STRUCTURE AND OPERATION OF THE NATIONAL TUBERCULOSIS LABORATORY NETWORKS IN THE AMERICAS REGION

Program "Strengthening TB laboratory diagnosis in the Region of the Americas, 2020-2023", a multi-country grant from the Global Fund.

A survey applied to the 17 national TB laboratory networks from Argentina, Bolivia, Chile, Colombia, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Mexico, Nicaragua, Paraguay, Peru, Dominican Republic, Suriname and Venezuela.

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STRUCTURE AND OPERATION

OF THE NATIONAL TUBERCULOSIS

LABORATORY NETWORKS

IN THE AMERICAS REGION

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Abbreviations and acronyms

DST Drug susceptibility testing

EQA External Quality Assessment

FQ Fluoroquinolones

GIS Geographic Information System

GLI Global Laboratory Initiative

H Isoniazid

HIV Human Immunodeficiency Virus

LAMP Loop-Isothermal Amplification

LED Light-Emitting Diode

LFIA Lateral Flow Immunochromatographic Assay

LJ Lowenstein Jensen

LPA Line Probe Assay LA

MH Ministry of Health

MTBC Mycobacterium Tuberculosis Complex

NRL National Reference Laboratory

NTBLN National Tuberculosis Laboratory Network

NTP National Tuberculosis Program

SM Smear Microscopy

SNL Supranational Reference Laboratory

MDR-TB Multidrug-Resistant Tuberculosis

PCR Polymerase chain reaction

R Rifampicin

RR-TB Rifampicin-resistant tuberculosis

RS Respiratory Symptoms

SOP Standardized Operating Procedures

TB Tuberculosis

UPS Uninterruptible Power Supply

WHO World Health Organization

XDR-TB Extensively drug resistant Tuberculosis

Introduction

The Strategy End Tuberculosis (TB) has set the goal of reducing the number of TB deaths by 95% and TB incidence rate by 90% between 2015 and 2035 and ensuring that no TB patients and their households face catastrophic costs as a result of TB disease. This Strategy was adopted by de World Health Assembly in May 2014. In the Region of the Americas, at the current rate of decrease in the number of TB deaths and incidence, the Strategy's goals and landmarks are unfeasible. Nevertheless, the landmarks for 2025, challenging as they are, can still be achieved. This requires the existing tools' implementation and expansion, coupled with the attainment of health universal coverage and implementation of initiatives to address TB determinants and social consequences (PAHO/WHO, 2020).

This strategy gives priority to TB early diagnosis, which should include systematic dormant TB screening (contacts and high-risk groups) and universal availability of drug susceptibility testing (DST). It highlights the essential role of labs and emphasizes that, in order to meet the goals, WHO-recommended TB rapid diagnoses, must be available to anyone with TB signs and symptoms. All bacteriologically confirmed TB patients should be tested for Anti-TB drug susceptibility to at least rifampicin (R), and all R-resistant TB patients should be tested for susceptibility to at least Fluoroquinolones (FQ).

In 2019 it was estimated that 13.1% of new cases and 17.4% of previously treated cases had resistance to isoniazid (H). This meant 1.4 million H-resistant incidental cases, 1.1 million of whom were susceptible to R. That is to say 11% of the total TB incidental cases had resistance to H while being susceptible to R. These persons with H-Resistant TB may not be detected in countries where diagnosis algorithms prioritize R-resistance detection, resulting in treatment failure (WHO, 2020).

WHO's estimations indicated that in 2020 TB had an incidence of 291,000 new cases and relapses in the Americas, representing a rate of 29 cases per 100,000 inhabitants. TB/HIV incidence was estimated at 29,000 cases and TB mortality in HIV-negative patients at 19,000 cases (rate 1.9 deaths per 100,000 inhabitants).

Among the 197,364 new cases and relapses notified in 2020, 27 % was tested using a rapid test at the moment of diagnosis, of 78% the HIV-infection status was known, 85% were pulmonary cases and 77% of the latter cases were bacteriologically confirmed; 4%

were children 4 to 14 years old. 4% of the new cases and relapses of which the HIV-coinfection status was known tested positive for HIV.

Forty-nine per cent of bacteriologically confirmed new cases and 54% of cases with treatment history were tested for resistance to R. RR/MDR-TB Laboratory-confirmed cases were 4,007 and pre-XDR or XDR TB were 210. The RR/MDR-TB cases that were tested for resistance to any FQ were 1,009.

Eighty percent of finance for National TB Programs (NTBP) was national, 9% international and 11% was not funded (WHO, 2021).

Accordingly, all NTPs should prioritize the development of a National TB Laboratory Network (NTBLN) that uses rapid modern diagnoses, has efficient referral systems, uses Standardized Operating Procedures (SOP) and proper quality assurance (QA) processes, and has the recommended biosafety and sufficient human resources. These priorities should be addressed as a whole in the strategic plans and be funded on a regular basis (WHO, 2016).

The emergence of molecular techniques has favorably broken new ground for the new TB diagnostic methods, being more sensitive, high-precision technologies that render results rapid. Their goal is to provide results in hours using connectivity systems set in the platforms to deliver real-time transmission of results to physicians, including identification of the species and Anti-TB Drug Resistance genetic marker detection (Rojano B, 2019).

WHO, together with Stop TB Alliance's Global Laboratory Initiative (GLI), has laid out indicators and goals to evaluate progress by a country towards meeting the objective of strengthening Stop TB Strategy laboratories (increasing access to TB rapid and accurate detection, securing universal access to anti-TB DST; strengthening the quality of laboratory services). Shifting towards the use of these techniques requires a large-scale effort that is coordinated by Health Ministries and supported by local and international partner organizations (WHO, 2016; GLI, 2017).

The capacity of countries for diagnostic tests was previously supervised according to the global goals, that described the number of microscopy centers for every 100,000 inhabitants and of culture laboratories for every million inhabitants. These global goals are no longer in use because of advance in diagnostic technologies and each country's need of specific goals on the basis of epidemiology and patient access (urban and rural populations, sample reference systems, etc.). The WHO recommends a method to determine each

country's specific goals in terms of the number of tests and facilities required for each of the main diagnostic technologies - microscopy, rapid techniques (including Xpert® MTB/RIF), culture and DST.

Information collection and analysis of activities conducted by the NTBLNs help recognize their strengths and weaknesses and check whether resources are enough to meet the diagnostic and surveillance needs for the NTBPs control activities. In 2007, the TB Program from the Region of the Americas conducted a study on NTBLNs in 19 countries. Its purpose was to find out whether laboratory organization and operation fulfilled the NTBP needs in terms of case detection in the 2005-2006 period. At the time, the density of labs that performed smear microscopy (SM) was as high or higher than the density standards recommended by the WHO. In most of these countries, traditional egg-based culture methods in solid medium were used, usually Lowenstein Jensen (LJ). Culture methods with early detection systems in liquid medium were used in few countries, generally in National Reference Laboratories (NRL) which gathered the majority of immunocompromised patients and where the use of rapid and sensitive diagnostic methods is a priority. It was also evident that there was an adequate integration between the NTBLN and the NTP of the different countries (Garzón C., 2007).

In 2012 in response to the growing technological innovation, a new situational analysis was carried out in order to identify needs and gaps in access to quality diagnosis, that form the basis for the development of a NTBLN strengthening plan. Due to the strong boost coming from the TB Program in the region to the spread of culture use, an important increase was observed in the number of labs that carried out cultures. A similar rise occurred in the access to automated liquid-culture methods along with the use of *Mycobacterium tuberculosis complex* (MTBC) rapid identification methods. The addition of the molecular methodology of Line probe assays (LPA), for the rapid molecular detection of MDR-TB, was still modest in the region. Only 11 of the 19 participating countries had access to second-line drug DST. Since this study was conducted in 2011, WHO has issued recommendations and updated guidelines on the use of various diagnostic tests. They featured rapid molecular tests (such as the Xpert MTB/RIF -and its upgrade Xpert MTB/RIF ultra- and loop-mediated isothermal amplification, TB-LAMP), Line Probe Assays for determination of susceptibility to first-line drugs (FL-LPA) and second-line drugs (SL-LPA) and a lateral flow immunochromatography assay for the detection of lipoarabinomannan antigen (LF-LAM) in urine of patients with severe immunodeficiency. NTPs needed to prioritize the

development of NTBLNs that included rapid modern diagnostic methods with efficient reference systems, use of Standardized Operating Procedures (SOP), proper quality assurance, adequate biosafety and sufficient human resources (Sequeira de Latini, M. D., 2014).

In 2017 a new study was conducted on the situation of NTBLNs' structure and organization with the participation of 20 countries of the Americas, thus becoming a basic element for the development of network strengthening plans (Nepotti J., 2017).

The Program "Strengthening TB laboratory diagnosis in the Region of the Americas, 2020-2023", a multi-country grant from the Global Fund, is designed to help to improve the quality of laboratory network TB diagnosis in the Americas by strengthening the capabilities that the region has built. Its specific goals are: i) to reinforce countries' commitment to sustainability in National (NRL) and Supranational (SNRL) Reference Laboratories through the supervision of activities and the development of management and promotion-related skills; ii) to promote the adoption of the international recommendations regarding TB diagnosis in national health policies and their implementation; iii) to contribute to the growth, coordination and implementation of information systems, connectivity and multiple platforms in the National and Regional TB Laboratory Networks, with an inter-programmatic approach. Nearly all countries have undergone transformations in terms of skills and network resources. Therefore, in order to fulfill the second goal, it is necessary to update the NTBLN information and integrate information about the sample transport system and the connectivity capacity by the use of multiple platforms and an inter-programmatic approach. This investigation is intended to update the former study on "Structure and Operation of the NTBLNs in the Americas" form 2017, including information collected in the year 2020. It should consider the sample reference system and the use of multiple platforms in order to make recommendations to decision-makers, suggesting an improvement plan for these systems

Methodology

A cross-sectional study was conducted. The target population were the laboratories that make up the NTBLNs of 17 countries in Latin America: Argentina, Bolivia, Chile, Colombia, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Mexico, Nicaragua, Paraguay, Peru, Dominican Republic, Suriname and Venezuela.

The study took place in 2021, but the questions about laboratory conditions, practices and techniques refer to the 2020 period.

To collect the information, a survey was carried out consisting of a structured questionnaire that was sent to NTBLN workers from all countries. The questionnaire sent to the labs from Guyana, Haiti and Suriname was translated into English.

Questions on the following issues were included:

a) NTBLN Structure:

a.1. Number of laboratories at every level

a.2. Activities performed by the laboratories

a.3. NTBLNs' relations with the NTBPs

a.4. Funding sources

a.5. Diagnostic tests performed (SM and culture, DST, Xpert MTB/RIF, mycobacteria identification, ICL, LPA, other)

b) NRLs

b.1. Techniques performed in the NRLs

b.2. Biosafety

b.3. Training, technical visits and research plans

c) Quality management

c.1. Quality assurance (External Quality Assessment (EQA) for SM, culture, DST, LPA y Xpert MTB/RIF, performance indicator monitoring)

d. Laboratory information and data management

e. Sample reference system (setup and structure)

f. NTBLN strengths and weaknesses

The system containing the questionnaire was available in an online version and was stored in a private hosting to always ensure data integrity and availability. It had a design where the form appearance could be adjusted to any device available (PC, laptops, tablets, smartphones and so on), therefore providing greater

flexibility in the filling of the survey. As for the access, it was gained via a link that was sent by email. The user received a unique password that allowed him to log in, save the progress and continue at another moment as he wished.

When answers were difficult to understand or additional information needed to be provided, referent professionals from the respective NTBLNs were contacted again to clear up doubts and/or send the necessary information.

The *online* questionnaire and system were previously evaluated and validated in a country.

The link to fill out the survey was sent to all countries on September 5th, 2021. All completed the survey, the last one in doing so sending back the survey on October 18th of the same year.

For the calculation of rates and proportions based on population estimates, the numbers provided by the responsible workers in each country were used.

As not every country presented complete information, the indicators denominator was variable. The results of 2020 were compared with those of 2016.

Results

National TB Laboratory Network Structure

The Region of the Americas has five TB SNLs located in Argentina, Chile, Mexico, the United States and Guadeloupe Island. The 17 countries that are recipient of the Global Fund grant can be seen in the following table, four of the SNLs being responsible for their NTBLNs

Table. Distribution of 17 countries by SNL

SNL Argentina	SNL Chile	SNL Mexico	SNL United States
Argentina	Chile	Mexico	Haiti
Guyana	Bolivia	El Salvador	Suriname
Paraguay	Colombia	Guatemala	
Peru	Ecuador	Honduras	
Venezuela	Dominican Rep.	Nicaragua	

NTBLNs are organized in a into tiered or pyramid structure: central, intermediate, local laboratories and sampling centers.

All surveyed countries have intermediate laboratories and only one, Suriname, has no local laboratory. Eleven countries provided information on the number of samples collecting centers. These parameters can be observed in Table 1.

Table 1. TB Laboratory Network Structure. Intermediate, local laboratories and sample collecting centers. Region of the Americas 2020.

COUNTRY	POPULATION	INTERMEDIATE LABS	LOCAL LABS	SAMPLE COLLECTING CENTERS
Argentina	45 376 763	26	702	-
Bolivia	11 500 000	9	704	0
Chile	19 678 363	42	142	-
Colombia	50 883 000	33	1 762	698
Ecuador	17 283 338	22	16	1 741
El Salvador	6 453 553	30	211	-
Guatemala	16 858 333	9	301	4 267
Guyana	786 552	3	16	10
Haiti	11 946 331	10	241	241
Honduras	9 904 607	46	246	-
Mexico	126 014 024	40	1 304	0
Nicaragua	6 595 672	6	173	173
Paraguay	7 252 672	19	135	135
Peru	33 675 304	30	1 870	5 400
Dominican Rep.	10 448 499	42	188	1 480
Suriname	500 000	2	0	10
Venezuela	32 605 423	10	90	11
TOTAL	407 762 434	379	8 101	14 166

In most of these countries, the activities that intermediate labs carry out are basically linked to Xpert® MTB/RIF performance, SM diagnosis and culture, quality control, supervision, information reception and processing, as observed in Table 2.

Table 2. Activities carried out by Intermediate Laboratories. TB Laboratory Networks. Region of the Americas, 2020.

Performed activities and tests	Countries (%)
Xpert MTB/RIF	16 (94)
Microscopic Examination	15 (88)
Culture	14 (82)
Quality Control	14 (82)
Supervision	12 (71)
Information Reception and Processing	12 (71)
Training	11 (65)
Research	6 (35)
LPA	5 (29)
Phenotypic Susceptibility Tests	4 (24)

In the 16 countries that have local laboratories, their activities basically include microscopic analysis execution, sample reception and referral and information transfer to intermediate labs or the NRL. Only in seven countries, local labs performed Xpert® MTB/RIF.

Relations between the NTBLN and the NTBP

Seventy-six percent (13) of the countries stated there is an official responsible for the NTBLN or a link between this Network and the Ministry of Health/TBNP

Twelve countries have an activity plan for the NTBLN that is written and agreed with the NTBP. Nine of them drafted this plan after 2019, the other three were drafted between 2016-2018

The activities that are done together with the TBNP are: participation in Advisory Technical Committees, preparation of the National TB Control Strategic Plan, evaluations of the NTP activities.

Table 3 presents the frequency of meetings between the NTBLN and the NTBP to assess together the activities that concern both. Most of the countries reported that these meetings are held on demand.

Table 3. Frequency of joint meetings between TBNPs and NTBLNs. TB Laboratory Networks. Region of the Americas, 2020.

Frequency	Total countries	Countries
On demand	10	Bolivia, Chile, Colombia, Ecuador, Guatemala, Honduras, Mexico, Peru, Dominican Republic, Venezuela
Monthly	6	Chile, Haiti, Nicaragua, Paraguay, Peru, Venezuela.
Quarterly	2	Guyana, Honduras
Biannual	2	El Salvador, Honduras
Annual	2	Honduras, Venezuela
Four-monthly	1	Suriname
Other	1*	Argentina

* Weekly/Fortnightly

Thirteen countries (76%) declared they sent information of NTBLN activities to the TBNP (quality management, operational indicators, training, NTBLN supervision, research). The frequency these countries sending information is observed in Table 4.

Table 4. Frequency of information transfer from the NTBLN to the NTBP. TB Laboratory Networks. Region of the Americas, 2020.

