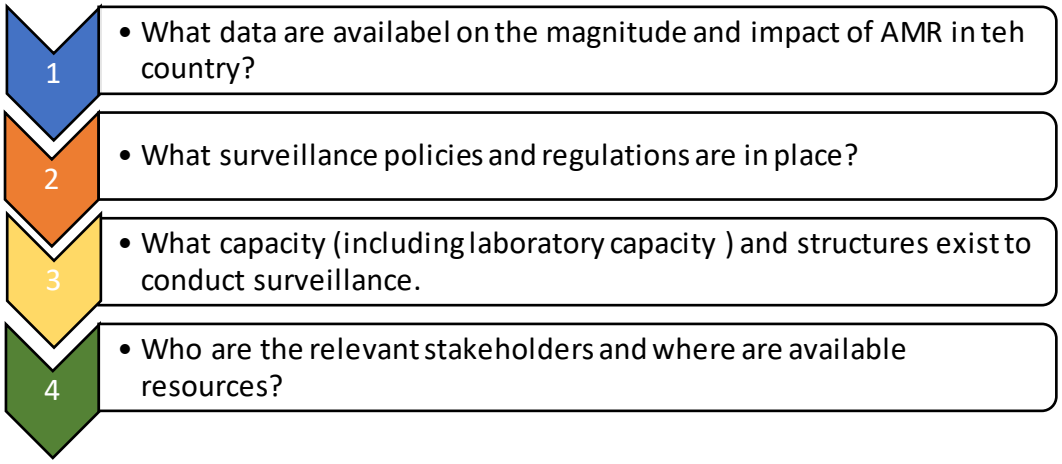
Annex 6: Flowchart 1A – Situational analysis for establishing a national surveillance system

1. **Conducting a situation analysis[1]:**
   Prior to initiating the process of establishing a national surveillance system, it is advisable to conduct a situation analysis.

2. **Questions to consider when conducting a situation analysis of the current**

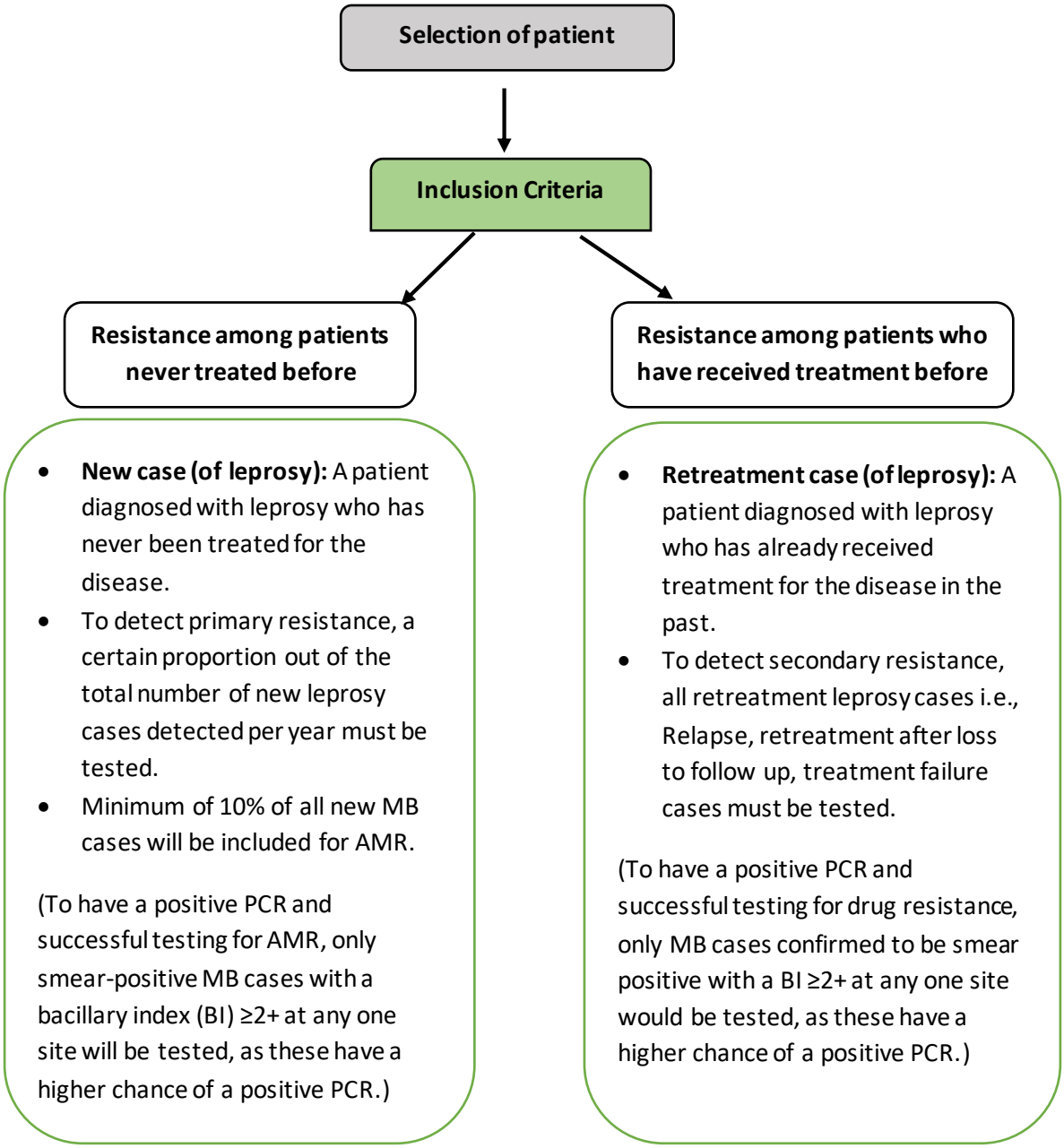


AMR situation:

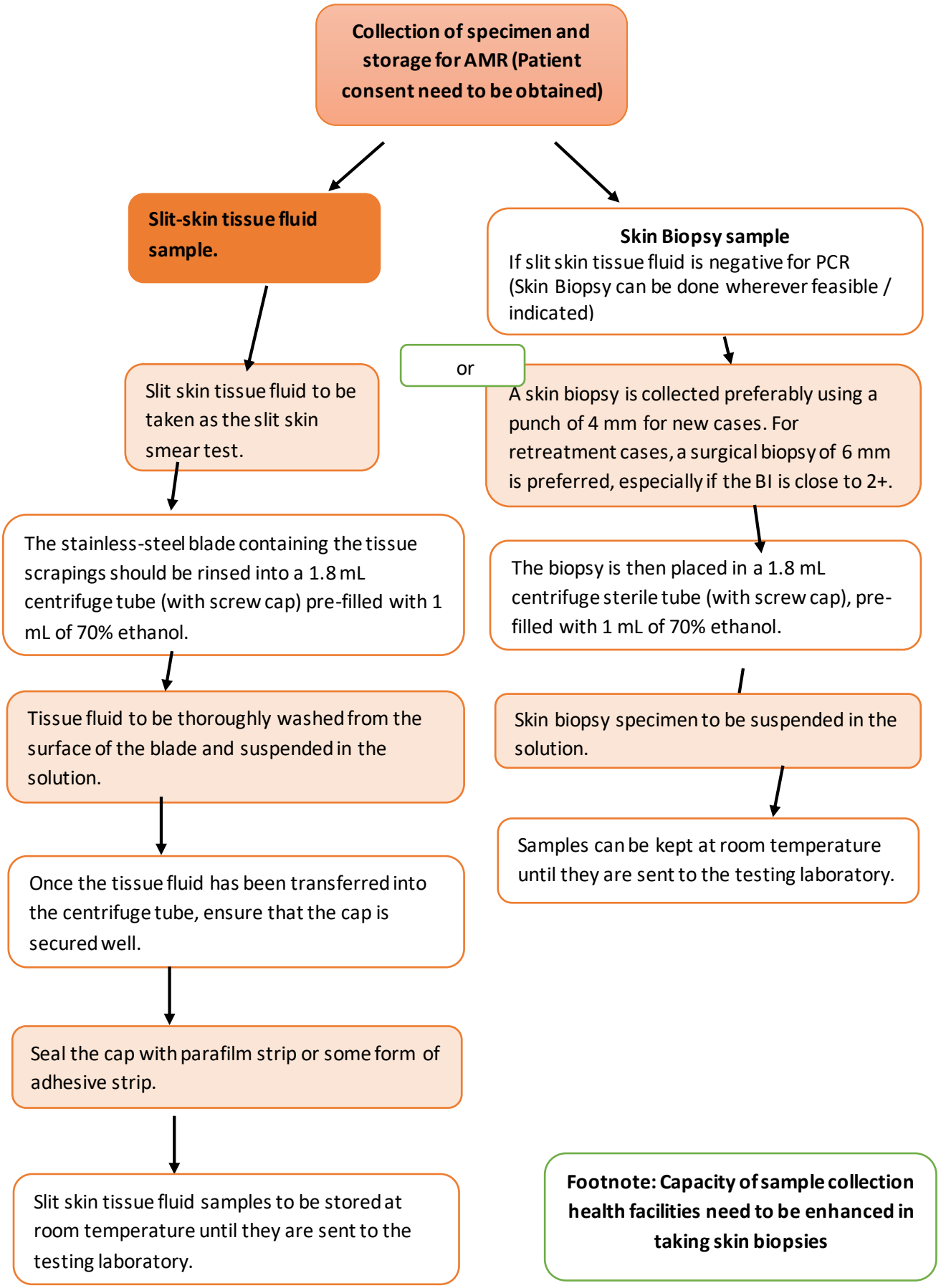


[1] A guide to planning, implementation, and monitoring and evaluation, National antimicrobial resistance surveillance systems and participation in the Global Antimicrobial Resistance Surveillance System (GLASS).

Annex 7: Flowchart 2 – Selection of patients for AMR surveillance



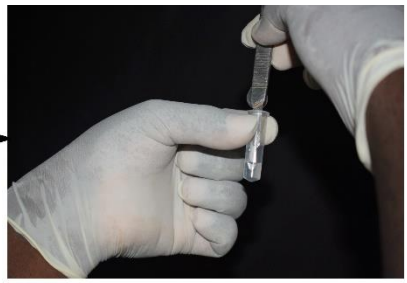
Annex 8: Flowchart 3 – Specimen collection and storage for AMR



SLIT SKIN SMEAR TISSUE FLUID COLLECTION FOR AMR

Microcentrifuge tube with 70% ethanol

Slit skin tissue fulid taken



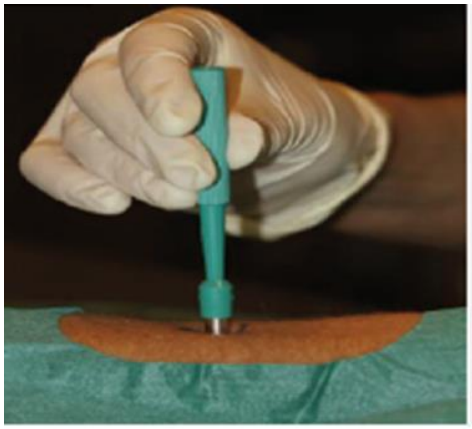
Blade rinsed thoroughly, to transfer material into the tube with 70% ethanol