Frequency	Total countries	Countries
Annual	6	Argentina, Bolivia, Chile, Honduras, Suriname, Venezuela
Monthly	5	Bolivia, Ecuador, Guatemala, Nicaragua, Dominican Republic
On demand	4	Argentina, Honduras, Dominican Republic, Venezuela

Quarterly	3	Haiti, Honduras, Paraguay
Biannual	2	Argentina, El Salvador

Funding Sources

Nine countries (53%) (Bolivia, Colombia, El Salvador, Guyana, Haiti, Honduras, Paraguay, Peru, Dominican Republic) had a specific budget for the fulfillment of the NTBLN activity plan, whose funding sources were:

- ❖ *National Government/national treasure*: All the countries with a fixed budget are funded by the national treasure, making it the leading funding source of the Laboratory Networks. In six/seven countries, this budget is 50% or higher (excluding Haiti and Honduras), and in five countries (Bolivia, Colombia, El Salvador, Guyana and Dominican Republic) is equal to or higher than 80%.

- ❖ The *Global Fund* finances the Laboratory Networks of eight countries (Bolivia, El Salvador, Guyana, Haiti, Honduras, Paraguay, Peru and Dominican Republic), but only in three networks (Haiti, Honduras and Paraguay) this budget is 50% of higher. In four of these Laboratory Networks (Bolivia, El Salvador, Guyana and Dominican Republic), the Global Fund invested 20% or less of the budget.

- ❖ None of the Laboratory Networks with a NTBLN-specific budget declared being funded by *Private Funds* and/or *NGOs*.

88% (15) of countries (excluding Chile and Ecuador) were engaged in project design to get financial resources for the NTBP and the NTBLN, where the funding sources were:

- ❖ Global Fund (stated by 12/15 countries) (excluding Peru, Dominican Republic and Venezuela)

- ❖ Funds from the Public Health Ministry (3/15) (Honduras, Paraguay and Dominican Republic)

- ❖ National Funds (3/15) (Guyana, Honduras and Venezuela)

- ❖ Scientific and Technologic Development and Innovation National Fund – Concytec Fondo Newton Paulet TB Alliance Banco Interamericano de desarrollo (1/15) (Peru)

Diagnostic tests performed by laboratories

Microscopy and culture

In Table 5, the number of laboratories that perform SM, culture, Anti-TB drug DST can be observed for the different countries that participated in the study.

In all the countries, Ziehl-Neelsen staining is standard, while in three (Argentina, Guatemala and Chile) conventional fluorescence is also used (with mercury or halogen lamps) and in 11 countries LED-lamp fluorescence is used (Argentina, Bolivia, Colombia, Chile, Guyana, Haiti, Mexico, Nicaragua, Paraguay, Peru and Suriname). In four countries (Colombia, Nicaragua, Chile and Haiti), there are over 10 labs that employ LED-lamp fluorescence technique.

Table 5. Laboratories that perform smear microscopy, culture, and DST. TB Laboratory Networks. Region of the Americas, 2020.

Country	Laboratories		
	SM	**Culture**	**DST**
Argentina	728	123	19
Bolivia	704	106	S/I
Chile	150	42	44
Colombia	1 745	197	77
Ecuador	263	22	S/I
El Salvador	211	6	1
Guatemala	310	10	4
Guyana	10	1	S/I
Haiti	241	2	S/I
Honduras	293	6	1
Mexico	1 345	40	S/I
Nicaragua	173	5	1
Paraguay	137	15	S/I
Peru	1 870	82	46
Dominican Rep.	248	16	2
Suriname	2	1	S/I

Venezuela	90	2	1
Total	**8 520**	**676**	**196**

Table 6 presents culture methods and/or media used in the different participant countries.

Table 6. Culture method and/or medium used by the NTBLNs. Region of the Americas, 2020.

COUNTRY	CULTURE MEDIUM					
	Lowenstein Jensen	**BACTEC MGIT 960/320**	**Acidified Ogawa**	**Middlebrook**	**Stonebrink**	**Bact Alert 3D**
Argentina	x	x	x		x	
Bolivia			x			
Chile	x	x				
Colombia	x	x	x	x		x
Ecuador			x			
El Salvador	x		x			
Guatemala	x	x				
Guyana	x	x				
Haiti	x	x		x		
Honduras	x		x			
Mexico	x	x		x	x	
Nicaragua	x	x				
Paraguay	x	x	x		x	
Peru	x	x	x			

Dominican Rep.		x	x			
Suriname	x			x		
Venezuela	x		x	x	x	

Xpert MTB/RIF

There is an increasingly high proportion of countries where the Xpert MTB/RIF technology is available. All 17 countries had labs equipped with GeneXpert equipment to execute this test (85% of the equipment belongs to labs in the public sector and 15% to labs in the private sector).

Of the 17 polled countries, seven stated that they applied Xpert MTB/RIF as a universal or primary diagnostic test (Chile, Ecuador, Guyana, Haiti, Paraguay, Dominican Republic, and Suriname), nine reported that they used it in prioritized groups, and one country (Honduras) gave no information on this topic. Of the countries that reported the use of the Xpert MTB/RIF test for priority group diagnosis, all (9) included patients with treatment history (in the following risk-related order: failures, recoveries after missing follow-ups, relapses), contacts of drug-resistant TB cases (household co-habitants, inmates or workers from health institutions or prisons where RR/MDR-TB cases have been confirmed), and immunocompromised patients (HIV-positive and diabetic). Eight countries (Argentina, Colombia, El Salvador, Guatemala, Mexico, Nicaragua, Peru, Venezuela) included as priority groups patients with positive sputum SM after completing the second month of treatment and patients diagnosed with negative SM turning into positive SM. Five countries (Argentina, Colombia, Guatemala, Nicaragua and Venezuela) included patients with poor treatment adherence and just three (Bolivia, Nicaragua and Venezuela) applied the test to patients with Anti-TB drug intolerance.

In table 7, the number of laboratories that feature GeneXpert equipment are shown as well as Xpert MTB/RIF test completions by participant country, the number of available modules, the number of Xpert MTB/RIF-examined samples and the percentage of Xpert MTB/RIF use per country based on the yearly capacity of available systems. To calculate the mentioned capacity of systems per year, the number of tests were estimated that could be made with the available modules per country, assuming each module can process 3 daily samples. On an 8-hour day, the estimated capacity per module totals 750 samples/year, approximately.

Only five countries provided information on the use of Xpert MTB/RIF in negative-SM patients (Argentina, Bolivia, Mexico, Dominican Republic, Venezuela). Among them, the percentage of Xpert MTB/RIF-examined negative-SM patients with MTB-result detected by this method varied from 5.9% in Mexico to 71.5% in Dominican Republic. Seven countries reported the use of GeneXpert equipment exclusively to diagnose TB (Table 8).

Table 7. GeneXpert system availability and application in the NTBLNs, Region of the Americas, 2020.

Country	Laboratories with GeneXpert	Modules	Xpert MTB/RIF examined samples	Yearly capacity of available systems [1]	Xpert MTB/RIF use (%) [2]
Argentina	12	35	872	26 250	3.3
Bolivia	17	68	9 106	51 000	17.9
Chile	41	164	28 626	123 000	23.3
Colombia	56	N/D	N/D	N/D	NA
Ecuador	30	N/D	8 424	N/D	NA
El Salvador	20	140	22 229	105 000	21.2
Guatemala	42	224	8 667	168 000	5.2
Guyana	7	28	1 056	21 000	5.0
Haiti	34	184	N/D	138 000	NA
Honduras	11	44	N/D	33 000	NA
Mexico	63	85	4 670	63 750	7.3
Nicaragua	N/D	N/D	1503	N/D	NA
Paraguay	23	86	N/D	64 500	NA
Peru	46	218	25 087	163 500	15.3
Dominican Rep.	28	122	12 933	91 500	14.1
Suriname	6	24	N/D	18 000	NA
Venezuela	2	8	208	6 000	3.5

[1] The annual capacity of available systems was calculated considering that 750 samples can be performed per year per module.
[2] Percentage calculated using as numerator the number of samples investigated by Xpert MTB/RIF and as denominator, the annual capacity of available systems.
N/D: No Data   NA: Non-applicable

Table 8. Infections or diseases for which the GeneXpert equipment available in the country is used for diagnosis

Use of GeneXpert units for Diagnosis	Total Countries	Country names
SARS-CoV-2	10	Argentina, Colombia, Guatemala, Guyana, Haiti, Honduras, Paraguay, Peru, Dominican Rep., Suriname
TB-exclusive	6	Bolivia, Chile, Ecuador, Mexico, Nicaragua, Venezuela
HIV	7	Colombia, Guatemala, Haiti, Paraguay, Peru, Dominican Rep., Suriname
Hepatitis	1	Colombia
ITS	1	Guatemala
Chlamydia y Mycoplasma	1	Argentina

In Graph 1, percentages are shown for Xpert MTB/RIF-detected MTB-RR result samples in the NTBLNs, by country.

Graph1. Percentages of Xpert MTB/RIF-detected MTB-RR result samples in the NTBLNs, by country. Region of the Americas, 2020.
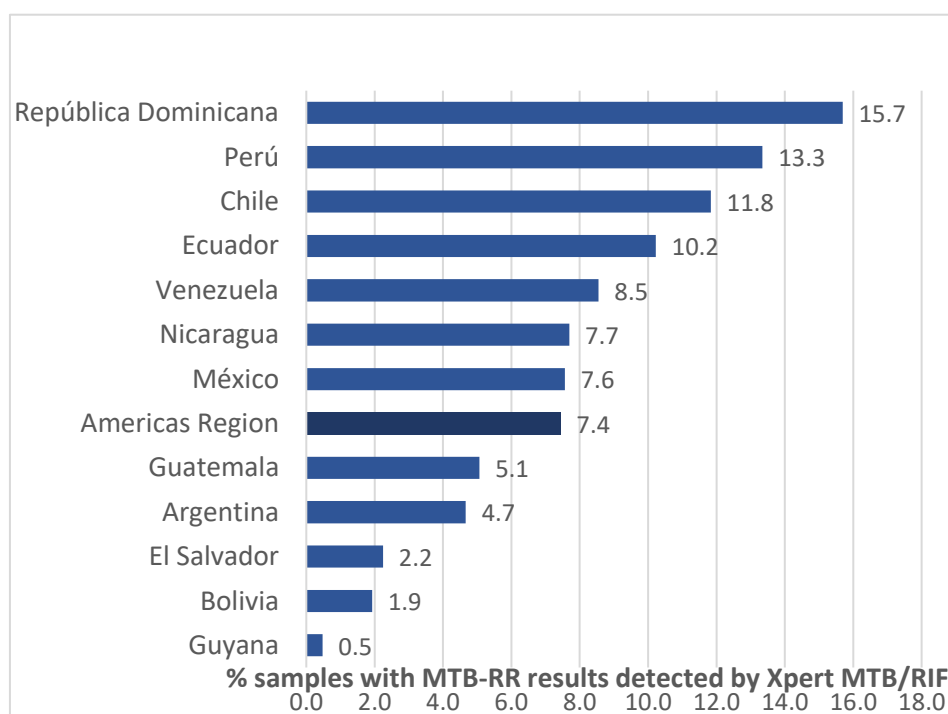
* Colombia, Haiti, Honduras, Paraguay, and Suriname are not included in the graph, because no information was provided for 2020.

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Mycobacteria identification

As to mycobacteria identification occurring in the NTBLN, including the NRL, in all participant countries there was at least one laboratory that made mycobacteria identification tests. The identified Mycobacterium species can be observed in Table 9.

Table 9. Mycobacterium Species identified in NTBLN laboratories

Identified mycobacteria	Total countries
Mycobacterium tuberculosis complex	17
Mycobacteria other than *Mycobacterium tuberculosis complex*	10
Mycobacterium bovis within the *Mycobacterium tuberculosis complex*	7

Ten countries (Bolivia, Colombia, Chile, Guatemala, Guyana, Haiti, Mexico, Nicaragua, Peru, and Venezuela) reported that they use Line Probe Assays (LPA) for *M. tuberculosis* Complex identification, along with Anti-TB drug-resistance detection. In Table 10, the methods that countries apply for LPA test performance can be observed.

Table 10. Methods applied by NTBLNs for LPA test performance. Laboratory Networks, Region of the Americas, 2020.

Method	Total countries	Countries
GenoType® MTBDRplus in isolates	10	Bolivia, Colombia, Chile, Guatemala, Guyana, Haiti, Mexico, Nicaragua, Peru, Venezuela
GenoType® MTBDRplus in biologic samples	8	Bolivia, Colombia, Chile, Guatemala, Mexico, Nicaragua, Peru, Venezuela
GenoType® MTBDRsl	9	Bolivia, Colombia, Chile, Guatemala, Haiti, Mexico, Nicaragua, Peru, Venezuela

Other nucleic acid identification tests

Fourteen of all 17 countries declared that they produced lateral flow immunochromatographic assays (LFIA) in their NRLs. The three countries that did not implement this technique are Bolivia, El Salvador and Suriname. Bolivia applies phenotypic tests and LPA, El Salvador phenotypic tests alone, while Suriname does not make species identification. Eight countries specified the number of NTBLN labs that performed LFIA, only four being shown to have more than five labs, Colombia (40), Dominican Republic (16), Peru (7) and Honduras (6).

Only six countries (35%) (Argentina, Colombia, Ecuador, Guatemala, Guyana and Paraguay) reported use of other nucleic acid amplification tests. Five of them apply it to TB diagnosis, three for Anti-TB drug susceptibility determination, and two for species identification (such uses not being mutually exclusive). In addition, Chile and Colombia declared that they used the BD MAX system for TB diagnosis (in the case of Colombia only for TB-MDR cases), while Guatemala reported use of the LAM test specifically for diagnosis in HIV-positive population, in Comprehensive Care Units.

Anti-TB Drug Susceptibility Testing

Of the total surveyed countries, 16 reported they performed first-line Anti-TB Drugs DST (the exception is Suriname). Table 11 shows the media/methods that are used by these countries' NTBLN laboratories to make DSTs and the number of laboratories that make use of them over 2020.

Table 11. First-line Anti-TB drug DST media and/or methods. National TB Laboratory Networks. Region of the Americas, 2020.

Susceptibility Test Media and/or Methods	Total countries	Country name
BACTEC-MGIT 960/320	11	Argentina (17), Colombia (6), Chile (1), Ecuador (1), Guyana (1), Haiti (2), Mexico (20), Nicaragua (1), Paraguay (1), Peru (1), Dominican Rep. (2)
Solid medium proportion method	10	Argentina (7), Bolivia (3), Ecuador (1), El Salvador (1), Guatemala (1), Honduras (1), Mexico (1), Paraguay (1), Dominican Rep. (1), Venezuela (1)
Nitratase test	3	Argentina (4), Paraguay (1), Venezuela
MODS	2	Paraguay (1), Peru (5)

Of the 16 countries that make DST of first-line drugs, all include H and R, 11 incorporate ethambutol (E), pyrazinamide (Z) and one adds streptomycin (S). Of the countries that make Z DST, two stated that they used the Wayne Method and two the BACTEC MGIT 960/320 Method. Of the countries that reported critical concentrations (CC) in the drugs that were used (Guatemala, Guyana, Honduras, and Haiti did not report), these concentrations match the last WHO recommendations in all cases, depending on the method or medium. Of the nine countries that make MGIT960/320, four (Argentina, Colombia, Paraguay and Dominican Republic) added the new CC recommendation of 0.5 mg/L for R.

Fifteen of all 17 countries reported that they made DST to second-line drugs (the exceptions are Guyana and Suriname). Argentina, Ecuador, Paraguay, and Dominican Republic indicated they used BACTEC MGIT 960/320 in addition to the solid-medium proportion method. Six countries use just BACTEC MGIT 960/320 (Colombia, Chile, Haiti, Mexico, Nicaragua, and Peru) and five use just the solid-medium proportion method (Bolivia, Guatemala, El Salvador, Honduras, and Venezuela).

In Table 12, the medications that countries use in second-line drug DST are presented.

Graph 2 shows the percentage distribution of TB cases (new and re-treated) informed using DST results for at least R, per country for the year 2020. While some countries reported 100% of cases using DST results (Ecuador and Bolivia), others were below 10% (such as Mexico, Venezuela, and Nicaragua).

Table 12. Drugs used in the second-line Anti-TB medication DST in the NTBNLs. Region of the Americas, 2020.

Drug	Total countries	Country
Group A		
Levofloxacin	13	Argentina, Bolivia, Colombia, Chile, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Paraguay, Dominican Rep., Peru, Venezuela
Moxifloxacin	10	Argentina, Colombia, Chile, Ecuador, Honduras, Mexico, Nicaragua, Paraguay, Peru, Dominican Rep.
Bedaquiline	6	Argentina, Colombia, Chile, Honduras, Mexico, Peru
Linezolid	5	Argentina, Colombia, Chile, Mexico, Peru
Grupo B		

Clofazimine	5	Argentina, Colombia, Chile, Mexico, Peru
Cycloserine	1	Haiti
Grupo C		
Amikacin	11	Argentina, Bolivia, Colombia, Ecuador, Guatemala, Haiti, Mexico, Paraguay, Dominican Rep., Peru, Venezuela
Delamanid	6	Argentina, Colombia, Chile, Honduras, Mexico, Peru
Ethionamide	5	Argentina, El Salvador, Honduras, Mexico, Venezuela
Capreomycin	3	Bolivia, Ecuador, Venezuela
Kanamycin	2	Bolivia, Paraguay
PAS	1	Haiti

Graph 2. Percentage of TB cases (new and re-treated) informed using DST results for at least Rifampicin. Region of the Americas, 2020.
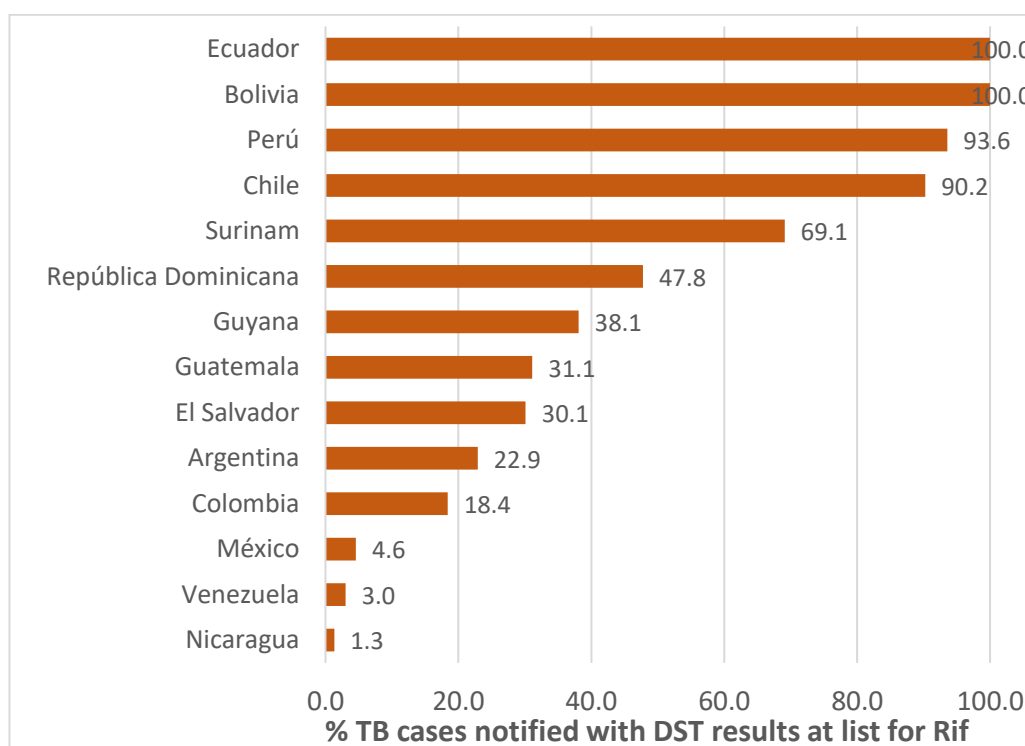
Techniques used in NRLs

The methodology types that NRLs applied for *Mycobacterium tuberculosis* drug susceptibility detection, isolation, identification, and determination are outlined in Table 13.

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Table 13. Methodology types applied for *Mycobacterium tuberculosis* drug susceptibility detection, isolation, identification, and determination. TB Laboratory Networks. Region of the Americas, 2020.

COUNTRY	SM AND CULTURE IN PULMONARY SAMPLES	SM AND CULTURE IN EXTRA-PULMONARY SAMPLES	LIQUID MEDIA WITH DST AUTOMATED READING	XPERT MTB/ RIF	LFIA	LPA
Argentina	NO	NO	YES	YES	YES	NO
Bolivia	NO	NO	NO	NO	NO	YES
Chile	NO	NO	YES	NO	YES	YES
Colombia	NO	NO	YES	NO	YES	YES
Ecuador	NO	NO	YES	NO	YES	YES
El Salvador	YES	YES	NO	YES	NO	NO
Guatemala	YES	YES	NO	YES	YES	YES
Guyana	YES	YES	YES	YES	YES	YES
Haiti	YES	YES	YES	YES	YES	YES
Honduras	YES	YES	NO	YES	YES	NO
Mexico	YES	YES	YES	YES	YES	YES
Nicaragua	YES	YES	YES	YES	YES	YES
Paraguay	YES	YES	YES	YES	YES	NO
Peru	NO	YES	YES	NO	YES	YES
Dominican Rep.	YES	YES	YES	YES	YES	NO
Suriname	YES	YES	NO	YES	NO	NO
Venezuela	YES	YES	NO	YES	YES	YES

Of the 17 NRLs, 11 perform SM and culture in pulmonary samples and 12 culture extra-pulmonary samples.

Of the 11 NRLs that use LPA, 10 apply this technique to detect H and R resistance as well as second-line drug resistance, while one country -Guyana- only uses LPA to detect

first-line drug resistance. Argentina has the equipment and applies this method depending on availability of reagents, which is why LPA-based diagnosis was discontinued in 2020.

In the NRLs that make cultures, the most frequent media were Lowenstein Jensen (12 countries) and MGIT 960/320 (eight countries). The remaining NRLs use the Ogawa medium (Honduras, Paraguay, Dominican Republic, and Venezuela), Stonebrink (Paraguay and Venezuela), Middlebrook (Venezuela) and visual reading MGIT (Guyana).

All NRLs perform Mycobacterium identification: 100% identify *Mycobacterium tuberculosis*, 9 (53%) identify *M. bovis* within the *M. tuberculosis* Complex and 14 (82%) perform identification of other mycobacteria beside the *M. tuberculosis* Complex.

The *M. Tuberculosis* Complex identification methods that NRLs use can be observed in Table 14.

Table 14. *M. Tuberculosis* Complex identification methods used in NRLs. TB Laboratory Networks. Region of the Americas, 2020.

Identification methods	Total countries	Country name
Lateral Flow Immunochromatographic Assay (LFIA)	15	Argentina, Colombia, Chile, Ecuador, Guatemala, Guyana, Haiti, Honduras, Mexico, Nicaragua, Paraguay, Dominican Rep., Peru, Suriname,
PCR	13	Argentina, Colombia, Chile, Guatemala, Guyana, Haiti, Honduras, Mexico, Paraguay, Dominican Rep., Peru, Suriname, Venezuela
Phenotypic tests	7	Argentina, Bolivia, El Salvador, Guyana, Nicaragua, Paraguay, Venezuela
LPA	2	Bolivia, Chile

Only two NRLs (Chile and Colombia) reported that they made *M. bovis* isolates using cultured samples in their facilities. In the case of Chile, it reported two isolates during 2020, the culture being made in liquid medium and the identification using LPA. The NRL from Colombia reported one *M. bovis* isolate in the same year and carried out the identification through a standardized species-distinguishing PCR.

Twelve NRLs (71%) provided Anti-TB DSTs universally, while the remaining 29% (Colombia, Guyana, Mexico, Dominican Republic, Venezuela) used DSTs for priority groups.

Only Suriname's NRL failed to make DSTs for first-line medication. The remaining NRLs used phenotypic methods, as outlines in Table 15. The solid-medium proportion method and BACTEC MGIT 960/320 were the most widely applied in first-line drugs.

Table 15. Phenotypic methods used for NRL first-line Anti-TB drug susceptibility tests. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Methods	Total countries	Country name
BACTEC MGIT 960/320	11	Argentina, Colombia, Chile, Ecuador, Guyana, Haiti, Mexico, Nicaragua, Paraguay, Peru, Dominican Rep.
Solid-medium proportion method	10	Argentina, Bolivia, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Paraguay, Dominican Rep., Venezuela
Nitratase test	2	Paraguay, Venezuela
MODS	1	Paraguay
Other*	2	Argentina, Paraguay

*CIM for MNT, Wayne

All NRLs that make first-line DSTs tested H and R. Only 11 (65%) NRLs tested E and 8 (47%) tested Z. Suriname NRL did not test any first-line drug.

15 (88%) NRLs make second-line DSTs (the exceptions are Guyana and Suriname). The phenotypic methods that the NRLs used are shown in Table 16. The same as for first-line drugs, the solid-medium proportion method y MGIT 960/320 were the most widely used.

Table 16. Phenotypic methods used the for NRL second-line DST. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

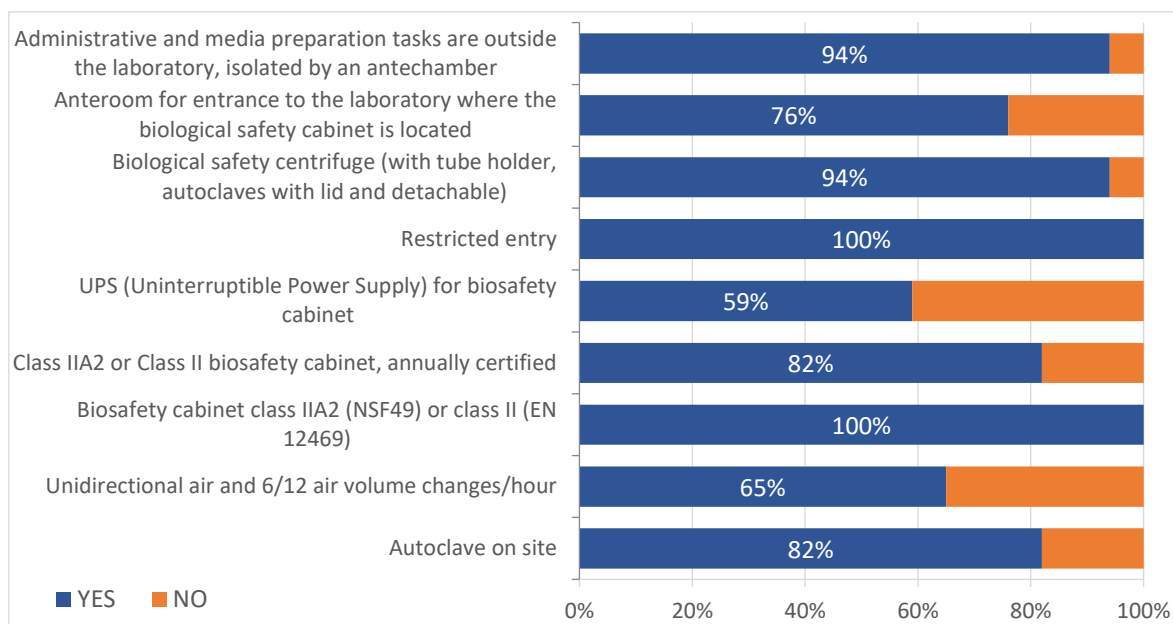| Phenotypic methods	Total countries	Country
Solid medium proportion method	8	Argentina, Bolivia, Ecuador, El Salvador, Guatemala, Honduras, Paraguay, Venezuela
BACTEC MGIT 960/320	7	Argentina, Colombia, Chile, Ecuador, Mexico, Paraguay, Peru
Liquid medium	2	Haiti, Dominican Republic
Nitratase test	1	Venezuela

The first-line drugs that were tested all 15 NRLs are the same as reported for these countries NTBLNs (Table 12).

Three NRLs perform other nucleic-acid amplification tests, whether for drug susceptibility detection, identification and/or determination, namely: MAS PCR IN Argentina, species identification in Colombia and Paraguay. Also, two RNLs mentioned they are implementing full genome sequencing (Argentina and Suriname, the latter outside the country).

Biosafety in NRLs

To fulfill the referential functions, the NRL needs to have safe facilities. The proportion of NRLs that feature a variety of infrastructure and biosafety minimal and essential requirements is displayed in Graph 3. Only the restricted access requirement was met by all 100% of the polled countries. Argentina, Chile, and Peru that met all the survey's biosafety conditions.

Graph 3. NRL biosafety requirements. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Requirement	YES	NO
Administrative and media preparation tasks are outside the laboratory, isolated by an antechamber	94%	
Anteroom for entrance to the laboratory where the biological safety cabinet is located	76%	
Biological safety centrifuge (with tube holder, autoclaves with lid and detachable)	94%	
Restricted entry	100%	
UPS (Uninterruptible Power Supply) for biosafety cabinet	59%	
Class IIA2 or Class II biosafety cabinet, annually certified	82%	
Biosafety cabinet class IIA2 (NSF49) or class II (EN 12469)	100%	
Unidirectional air and 6/12 air volume changes/hour	65%	
Autoclave on site	82%	

Thirteen countries declared that they get an annual certification of NTBLN biological safety cabinets (BSC). Six of them have 100% of their BSC certified (Argentina, Guyana, Haiti, Nicaragua, Paraguay, Dominican Republic), three between 65-85% of their BSC (Colombia, Chile, Peru) and the rest less than 50% (Guatemala, Mexico, Venezuela). One country gave no information of the percentage.

In relation to occupational health programs, whose goal is to create a safe working environment, 11 countries (65%) stated that they have planned yearly medical checkups. However only five perform PPD intradermal test annually, and seven include chest x-rays on a year or two-year basis. Some countries include other kind of medical examinations, such as routine analyses, serology, cardiovascular tests, gynecology tests, vaccination card, formol detection, and so on.

NRL training, technical visits and research plan

Three of all 17 study participant countries' NRLs, declared that they had a research plan involving the NTBLN laboratories (Colombia, Haiti y Peru), and 10 (Bolivia, Colombia, Ecuador, El Salvador, Guyana, Haiti, Honduras, Mexico, Nicaragua, Paraguay) indicated that they had a training program that was developed later than 2016 (seven made this program in 2020-2021).

Ten countries also ran training courses virtually during 2020, being conditioned by the Covid-19 pandemic context. The course subjects were update in diagnostic methods,

diagnostic algorithms, quality control and data analysis, informational system, biosafety, TB and Covid-19, Xpert MTB/RIF and sample transport. Only six NRLs (Colombia, Chile, Guatemala, Haiti, Paraguay, Peru) suggested that these virtual courses could be submitted to the Regional Laboratory Network in make them available in other countries.

Thirteen NRLs (76%) ran training activities to their NTBLNs over 2020. The subjects that they covered are described in Table 17.

Table 17. Subjects covered in training courses that were run by the NRLs to their NTBLNs during 2020. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Subjects	Total countries
Xpert MTB/RIF test	7
Microscopic analysis	5
Biosafety	5
Quality control	4
Sample reference system	4
Culture	3
Susceptibility identification and test	3
Information system	3
Other genotypic diagnostic techniques	1

In connection with trained laboratories and people, the number of laboratories that were given training in each country and the total trained personnel is presented in Table 18.

Table 18. Trained laboratories and personnel during 2020. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Country*	Total laboratories (Intermediate + local)	Total trained laboratories	% Coverage	Total trained personnel
Argentina	728	30	4.1%	180
Bolivia	713	10	1.4%	30
Chile	184	-	-	150
Colombia	1 795	1 413	78.7%	2 390
Ecuador	38	-	-	100

El Salvador	241	3	1.2%	5
Guatemala	310	29	9.3%	120
Guyana	19	6	31.6%	40
Haiti	251	25	9.9%	40
Nicaragua	179	10	5.6%	20
Paraguay	154	25	16.2%	200
Peru	2 000	60	3.0%	600
Suriname	2	2	100%	6

*Only includes the 13 RNLs who reported they were given training during 2020.

In relation to technical visits, supervision, or monitoring, 16 NRLs stated that they have a standardized guide to conduct them. However, 11 NRLs conducted then over 2020 (Table 19).

Table 19. Local and intermediate laboratories that had a technical visit, on site or virtually, by the NRL over 2020. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Country	Total intermediate labs	Total on-site visited intermediate labs	Total virtually visited intermediate labs [1]	Total local labs	Total visited local labs [1]
Bolivia	9	9	0	704	0
Chile	42	0	7	142	0
Colombia	33	33	33	1 762	60
El Salvador	30	3	0	211	0
Guatemala	9	7	-	301	45
Guyana	3	3	-	16	-
Haiti	10	10	0	241	241
Nicaragua	6	6	-	173	39
Paraguay	19	6	17	135	0
Peru	30	10	30	1 870	5
Suriname	2	1	1	0	0

[1] A single visit per lab was recorded, but some NRLs visited some labs more than once.

Quality management

The quality management system is defined as "coordinated activities to manage and control an organization in terms of quality" In this system all operational aspects of a laboratory, from the organizational structure to processes and procedures, must be addressed to assure quality, considering the workflow from patient care to result notification. A complete and systematic quality assurance program allows laboratories to achieve and maintain high standards of accuracy and skill in tests to guarantee results reliability and replicability.