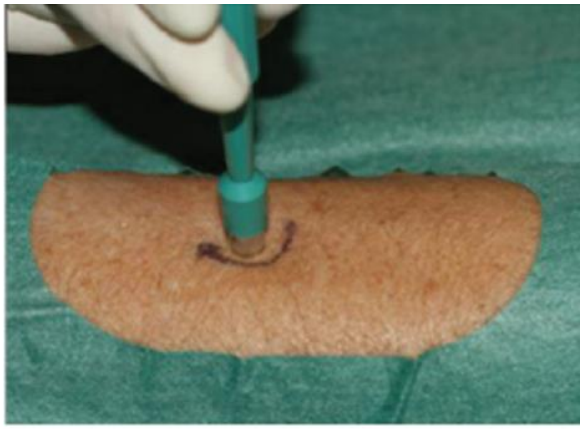
Ensure the cap is secured well

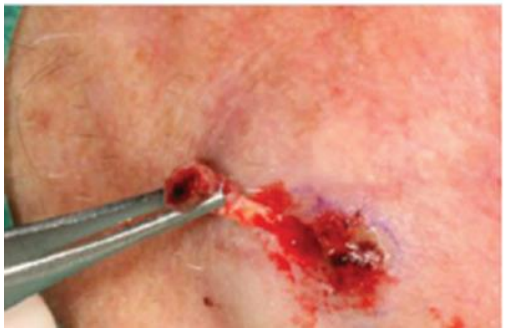
Seal the cap with parafilm strip

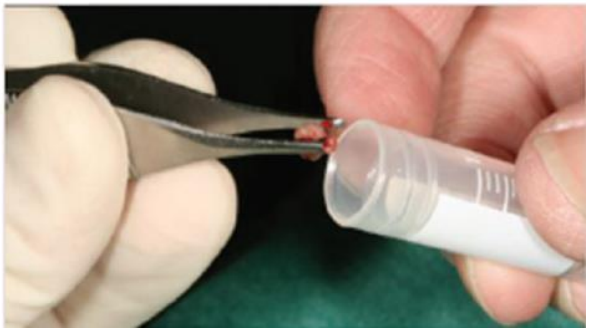
Proceed for packaging

SKIN BIOPSY COLLECTION FOR AMR

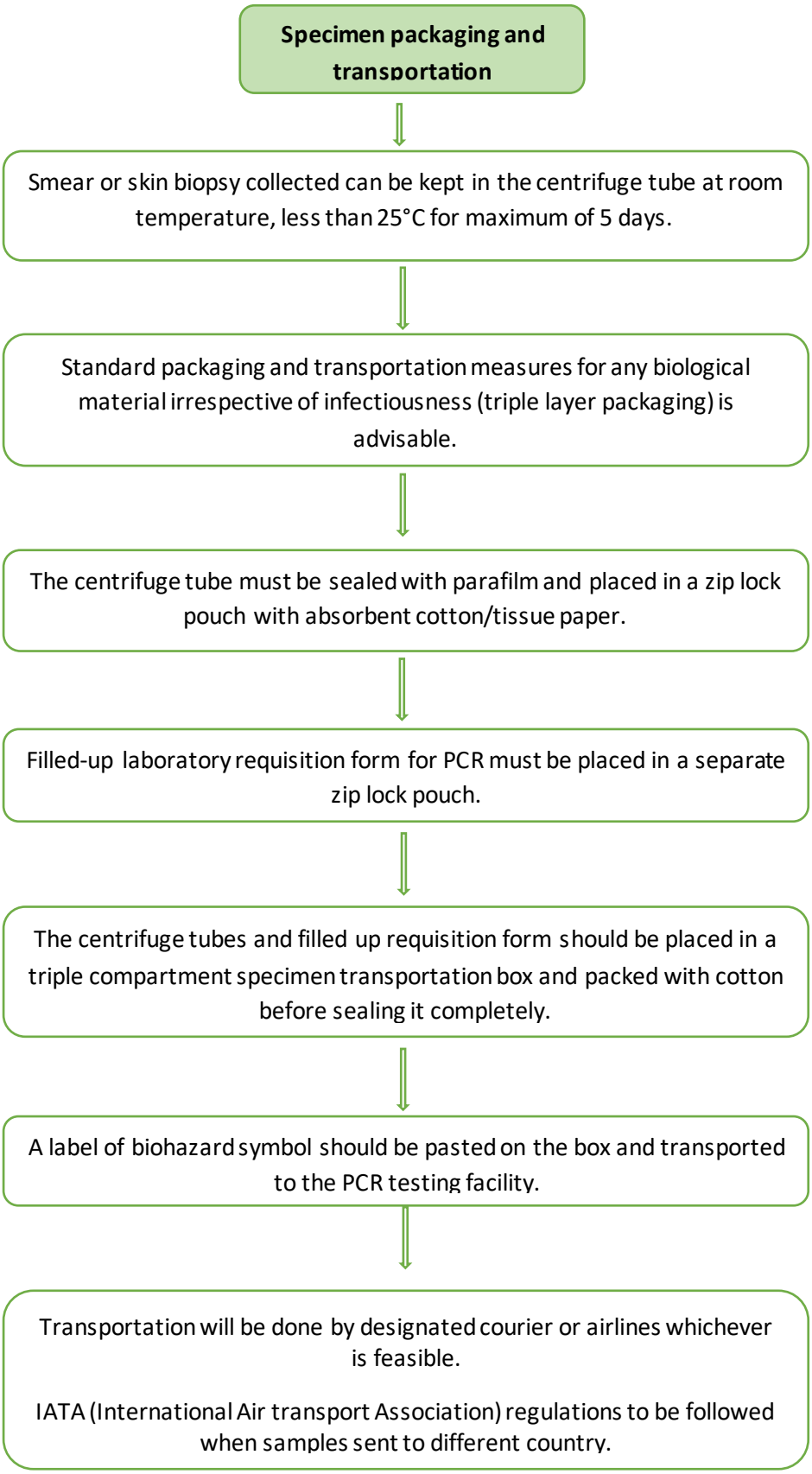




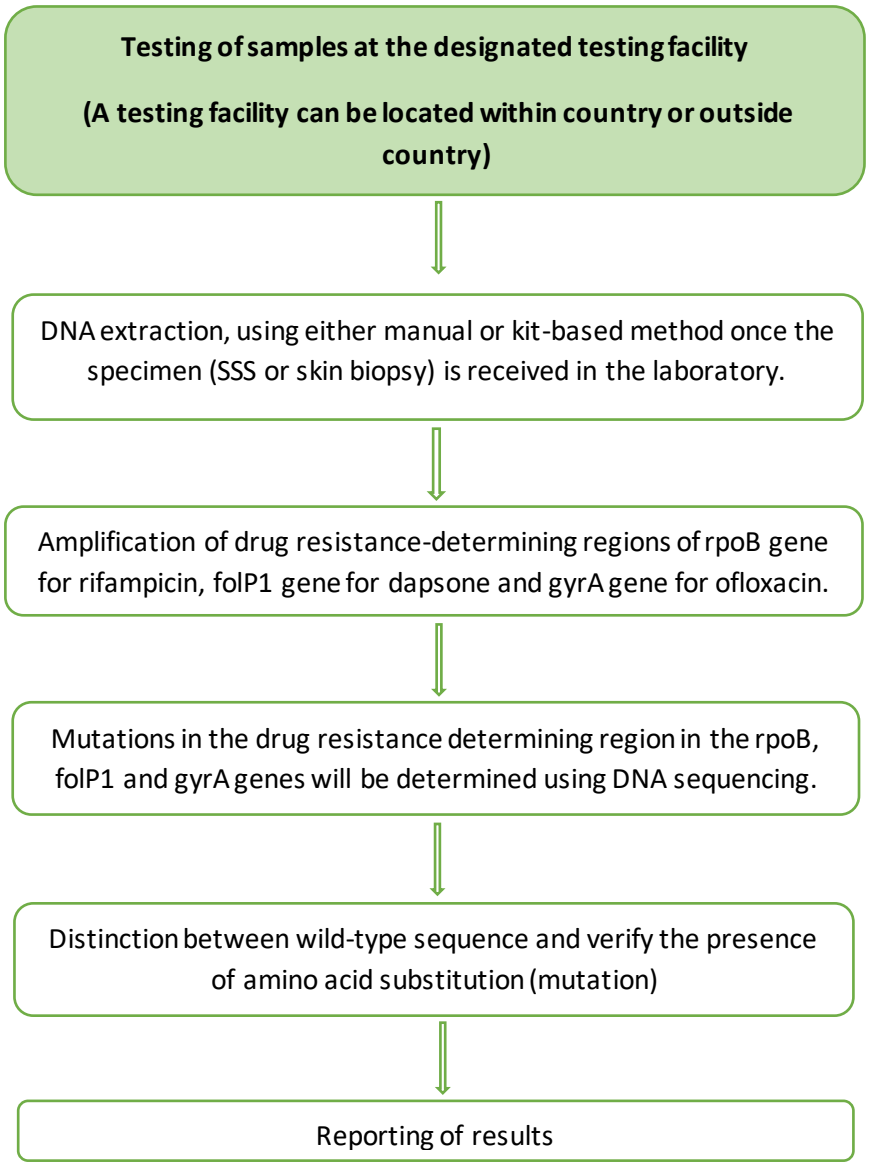




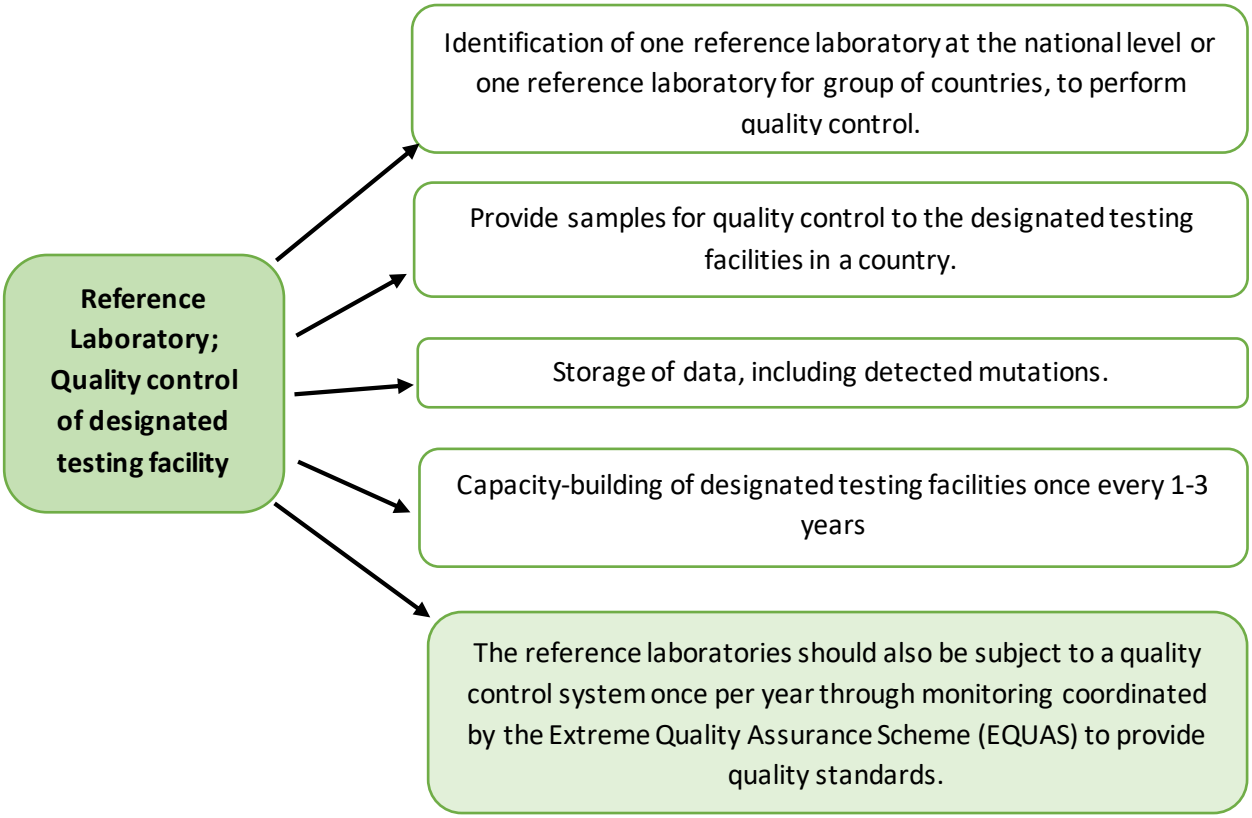
Annex 9: Flowchart 4 – Packaging and transportation of to the designated testing facility



Annex 10: Flowchart 5 – Testing at the designated testing facility



Annex 11: Flowchart 6 – Reference laboratories; quality control of designated testing facility



Annex 12: Flowchart 7 – Capacity of health staff at various levels

Level	Personnel involved	Capacity to be built on these activities
Level 1 Sample collection health Facility	• Clinicians/Medical Officer • Lab technician • Health workers	1. Diagnosis of Leprosy 2. Selection of patient for AMR as per the inclusion criteria 3. Collection of Slit skin tissue fluid 4. Collection of Skin Biopsy. 5. Packaging and transportation of specimen.
Level 2 Designated testing facility	• Molecular Biologist	1. DNA extraction, 2. PCR and Sequencing for folP1, rpoB and gyrA gene mutations 3. Reporting of results. 4. Sending specimens to the reference laboratory for quality control.