Six countries (Bolivia, Ecuador, Guyana, Honduras, Paraguay y Suriname) have no up-to-date Quality Management manuals. In countries that do have manuals they date from the year 2016 and, the remainder was written later than 2018. In terms of SM, Paraguay, Honduras, and Suriname have no up-to-date manuals. As for the Culture Manual, Suriname is the only country where there is none, while 63% of the countries that have these guides wrote them after the year 2018 (range 2007-2021). One country (Honduras) failed to provide the year of production. Four countries (Colombia, Nicaragua, Paraguay, and Suriname) are wanting in Guides for Diagnosis using Xpert MTB/RIF. 11 countries reported that their guides were written in 2018 or in a subsequent year (range 2018-2021, Ecuador y Haiti failed to provide the year). It could also be established that only 2 countries (Paraguay y Suriname) have no DST Manual. In the other countries, all manuals were written in 2018 or in a subsequent year (range 2018-2021, Honduras failed to provide a year) (Graph 4).

Graph 4. Number of countries that have standardized Guides. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
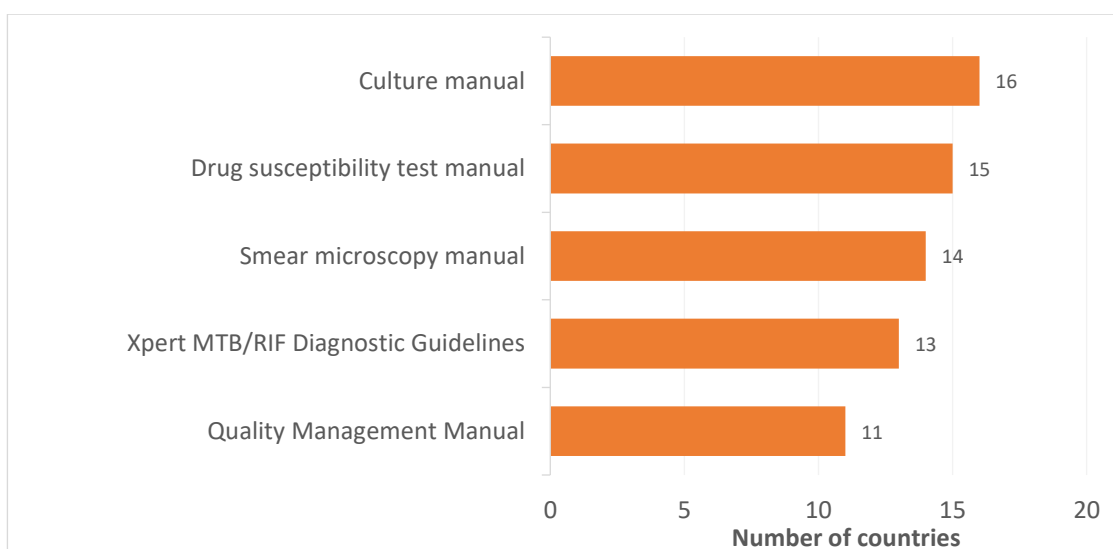
Except for one country (Guatemala), all NRLs have SOPs of the implemented and standardized tests. Three countries (Argentina, Honduras, and Guatemala) do not have SOPs in all intermediate-level labs, and eight countries in local-level labs. Biosafety's SOPs are missing in 6 NRLs LRN (Colombia, Bolivia, Guatemala, El Salvador, Honduras, Venezuela), and in 10 countries at intermediate level (Argentina, Colombia, Bolivia, Guatemala, Guyana, El Salvador, Honduras, Paraguay, Peru, Venezuela) and in 11 countries at the local level (the latter countries together with Suriname).

Fourteen countries featured Internal Control Records both in NRLs and in intermediate-level labs, and nine countries have them in local labs.

NRLs from Chile, Mexico, Peru, and Suriname have gotten certification according to the standard ISO 15 189 or 17 025. None of the countries reported that any other laboratory, apart from the NRL, have been certified according to this standard. Four NRLs certified techniques/procedures: Chile's NRL certified LPAs for first and second-line drug DST; Mexico's and Suriname's, SM by Ziehl-Neelsen technique; Peru, first-line drug LPAs.

Quality Assurance

Quality assurance, as a part of the Quality Management System, is a series of activities intended to assess work for the measurement of a product's quality (in our case, called diagnosis). As such, QA helps detect the presence of faults in the development of the product itself and establish correction measures where and when they are needed to keep a diagnosis of certainty that helps to optimize patient clinical management and, indirectly, enhance the effectiveness of epidemiological surveillance.

The elements that are believed to be key in a quality assurance program are:

a) Internal quality control

b) External quality assessment (EQA)

c) Performance indicator monitoring

d) Continuous improvement

Indirect SM Quality External Assessment

Its goal is the identification of laboratories with technical or operational flaws and these flaws causes. The EQA that is used for SMs can be performed using two methods:

• Routine re-reading of network laboratories' slides: this method is used by the supervisor laboratory to re-read a sample of the SM slides that are routinely made by network laboratories. The laboratory assesses the quality of not just the microscopic reading but also other technical aspects, such as the characteristics of smear production, staining and the type of samples that are processed by labs in their routine work.

• Panel submission form the NRL: generally, the reading quality alone is assessed. When uncolored smears are included, the quality of the staining can also be assessed. It is not helpful to appraise the laboratory's routine work.

In all NTBLN 17 countries, SM EQA is made for at least slide re-reading, but some didn't make EQA over 2020. Eight countries (41%) regularly carry out both methods (panel submission and slide re-reading) (Argentina, Bolivia, Colombia, El Salvador, Guyana, Mexico, Peru and Suriname), while the other nine (59%) carry out just slide re-reading. Coverage by each method can be calculated independently, but with the existing information, it is not possible to calculate EQA global coverage for each country (Graph 5). In 2020, two countries (Mexico and Suriname) failed to do slide re-reading and two countries did not report whether they did (Honduras and Paraguay). Four countries did not submit panels in 2020 (Argentina, El Salvador, Mexico, and Suriname).

Graph 5. Coverage (%) of Microscopy External Quality Assessment using the slide re-reading and panel submission methods. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
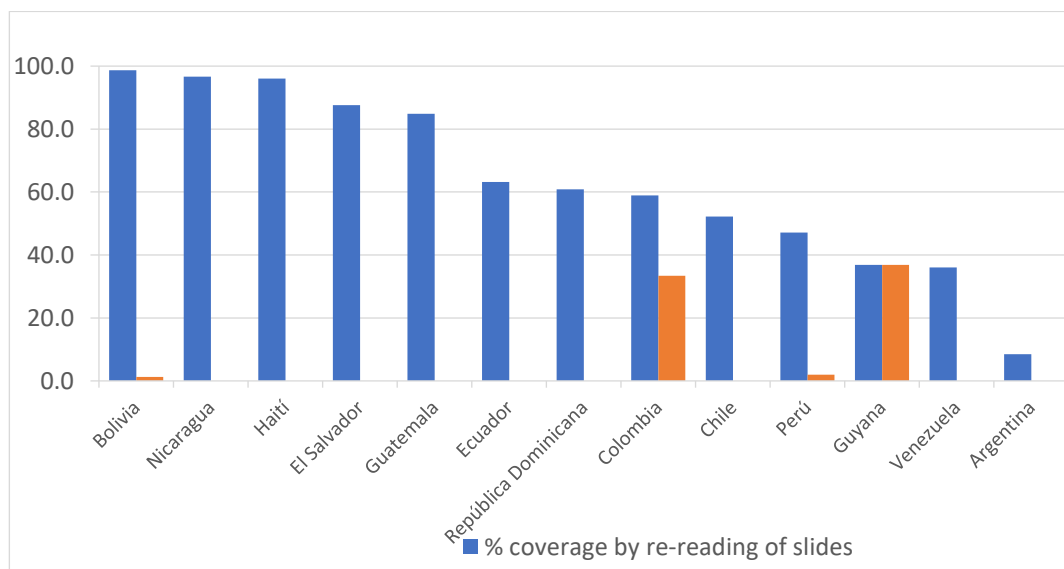
Slide panel submission coverage

Eight countries make slide panel submissions, but only four countries did it over 2020. 79% to 100% of participant microscopists produced an acceptable quality, as observed in Table 20.

Table 20. External quality assessment. Panel submission form. Acceptable quality Microscopists. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Country that makes EQA in slide panel submission form	Total assessed microscopists	Total acceptable-quality microscopists	Acceptable quality %
Bolivia	20	20	100
Colombia	691	546	79
Guyana	7	7	100
Peru	40	39	98

Slide re-reading coverage

All surveyed countries regularly use this method, but during 2020 it was implemented by 13 countries. Three countries did not report the number of labs with acceptable quality (Graph 6)

Graph 6. Microscopy External Quality Assessment. Slide re-reading form, acceptable quality laboratories. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
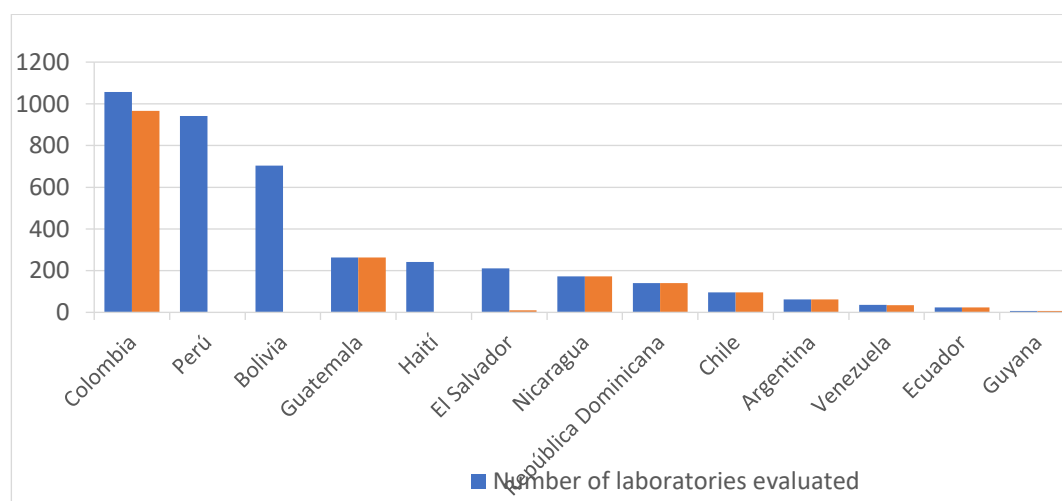
Bolivia, Haiti and Peru did not report the number of laboratories with acceptable quality.

In the NTBLNs, a variety of standards were set to rate a laboratory with an acceptable performance level, based on the number, error type (false negatives and false positives, low and high), and concordance. Percentages of false positives and false negatives between 0%-5%, concordances higher than 90% were accepted without identification of false positives and high negatives.

The percentage of false positives was reported by 10 of the countries that did slide re-reading and got a range of 0.03% - 13%, but 80% was lower than 1%. The percentage of false negatives was reported by 10 of the countries that did slide re-reading and got a range of 0% - 26%, but 70% of countries were rated below 1%.

Indirect Culture Quality External Assessment

Sensitivity of the media prepared in the laboratory network may present marked variations depending on the experience of medium makers, procedures the quality of some critical supplies that are used (such as eggs). It is advisable that on a year or two-year basis depending on feasibility and network size, culture medium quality is controlled and monitored in all the laboratories that make egg-based media (Lowenstein Jensen and Stonebrink) or neutral Middlebrook 7H11/7H10 in a single experience, including the firms that market some of these prepared media.

Eight countries (47%) declared that in 2020 they tested the quality of the culture media that is made by medium-producing laboratories. Evaluated laboratories had a coverage range of 77,5%-100%, five of them got 100% of acceptable quality and six laboratories had a range between 83%-95% of acceptable quality. Besides, 11 countries (65%) reported availability of trademark culture media, 7 of which (64%) include this type of medium in their culture medium quality assessment (Table 21, Graph 7).

Table 21. Culture medium quality assessment. Evaluated and acceptable-quality laboratories. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Country	Total laboratories producing culture media	Total assessed labs	% of coverage	Total labs with acceptable quality	% with acceptable quality
Argentina	32	29	91%	24	83%
Bolivia	4	4	100%	4	100%
Guyana	1	1	100%	1	100%

Mexico	40	31	77,5%	27	87%
Nicaragua	1	1	100%	1	100%
Peru	69	63	91%	60	95%
Dominican Republic	1	1	100%	1	100%
Venezuela	2	2	100%	2	100%

Graph 7. Graph 7. Culture Quality Assessment. Culture medium quality. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
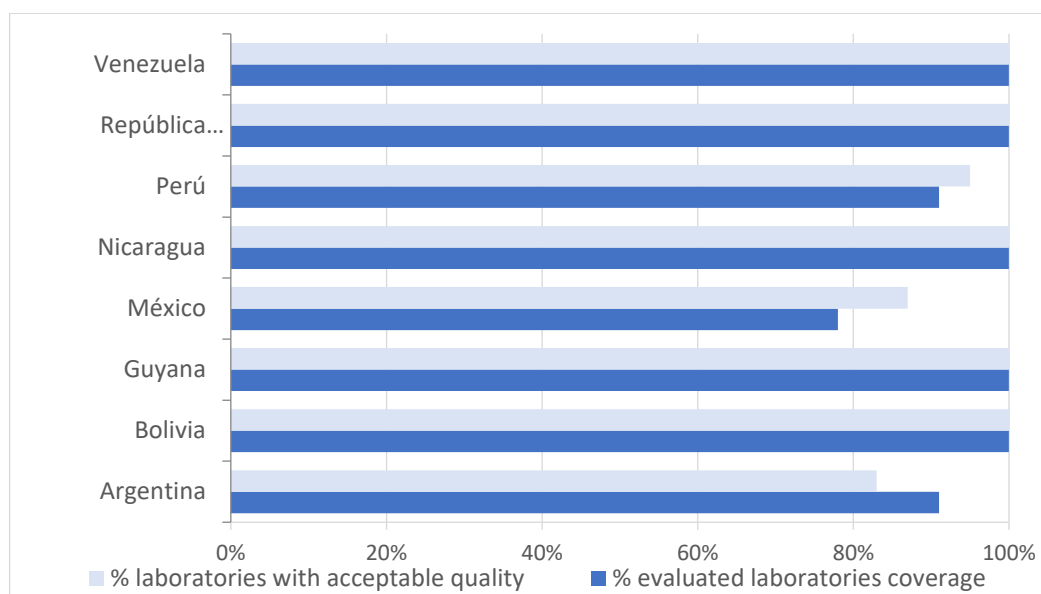
Indirect External Quality Assessment of the Anti-TB drug susceptibility test

Ten countries (59%) stated that they used the panels from the SNL to send to the NTBLN. In eight countries (Argentina, El Salvador, Guatemala, Guyana, Nicaragua, Peru, Dominican Republic and Venezuela) quality was acceptable in a range of 83%-100% of network laboratories for H and R, and in six countries (El Salvador, Guatemala, Guyana, Peru, Dominican Republic y Venezuela) it was 100% for Amikacin/Kanamycin. Of the latter countries only Venezuela failed to achieve 100% of acceptable quality for FQ. Nonetheless, EQA coverage in countries featuring more than one DST laboratory, like Peru, Guatemala, Argentina, was 20%, 25% y 32% respectively.

10 NRLs (59%) also participated in the proficiency test (for DST-quality assessment) that was sent by the SNL during 2020. The LRNs that did not participate quoted as causes financial constraints and those linked to the Covid-19 pandemic.

Two countries rely on other conventional methods for DST quality control: Venezuela reported Nitratase Test only in the NRL and Suriname sends genome sequencing over to the Netherlands for susceptibility confirmation.

LPA External Quality Assessment

Of the 11 countries which perform LPA tests in their NTBLN only three (28%) evaluate the quality of the labs that use this technique, based on parameters/methodologies that are quoted in table 22.

Table 22. Methodologies to evaluate LPA quality. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Methodologies to evaluate LPA quality.	Total countries
Response time supervision	3
Isolate panel submission	3
DNA extract submission	1
Non-interpretable result number and percentage monitoring	1

Xpert MTB/RIF Quality External Assessment

Of all 17 countries, 14 (82%) perform quality external assessment of laboratories applying this technique (apart from Guatemala, Haiti, and Suriname). The methodologies that are used for quality assessment are detailed in Table 23.

Table 23. Methodologies to assess Xpert MTB/RIF quality. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Methodologies to assess Xpert MTB/RIF quality	Total countries
Isolate Panel Submission	10
DNA-extract Panel Submission	7

Guyana, Honduras, and Nicaragua RNLs use both methodologies to assess Xpert MTB/RIT quality.

Performance Indicator Monitoring

Monitoring performance using laboratory quality indicators, also known as performance indicators, is a convenient way to know the quality of laboratory results and identify improvement areas.

They are useful for internal and external evaluation, depending on whether the evaluation is done by the laboratory itself by comparing its results with the expected ones (internal quality control) or whether the evaluation is done by an external lab and results are compared with those of other laboratories in the network (EQA).

In order to implement this type of control, all laboratories should gather and process testing data on a regular basis, using a standardized format for data documentation. Expected values must be established for every monitored indicator and any inexplicable change in indicators need to be investigated.

Microscopy performance indicators

Thirteen countries (76%) possess guidelines/manuals featuring TB diagnostic bacteriological test performance indicators. As many countries make use of performance indicators for SM evaluation, but four countries do not use indicators in all network laboratories: Argentina, Guatemala, Peru y Suriname. All the countries use SM positivity as diagnosis and 62% of countries record time of response.

Graph 8. Microscopy Performance Indicators. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
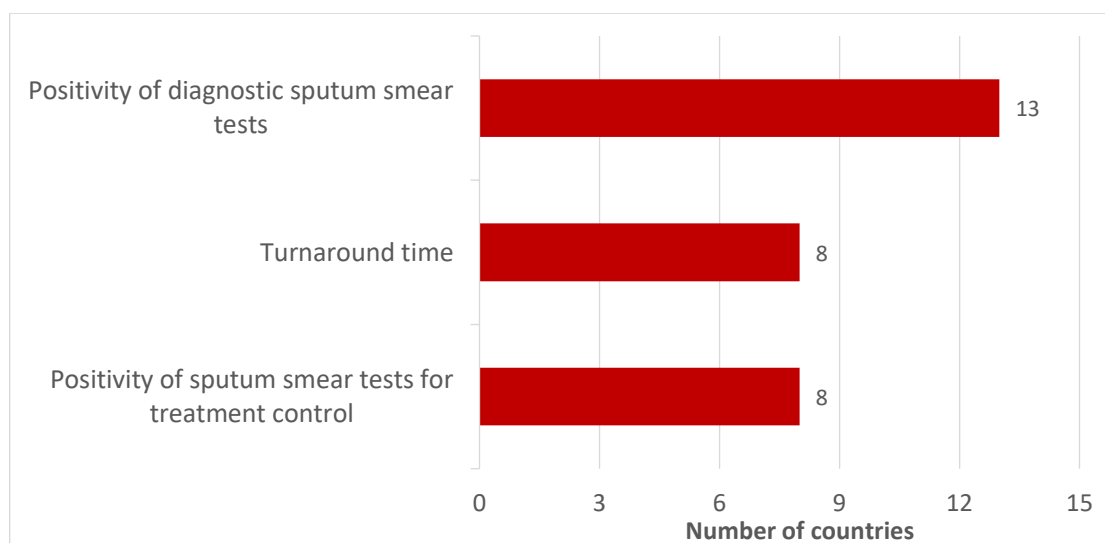
Culture medium performance indicators

By regularly monitoring quality through laboratory-determined performance indicators in the process of internal quality control, unconventional technical procedures can be detected capable of having an impact in culture quality and therefore in the diagnostic quality in the network.

13 countries (76%) reported that they use performance indicators for culture evaluation. 12 of them gather and process information on a regular basis at a central level for the NRL/Network coordinator. Guatemala, Peru and Suriname stated they don't use such indicators. The performance indicators that are used in culture evaluation can be observed in Graph 9.

Graph 9. Culture evaluation performance indicators. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
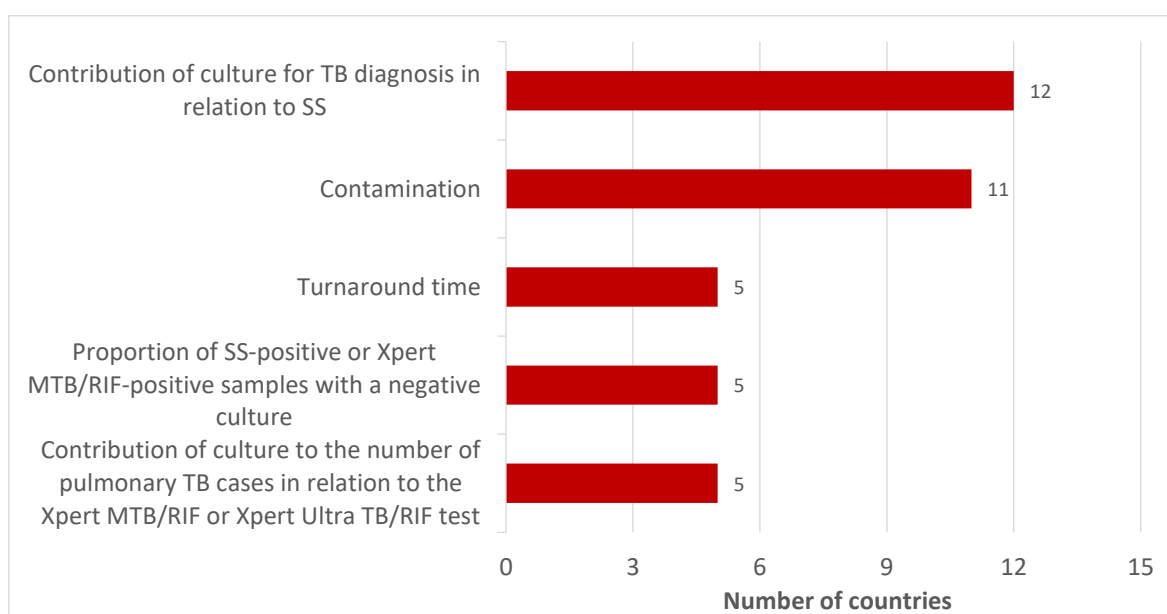
Culture contribution for TB diagnosis in connection with Sputum Microscopy

This quality indicator assesses the contribution that culture makes pulmonary TB diagnosis in adult patients. Between 20-30% of cases are expected to be confirmed using culture alone. A range of 15-20% of bacteriologically confirmed cases are expected to be cases with negative SM and positive culture.

12 countries assess this indicator (except for Guatemala, Haiti, Paraguay, Peru and Suriname), six of which (50%) provided information about the percentage of culture contribution in connection with SM. A contribution range for culture of 5-17% was reported

by these six countries. The countries that provided no information of this indicators are: Colombia, Chile, Ecuador, Honduras, Nicaragua and Dominican Republic.

Culture contribution to the number of TB pulmonary cases in connection with Xpert MTB/RIF or Xpert MTB/RIF Ultra test

The expected range is that around 10% of bacteriologically confirmed cases are negative Xpert MTB/RIF cases and positive culture (for a population whose proportion of SM-negative cases with positive culture is 20%). In populations whose proportions of negative-SM cases with positive culture amounts to 50% (HIV positive), the culture contribution should be between 15-25%. With the use of the cartridge Ultra, culture contribution will be lower than described.

Of the five countries (Colombia, Guyana, Honduras, Nicaragua, and Paraguay) that declared that they analyze this indicator, only two, provided information of the proportion of culture contribution in relation to the Xpert test, which was 1% and 21% respectively.

Proportion of positive-SM or positive-Xpert samples with negative culture

Culture positivity should correlate with the SM result. Even so a small proportion of respiratory samples that are processed for diagnosis (which should not surpass 2-3%) with a positive SM result can be expected to test negative for culture.

Of five countries (Argentina, Colombia, El Salvador, Guyana, Paraguay) that assess this indicator, none gave information of the indicator's value in their country.

Contamination

When samples are not properly decontaminated, either because a fault occurs during the culture's analytical stage or samples have not been preserved in the proper fashion during their transport, enhancing bacterial load, the percentage of contaminated tubes increases. The value should not be higher than the average that is considered normal for the percentage of solid-medium (3-5%) or liquid-medium (8-10%) tube contamination.

Of 12 countries that assess this indicator, seven (58%) provided information about the percentage of contamination in 2020. Six of these countries confirmed that this indicator was below 6.5%. The five countries that do not use it are: Ecuador, Guatemala, Haiti, Peru y Suriname.

Response time

Timely notification of results is fundamental for patient clinical care. Only five countries assess this indicator (Colombia, Chile, El Salvador, Nicaragua, Paraguay).

Susceptibility Test performance indicators

Only two countries use SM performance indicators (Honduras and Dominican Republic), one of which (Honduras) did not specify which indicators. Dominican Republic monitors resistance to H (27%) y a R (15.3%) and response time (21 days).

LPA Performance Indicators

No country uses LPA performance indicators.

Xpert MTB/RIF performance indicators

Nine countries (53%) use performance indicators based on the parameters that are shown in Graph 10. Countries that don't use these indicators are Argentina, Bolivia, Colombia, Guatemala, Haiti, Nicaragua, Suriname y Venezuela.

Graph 10. Xpert MTB/RIF Performance indicators used by each country. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
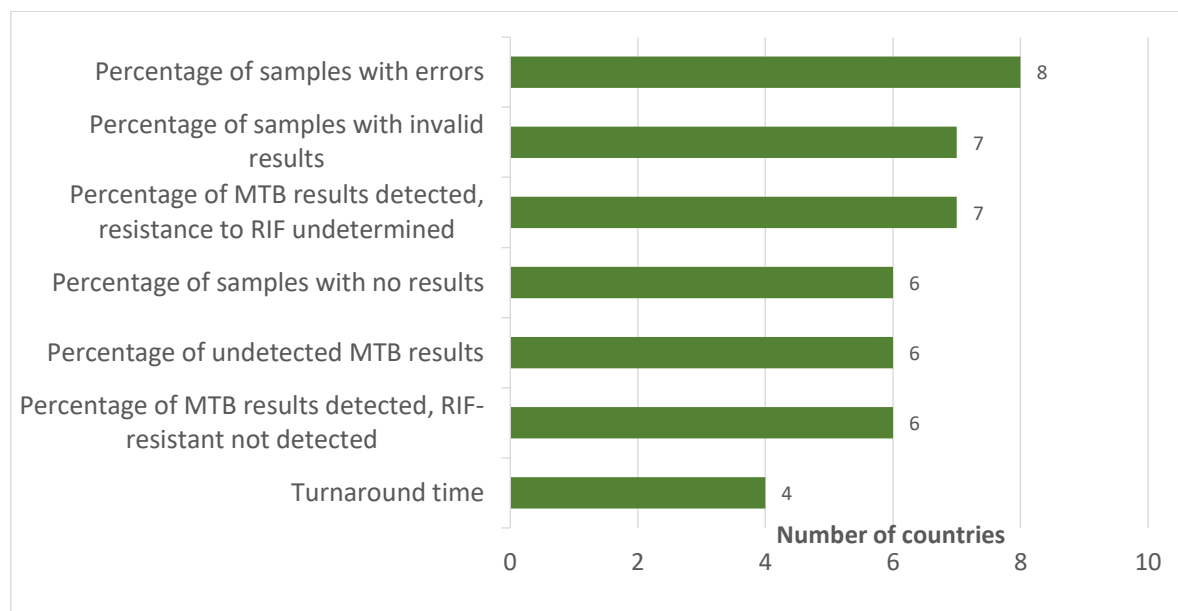

Laboratory information and data management

Information is an essential tool for TBNP success, as it enables constant and truthful knowledge of every activity and the impact it has on the population.

A total of 15 (88%) countries collected NTBLN operational information over 2020. The two countries not to gather such information were Bolivia and Venezuela. The most frequently used format for that purpose is forms sent by e-mail (Graph 11: the compilation formats that are used are not mutually exclusive)

Graph 11. Operational information collection formats. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

- National Informatized System (6)
- Forms sent by e-mail (12)
- Others* (4)
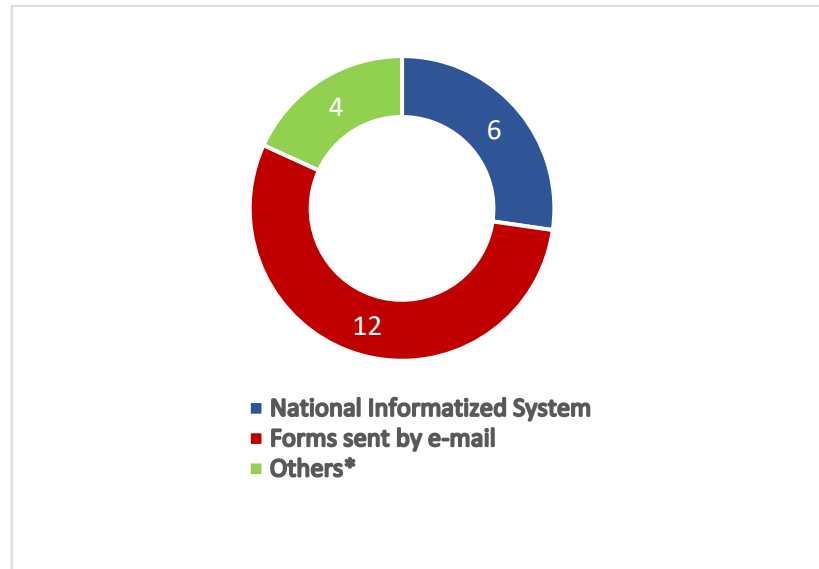
*Other: PPT template, standardized Excel, Hard copies, Standardized reports

A total of 12 (80%) countries produces feedback of the gathered operational information, three countries don't do this (Ecuador, Guyana y Paraguay) and two countries did not inform on the subject.

The most often used information feedback means were national meetings (Graph 12: the feedback means that are used are not mutually exclusive).

Graph 12. Feedback means of collected operational information. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

- National meeting (8)
- Annual report (7)
- Others* (3)
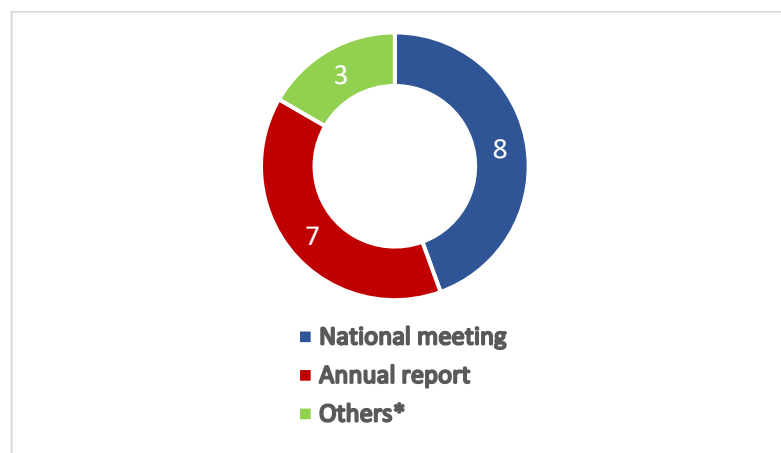
*Other: Meetings, Virtual Meetings, Analysis Panels.

As for the NTBLN Information System, eight countries (Argentina, El Salvador, Haiti, Mexico, Nicaragua, Paraguay, Peru, Suriname) have an information system available online. In Mexico, Paraguay and Peru, the system is integrated into the NTBP system; in Argentina, El Salvador and Nicaragua, the system belongs to the MH surveillance system, and Haiti y Suriname gave no information on this subject. Only Argentina, Mexico and Nicaragua declared that they could transfer information from the NTBP/MH and the NTBLN system.

The information system coverage for 14 countries during 2020 is shown in Graph 13, with a arrange of 4%-100%. 10 of these countries (71%) have a coverage above 75%. Guatemala, Dominican Republic, and Venezuela gave no information of coverage.

Graph 13. Information system coverage (%) per country. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
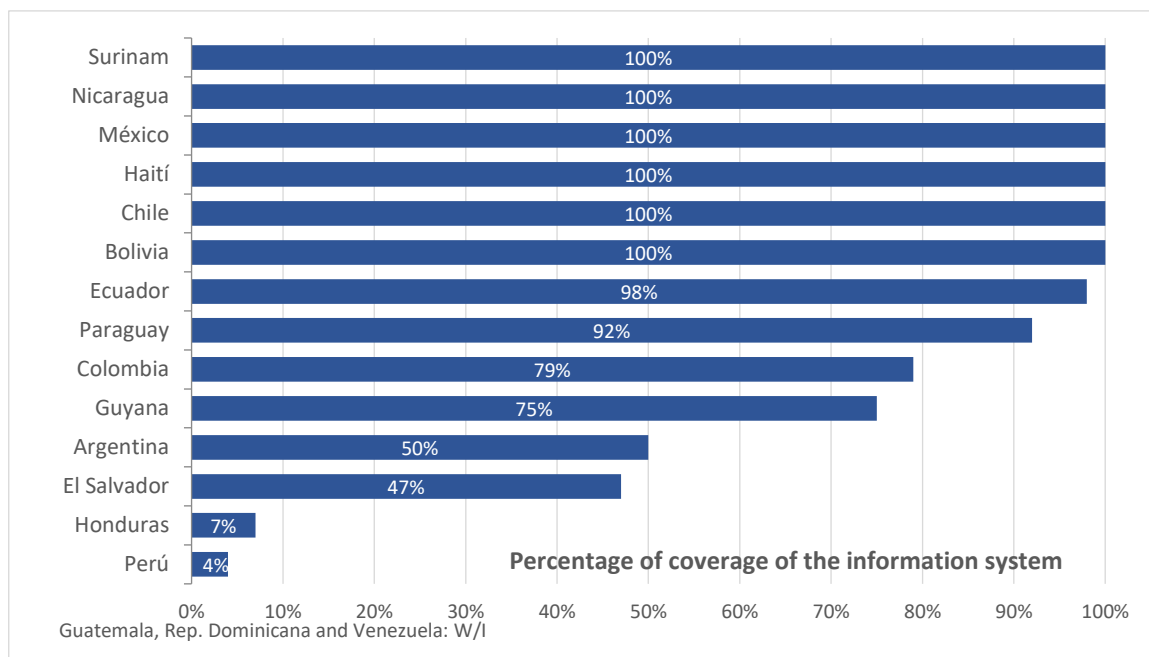
Only two countries (Haiti and Peru) reported that they have connectivity in the GeneXpert units for real-time result transmission; none of them rely on a commercial software for GeneXpert equipment connectivity.

SAMPLE REFERENCE SYSTEMS

Referral systems play a significant part in securing access to laboratory services, as they allow patients to receive care and treatment at a single place while samples are transferred to different levels of the laboratory network to be subjected to tests of varying

complexity. Reference systems can be an efficient means to boost access to diagnosis in areas where tests are not available, prevent the need for and costs associated with travel and lead to equity in access to health.

Sample Reference System organization and structure

Policies and guidelines

A well designed and managed reference system is the foundation of a rock-solid diagnosis network. It is important that programs, donors and partners the importance of sample reference mechanisms and service provider respective coverage, costs, efficiency, and effectiveness. POS, guidelines and policies are also essential to develop a suitable sample reference system.

Graph 14 shows how countries that have a sample reference system organize them according to government ministries/divisions (divisions are not mutually exclusive). In 13 countries (76%), the MH possesses a sample reference system. This reference system organization by country is observed in Table 24.

Graph 14. Government ministries/divisions that have a Sample Reference System. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
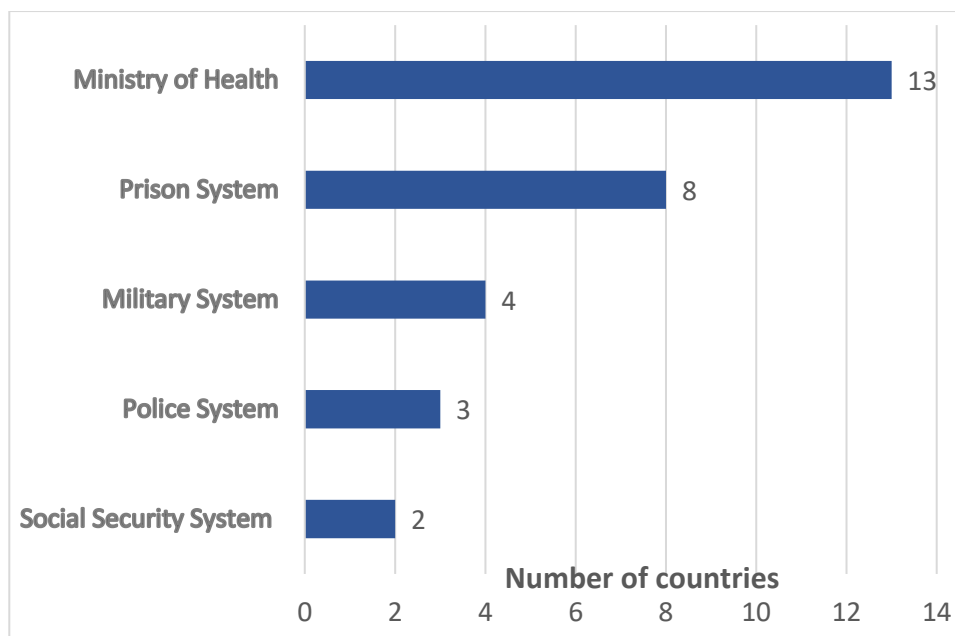
Table 24. Government areas that have a sample reference system by country. Laboratory Networks, 2020

COUNTRY	Government areas that have a sample reference system by country.				
	Ministry of Health	Military System	Police System	Correctional System	Social Security System
Argentina	x				
Bolivia	x				
Chile	x			x	
Colombia	x	x	x	x	x
El Salvador	x	x		x	x
Guatemala	x			x	
Guyana	x			x	
Honduras	x				
Mexico	x				
Nicaragua	x				
Peru	x	x	x	x	
Dominican Rep.	x	x	x	x	
Suriname	x			x	
TOTAL	**13**	**4**	**3**	**8**	**2**

Ecuador, Haiti, Paraguay, and Venezuela provided no information

El Salvador, Honduras, and Mexico have a national comprehensive strategic laboratory plan that includes a sample reference system. Only Guyana has a comprehensive strategic plan that includes a TB-specific system.

In 65% of the countries, there are national policies and procedures to manage laboratory data security and patient data confidentiality, while in 75%, regulations exist for biological product packing and transport. This information organized by country can be observed in Table 25.

Graph 15. Policies and guidelines concerning sample reference systems and patient data security. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
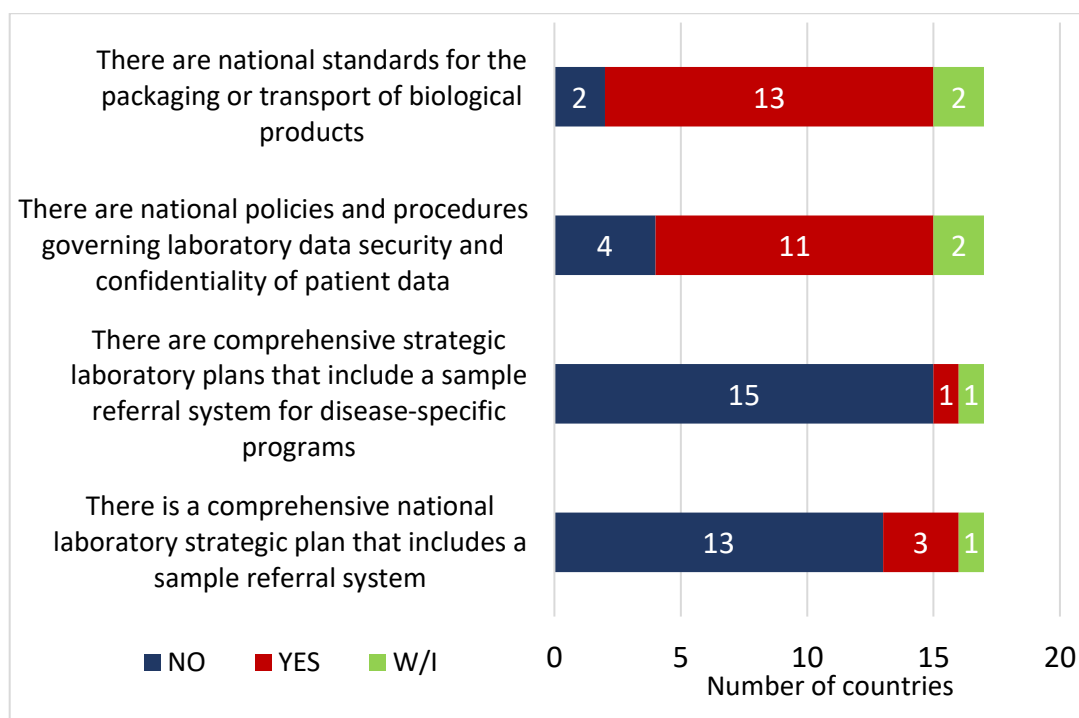
W/I: without information

Table 25. Policies and guidelines concerning sample reference systems and patient data security, by country. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

Country	There are laboratory comprehensive strategic plans that include		There are national procedures/regulations to manage	
	A sample reference system	A sample reference system for disease-specific programs	Laboratory data security and patient data confidentiality	Biological material packing and transport
Argentina			x	x
Bolivia				x

Chile			x	
Colombia			x	x
Ecuador			x	x
El Salvador	x			x
Guatemala				x
Guyana		x		x
Honduras	x		x	x
Mexico	x		x	x
Nicaragua			x	
Peru			x	x
Dominican Rep.			x	x
Suriname			x	x
Venezuela			x	x
TOTAL	**3**	**1**	**11**	**13**

Haiti and Paraguay: No information

In relation to the main partners/donors that support laboratory services in countries, as shown in Table 26, the Global Fund is the main partner/donor. In four countries, (24%) those services are not supported by any partner/donor whatsoever.

Table 26. Nain partners/donors that support country-wide laboratory services. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

partners/donors that support country-wide laboratory services	Total countries	Country name
Global Fund	10	Bolivia, El Salvador, Guatemala, Guyana, Haiti, Nicaragua, Paraguay, Peru, Dominican Rep., Suriname
Ministry of Health	4	Chile, Guyana, Honduras, Suriname
PAHO	4	Guatemala, Guyana, Dominican Rep., Suriname
General System of Health Social Security	1	Colombia

Roles, responsibilities, coordination

In Colombia, Guyana and Nicaragua's MH, there is a technical working group who is responsible for any sample referral-related incident. In 7 countries, there is a contact person responsible for the NTBLN (Bolivia, Guyana, Honduras, Mexico, Nicaragua, Dominican Republic, Suriname) (Graph 16).

Graph 16. Roles and responsibilities in relation to sample referral systems. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
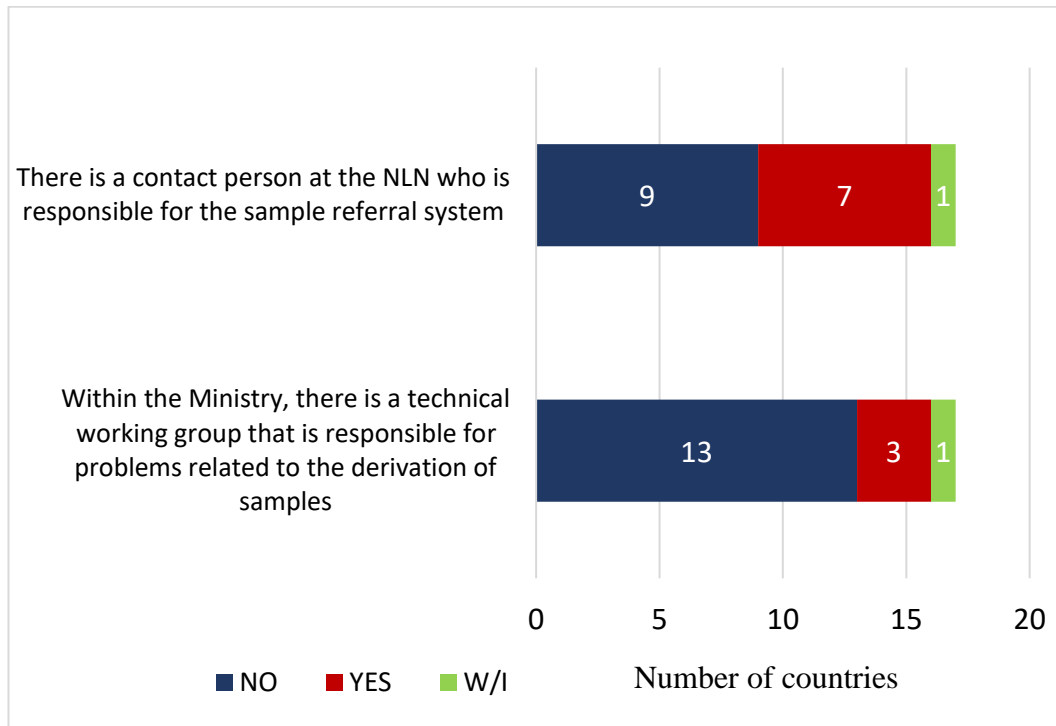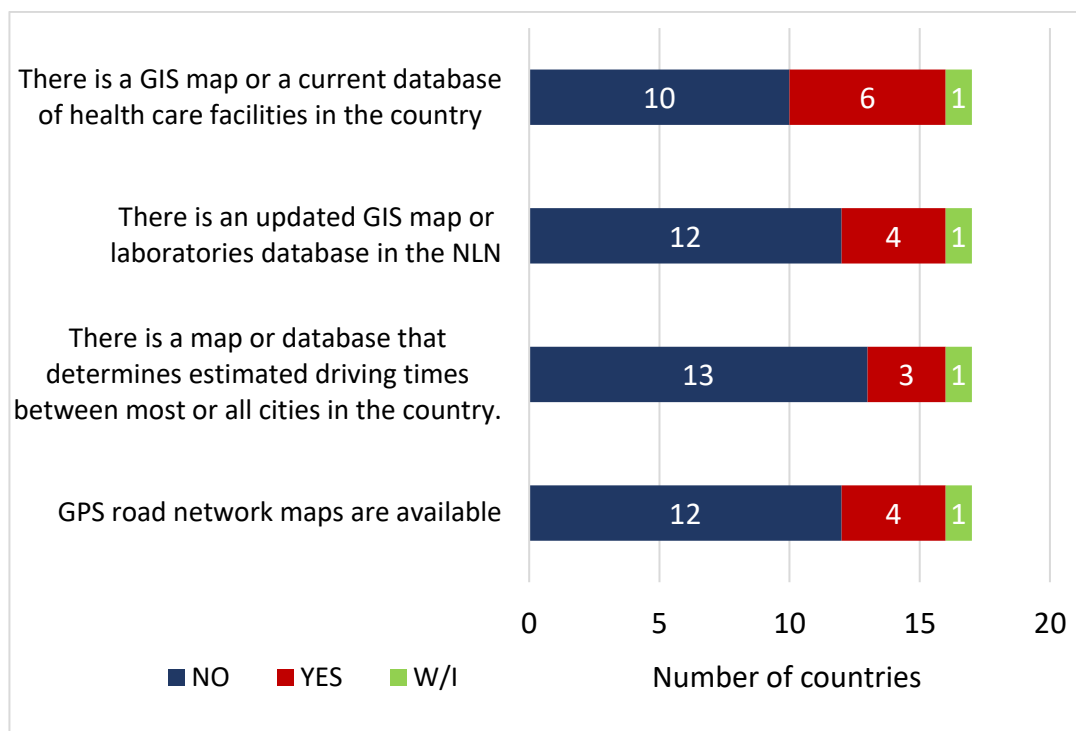

W/I: without information

Geographic information system

Map availability through geographic information systems (GIS) is presented in Graph 17.

Graph 17. Map availability through a geographic information system (GIS) Tuberculosis Laboratory Networks. Region of the Americas, 2020.

W/I: without information

Private service offers

Regarding private service offers, in 14 countries (82%) there are other kind of laboratories (private, academic, military, animal health and environmental) that can be integrated into the NTBLN. IN 13 countries (76%) public labs provide services to the private health sector.

Communication and information

Features of communication systems are specified in graph 18. In 53% of countries, there is a formalized system of communication within the NTBLN, and 47% have ID number for patients in the national health information system. Such information by country can be seen in table 27.

In 76% of the countries, a national standard is applied for TB patient laboratory reports. 70% of those countries use these standards to report, while the remaining 30% use them in some labs of their country's network.

Graph 18. Communication system and information type at the Tuberculosis Laboratory Networks. Region of the Americas, 2020.
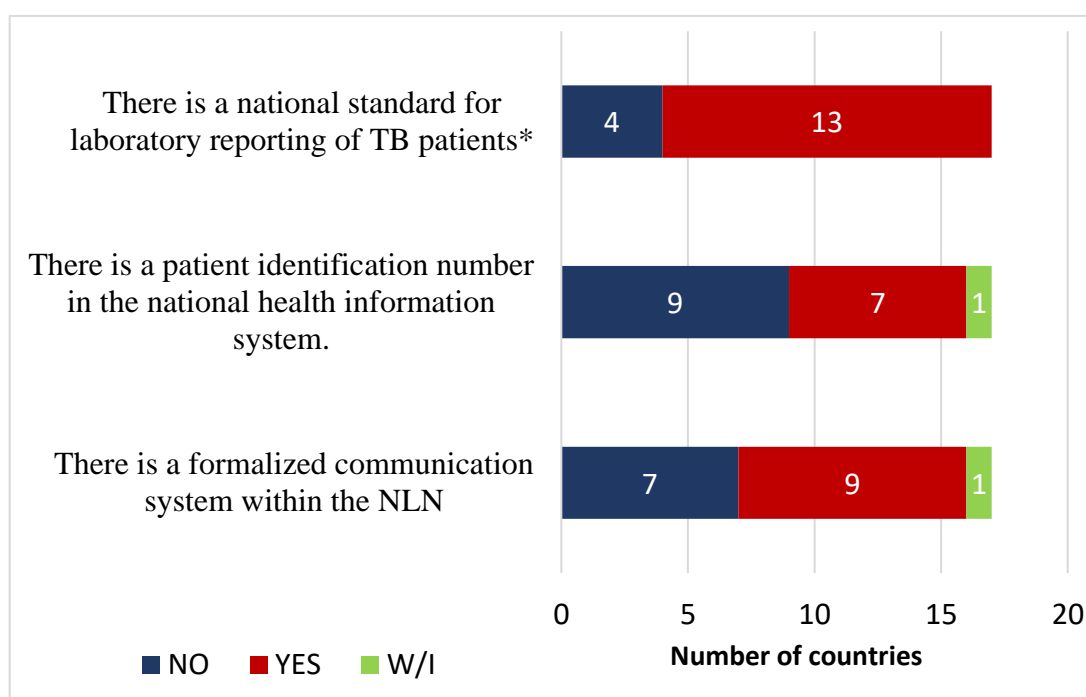

Table 27. Communication system availability and information type at the Tuberculosis Laboratory Networks by country. Region of the Americas, 2020.

	YES	NO	N/I
There is a formalized system of communication within the NTBLN	Colombia, Guyana, Honduras, Mexico, Nicaragua, Paraguay, Peru, Dominican Rep., Suriname	Argentina, Bolivia, Chile, Ecuador, El Salvador, Guatemala, Venezuela	Haiti
There is an ID number for patients in the national health information system	Argentina, Colombia, Guyana, Mexico, Nicaragua, Peru, Dominican Rep.	Bolivia, Chile, Ecuador, El Salvador, Guatemala, Honduras, Paraguay, Suriname, Venezuela	Haiti
There is a national standard for TB-patient laboratory reports	Argentina, Bolivia, Chile, El Salvador, Guyana, Haiti, Honduras, Mexico, Nicaragua, Paraguay, Peru, Dominican Rep., Venezuela.	Colombia, Ecuador, Guatemala, Suriname	-

Connectivity

In relation to the existing degree of connectivity at the networks' central level, 14/17 countries are connected via Internet (except for Nicaragua, Suriname, and Venezuela), eight do so via mobile networks (Argentina, Bolivia, Colombia, Guatemala, Guyana, Honduras,

Peru and Dominican Republic), three via wireless data (Colombia, Peru, Dominican Republic), and one via the internal Local Network (Nicaragua). Venezuela and Suriname reported that they have no type of connectivity at the central level.

The degree of connectivity that the NTBLNs have in each country at a central and intermediate level can be seen in Table 28.

Table 28. The degree of connectivity in different countries' NTBLNs at a central and intermediate level. Region of the Americas, 2020.

Connectivity degree among health establishments	At central level (Countries)	At intermediate level (Countries)
Mobile networks	Argentina, Bolivia, Colombia, Guatemala, Guyana, Honduras, Peru, Dominican Republic.	Argentina, Bolivia, Colombia, Guatemala, Guyana, Honduras, Peru, Dominican Republic, Venezuela.
Internet	Argentina, Bolivia, Chile, Colombia, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Mexico, Paraguay, Peru, Dominican Republic.	Argentina, Bolivia, Chile, Colombia, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Mexico, Paraguay, Peru, Dominican Republic.
Wireless data	Colombia, Peru, Dominican Republic.	Argentina, Colombia, Peru, Dominican Republic.
Other*	Nicaragua	Nicaragua

*Internal local network

Transport system.

In nine countries (53%), there are national systems of sample transport and referral, seven of which feature a definite structure for the sample reference system.

At a central level, sample transport is undertaken by national-health workers from health establishments in 11 countries. Eight do sample transport via private mail, eight via courier service and five employ independent private commission agents.

The sample transportation systems existing in each country both at central and intermediate/local lever are shown in Table 29.

Table 29. Sample transport systems existing in each country's NTBLN according to structural level. TB Laboratory Networks, Region of the Americas, 2020.

Sample transport systems currently available in the country	At Central Level (Countries)	At Intermediate/Local (Countries)
Private mails	Argentina, Chile, Colombia, Ecuador, Paraguay, Peru, Dominican Republic, Venezuela.	Argentina, Ecuador, Paraguay, Venezuela.
National Health workers from the health establishment	Chile, Colombia, Ecuador, El Salvador, Guatemala, Guyana, Mexico, Nicaragua, Dominican Republic, Suriname.	Argentina, Bolivia, Chile, Colombia, Ecuador, El Salvador, Guatemala, Guyana, Mexico, Nicaragua, Paraguay, Peru, Dominican Republic, Suriname.
Courier service	Argentina, Bolivia, Ecuador, Guatemala, Honduras, Mexico, Peru, Dominican Republic.	Argentina, Bolivia, Colombia, Ecuador, Guatemala, Honduras, Mexico, Dominican Republic.
Independent private commission agents	Argentina, Colombia, Honduras, Paraguay, Peru.	Argentina, Colombia, Honduras, Peru.
Other	Guyana, Venezuela	Guyana, Venezuela

To date in five countries there is someone in charge of the NTBLN sample referral system at a Central Level, and in seven countries they are appointed at an Intermediate/Local level.

Table 30 shows the country distribution according to who funds sample transport between the different laboratory levels.

Table 30. Funding of TB sample transport Tuberculosis Laboratory Networks. Region of the Americas, 2020.

| Sample transport-funding entity	Total countries
Hospitals	9
National Health Ministry	8
Regional/provincial/local Ministries	8
Reference Laboratories/Network Coordination	4
Global Fund	3*

*Bolivia, Honduras, Paraguay

Documentation and Training

SOPs and guidelines are necessary for sample referral, including sampling collection policies and procedures, packing, transport, temperature control or cold-chain preservation, transport monitoring, biosecurity, leak containment and result delivery. Referral forms and records, tracking process of surveillance chain receipts and forms, transport registers and data compilation tools for follow-up and evaluation purposes should be available. All the health staff and transporters should be trained and sensitized.In 14 countries (82%) there is an available laboratory manual/guide with information on transport, packing, transit, response times, etc. As to health establishments, other than the NRL, that have those SOPs, nine countries reported that they are available at all establishments, five indicated that only a few health establishments have them, two reported than none have them, and one country provided no information.

Information about the existence of a sample collection, preservation, shipment, packing, transport, reception, and response-time manual or SOP is detailed in Graph 19. It also includes laboratory personnel, clinician, and transporter training.In 65% of countries, the NTBLN laboratory personnel is trained in SOPs for sample collection, referral, packing, transport, and reception, while in 53% of those countries, the clinical staff that care for TB patients is trained. In 59% of the countries, conversely, there was no knowledge whether transporters are trained in biosecurity and leak containment.

Graph 19. Documentation, registers, and SOPs associated to sample biosecurity, transport, collection, and reception. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
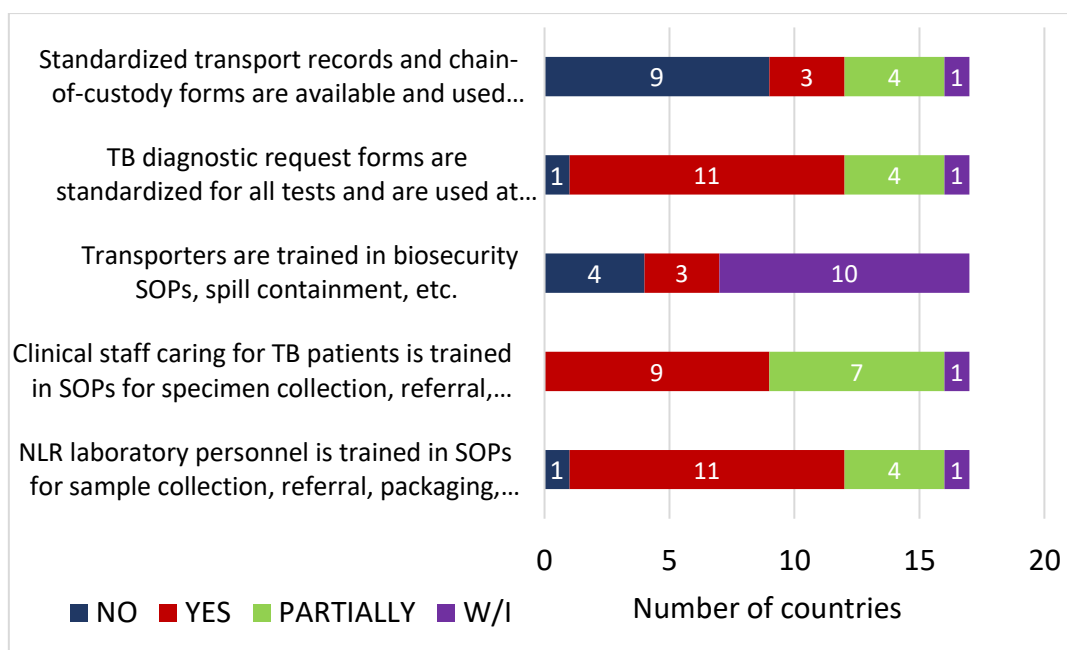
W/I: without information

In relation to a three-layer package use for international-scale sample transport, it is in use in most of the countries, while locally is hardly ever used (Graph 20).

Graph 20. Use of three-layer packages for sample transport. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
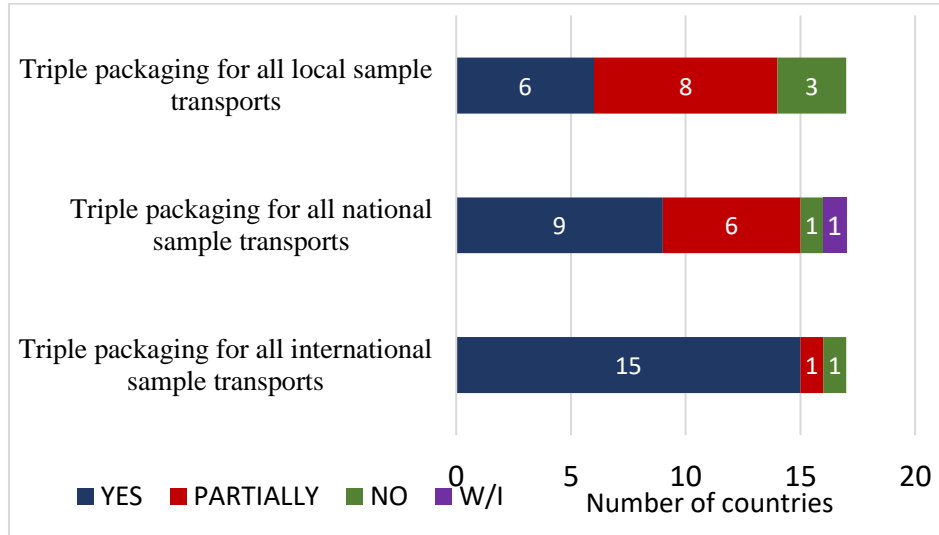
W/I: without information

Result Communication

Communication systems should be properly constructed and implemented based on well-documented procedures. It is fundamental that information is shared about, for example, a delay in giving back results, test interruptions, top-priority result notification, and tracking of lost or rejected samples. The number of countries whose NTBLNs make use of different formats for result delivery are seen in Graph 21. The ways of result delivery are not mutually exclusive, more than one being possible at the same time. Those countries are listed in Table 31.

Graph 21. Laboratory test result delivery format. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
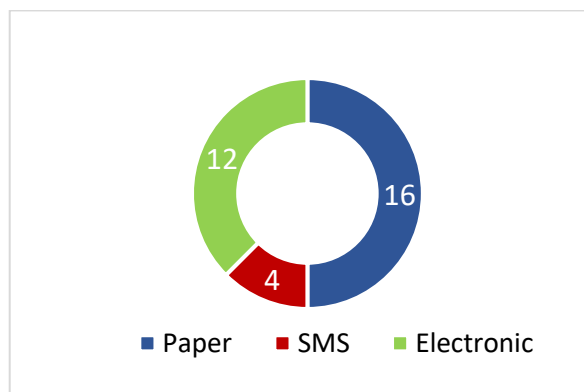
Table 31. Laboratory test result delivery format at NTBLNs by country.
TB Laboratory Networks. Region or the Americas, 2020.

Laboratory test result delivery format			
Country	Paper	SMS	Electronically
Argentina	x	x	x
Bolivia	x		
Chile	x		x
Colombia	x		x
Ecuador			x
El Salvador	x		
Guatemala	x	x	x
Guyana	x		x
Haiti	x		
Honduras	x		x
Mexico	x		x
Nicaragua	x		x
Paraguay	x		x
Peru	x	x	x
Dominican Rep.	x	x	x
Suriname	x		
Venezuela	x		
TOTAL	16	4	12

Haiti, Mexico, and Peru have a system that makes it possible to monitor a sample from the referral lab to the test lab. In Mexico, Nicaragua, and Peru there is another system whereby results and reports can be monitored to know when results are not sent back to doctors, nurses or other test requesters.

Six countries possess a system that allows them to know sample quality and their rejection (Chile, El Salvador, Guyana, Mexico, Paraguay, and Peru). Ten countries have sample rejection forms (Chile, Ecuador, El Salvador, Guyana, Honduras, Mexico, Paraguay, Peru, Dominican Republic, and Suriname) (Graph 22).

Graph 22. Systems for monitoring samples and results. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
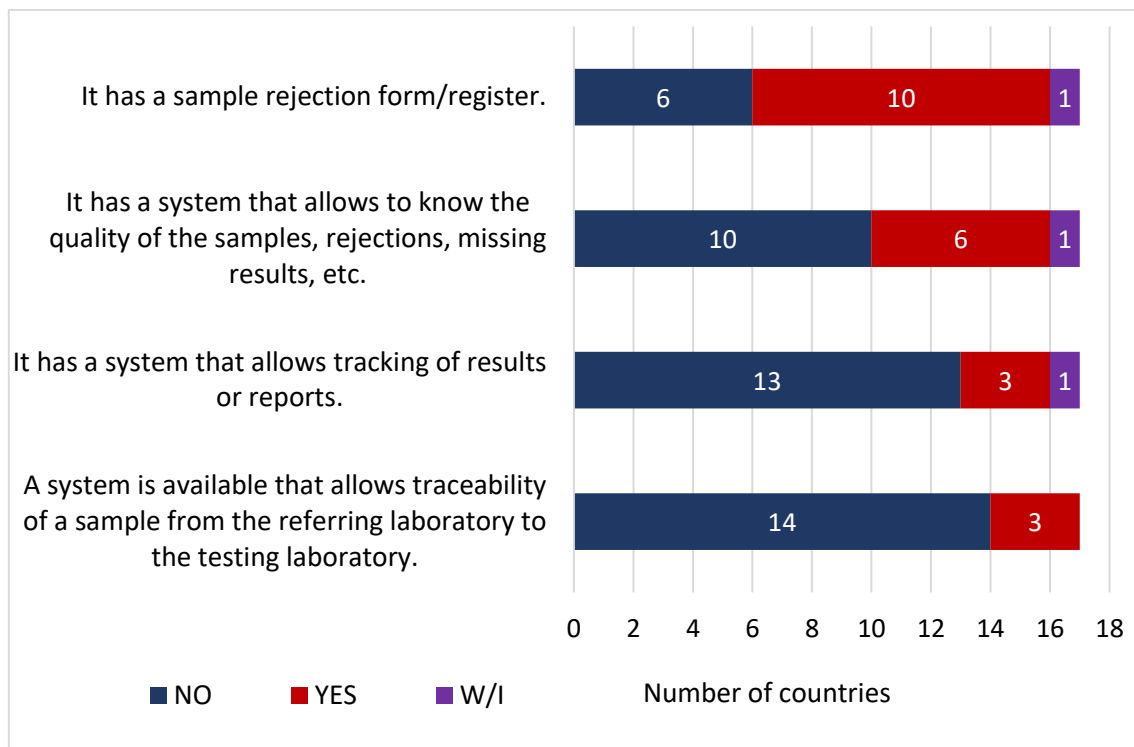
Monitoring, quality assessment and system performance

It is critical to monitor the sample reference system to make sure that good quality samples arrive at test sites at the right time, results are rapidly sent back, and biosecurity measures are observed according to national and international standards. This requires standardization or records and forms that are currently being used in all systems, as well as quality control throughout sample collection, packing and transport. Records (also known as surveillance chain documents) should be sent together with the samples and be signed by the senders and the recipients all along the journey to create a monitoring system.

There are seven countries (41%) where information is compiled on the response time that elapses from collection of the sample until the result submission to the lab, the treating doctor or the patient (Chile, Ecuador, Guyana, Mexico, Nicaragua, Peru, Dominican Republic). The same number of countries (Ecuador, El Salvador, Guyana, Nicaragua, Peru, Dominican Republic, Suriname) know the proportion of sample collecting centers that are involved in the present sample reference system

Besides, there are six countries (35%) use some kind of system (such as barcode labels and scan with step-by-step date/hour/name registration) during the referral process.

There are four countries (Chile, Ecuador, Guyana, Dominican Republic) that compile information about the number of referred samples, completed deliveries, and submitted samples where a result was sent back).

Innovation

As can be seen in Graphs 23, 24 and 25, a tight budget, lack of infrastructure/biosecurity in laboratories and insufficient human resources were by and large the main reasons or difficulties for implementing and expanding the use of rapid techniques (Xpert MTB/RIF, LPA, ICL), the use of BACTEC MGIT 960/320 and universal DST access for all TB patients.

Also, for the use BACTEC MGIT 960/320, bureaucratic hold-ups in the procurement/importation processes added up significantly to the difficulties in implementing this method.

Graph 23. Reasons and causes that hindered rapid test implementation (Xpert MTB/RIF, LPA, ICL) in the NTBLNs. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
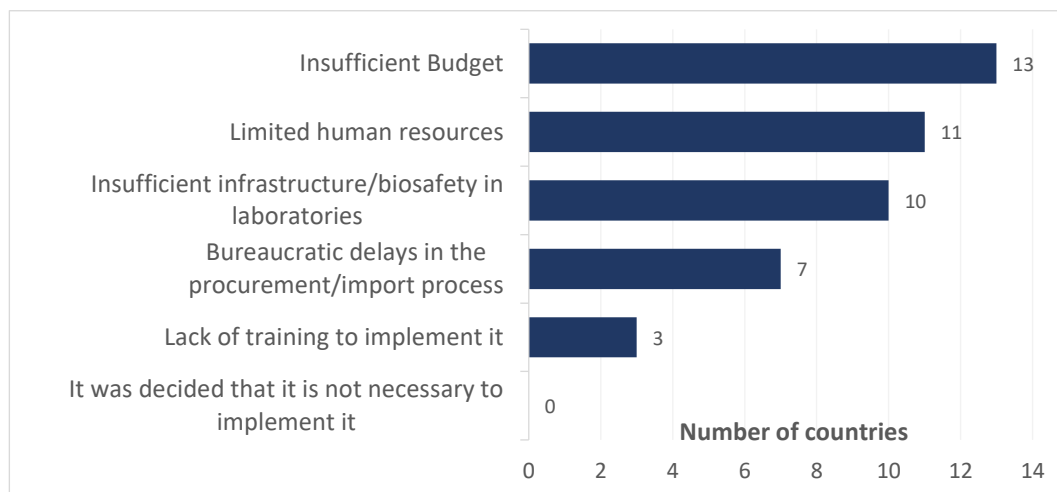
Graph 24. Reasons and causes that hindered BACTEC MGIT 960/320 implementation in the NTBLNs. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
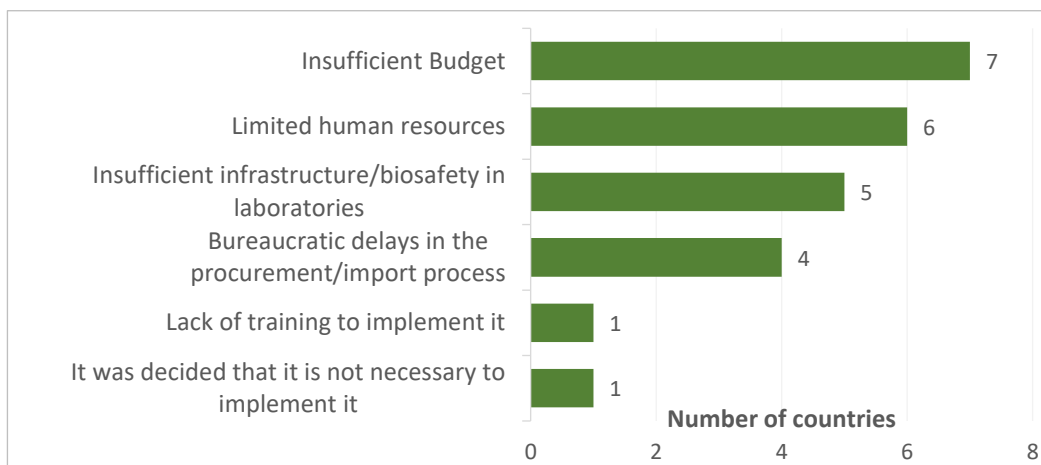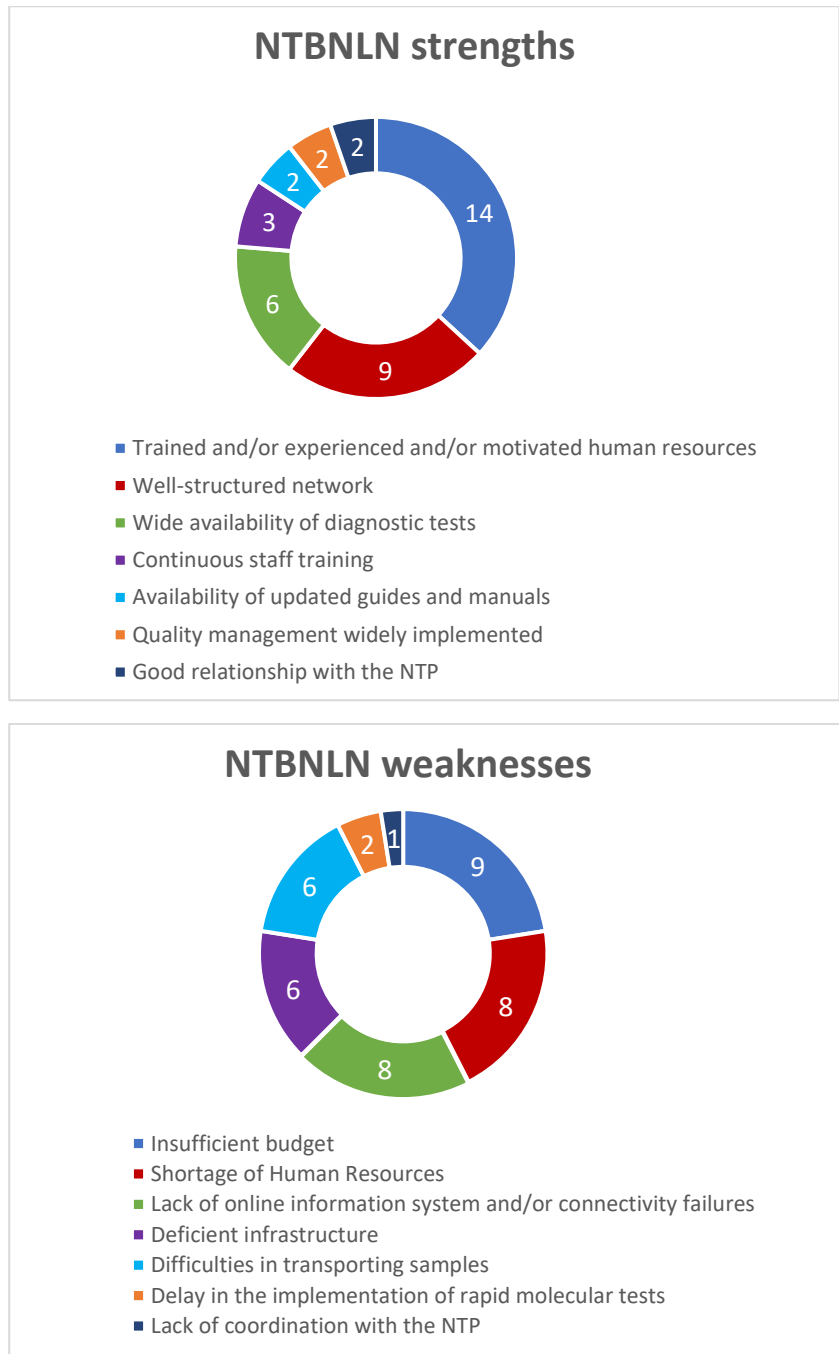

Graph 25. Reasons and causes that hindered implementation of Susceptibility Test universal access for all TB patients in the NTBLNs. Tuberculosis Laboratory Networks. Region of the Americas, 2020.
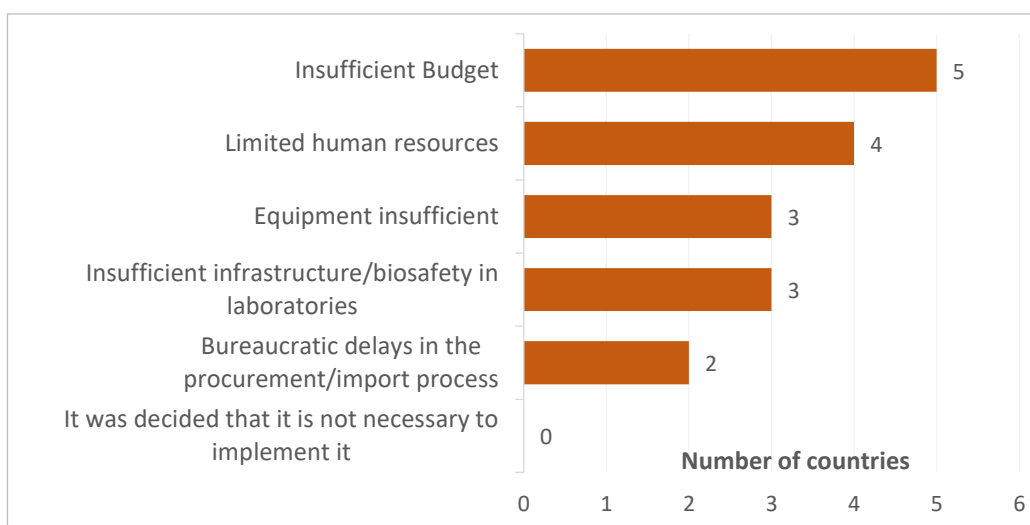
Strengths and Weaknesses of NTBLNs

The absolute distribution of the strengths and weaknesses reported by the NTBLN are observed in Graph 26.

Graph 26. Country absolute distribution in terms of Strengths and Weaknesses of the NTBLN. Tuberculosis Laboratory Networks. Region of the Americas, 2020.

NTBNLN strengths

- Trained and/or experienced and/or motivated human resources
- Well-structured network
- Wide availability of diagnostic tests
- Continuous staff training
- Availability of updated guides and manuals
- Quality management widely implemented
- Good relationship with the NTP

NTBNLN weaknesses

- Insufficient budget
- Shortage of Human Resources
- Lack of online information system and/or connectivity failures
- Deficient infrastructure
- Difficulties in transporting samples
- Delay in the implementation of rapid molecular tests
- Lack of coordination with the NTP

The NTBLN main strengths and weaknesses as reported by each country can be observed in tables 32 and 33.

Table 32. NTBLN three main strengths as reported by countries. Region of the Americas, 2020.

COUNTRY	STRENGTH						
	Qualified and/or experienced and/or qualified human resources	Well-structured network	Widely implemented quality management	Broad diagnostic test availability	Personnel continuous training	Good relations with the NTBP	Up-to-date guideline and manual availability.
Argentina	X	X				X	
Bolivia	X	X					
Colombia	X	X		X			
Chile	X	X		X			
Ecuador	X			X	X		
El Salvador	X	X					
Guatemala	X	X		X			
Guyana	X						
Haiti	X	X					
Honduras		X					X
Mexico	X		X				
Nicaragua		X			X		
Paraguay	X						
Peru			X	X	X		
Dominican Rep.	X			X			X
Suriname	X						
Venezuela	X					X	

While countries were asked about the three main strengths of NTBLNs, some mentioned just two and other more than three. In the latter case only the three top weaknesses were included. Among the strengths not mentioned in the table are periodical visit continuity (Nicaragua), good communication between laboratories (Guyana and Paraguay), real-time information availability (Haiti), collaboration with the SNL (Suriname), online information system (Argentina), widespread use and decentralization of rapid test diagnosis (Colombia and Ecuador).

Table 33. NTBLN three main strengths as reported by countries. Region of the Americas, 2020.

COUNTRY	WEAKNESSES						
	Insufficient budget	Delay in rapid molecular test implementation	Deficient infrastructure	Lack of coordination with the NTBP	Lack of online information system and/or connectivity issues	HR shortage	Sample transport-related issues
Argentina	X	X	X				
Bolivia	X			X			
Colombia					X		X
Chile		X			X		
Ecuador			X		X		X
El Salvador			X		X	X	
Guatemala					X	X	X
Guyana						X	
Haiti	X					X	X
Honduras	X		X			X	
Mexico	X					X	
Nicaragua					X		X
Paraguay	X				X		X
Peru			X			X	
Dominican R.	X				X		
Suriname	X						
Venezuela	X		X			X	

Other key weaknesses that were expressed by country representatives were: difficulties in procurement procedures (Guyana), lack of a plan for equipment maintenance (Dominican Republic), lack of plans in general (Suriname), lack of training for human resources (Suriname), regions with little access to diagnostic algorithms (Colombia) logistic issues (Haiti). Some countries pointed to more than three weaknesses, such as Argentina regarding the lack of acknowledgement of the provincial TB laboratory network management within the laboratory organizational structure, or trouble in the sample reference system (Honduras, Argentina), or lack of political commitment (Bolivia).

Shortage of human resources was mentioned by almost all the countries as a weakness (including Argentina). In referring to shortage of human resources (both for laboratory work and administrative tasks) various reasons are quoted: staff retirement, a

proportion of human resources being assigned to the COVID area, lack of staff training and/or or high staff renewal.

Discussion

This study has been dedicated to updating information about the structure and operation of the NTBNLs in the Region in relation to the last study which was conducted in 2017 and identifying network strengths and weaknesses. In the process, their needs can be determined to strengthen diagnostic capacity in the context of the Stop TB strategy.

For the first time, information was added about the sample reference system, which is key for timely diagnostic access, and the use of multiple platforms to boost the optimization of the existing diagnostic systems. Some results will be suitable to compare with the 2017 survey results, where information was gathered from the year 2016, but most new indicators that were suggested to move forward with the Stop TB strategy goals will be addressed for the first time. TB laboratory networks are organized into three structural level: central, intermediate, and local. Small countries can have a lower level and large countries a higher level. There could be an additional, peripheral level that is related to sample collecting centers, with or without preliminary processing. In most of the NTBLNs from countries involved in the study, the activities that are done by intermediate laboratories are basically associated to the use of Xpert MTB/RIF, SM and culture-based diagnosis, quality control, information reception and processing, training, and fulfillment of technical visits. Only in 41% of countries GeneXpert units are found in local-lever laboratories, even though this test is recommended for peripheral level. This may be due to the scarce availability of equipment, which is in principle assigned to intermediate-level laboratories with working capacity to receive referrals from other laboratories.

One of the mainstays of the Stop TB strategy lies in bold policies and support systems. Therefore it is essential to develop a National Strategic Plan and an activity plan for the NTBLN that should be agreed upon by the NTBP and arranged with other organizations, communities or public and private health institutions in order to garner enough political commitment for resource allocation. Some countries are still bereft of an activity plan for the NTBLN that is jointly written with the NTBP as a part of the National Strategic Plan. There are moreover countries who have no one in charge of the NTBLN, which is vitally important for management purposes and is critical for coordinated work with laboratories, as well as the NTBP.

In relation to the study of 2016, an almost twofold increase was observed in 2020 in the proportion of countries that apply LED lamp fluorescence microscopy, this value shifting from 35% in 2016 to 65% in 2020. Also compared with 2016, the proportion of countries that use Lowenstein Jensen (LJ) medium and Stonebrink fell by 7.6 to 7.4 percentage points respectively. The proportion of countries that use automated culture methods remained stable at around 70%, which came as no surprise considering that most of them prioritized Xpert implementation. What is striking is that an increase by 8.8 percentage points as compared with 2016 was noted in the proportion of countries that use Ogawa medium (Kudoh method), because these are less sensitive culture media than LJ and the liquid medium.

The Stop TB Strategy has set its target at reducing TB incidence rate by 90% between 2015 and 2035 and TB-caused deaths by 95%. The laboratory component is vitally important to reach those goals, since two key elements for the strategy's success are early diagnosis and DST performance for any detected TB case. The number of units for making the Xpert MTB/RIF rapid test rose dramatically between 2016 and 2020. Equipment multiplied from 1.5 to over 35 times in the 14 countries where this information is available in both study periods, only Venezuela stayed with two units, like in 2016. In 2016 Peru was the sole country to report no equipment; in 2020 it reported 46. The number of labs that possessed Xpert units were also observed to have increased. The average of labs and their range varied from 8.9 (0-49) in 2016 to 24 (2-63) in 2020. The spread in rapid test implementation is very encouraging toward the goal of the Stop TB Strategy, which recommends that rapid TB diagnosis should be available for any person with TB signs of symptoms and that every patient with clinically confirmed TB should have an anti-TB drug DST made at least for R.

While trying to estimate the use percentage of the Xpert MTB/RIF test (by comparing system yearly capacity with the number of samples that were examined with this method), 41% of the countries did not have one or more of the data required to make such estimation. In the remaining 59%, the number of completed tests were far below the equipment capacity (min: 3.3% in Argentina; max: 23.3% in Chile). This poor use might be connected with there not being the necessary number of cartridges because of the networks' insufficient budget and the lack of economic wealth to make use of all modules. This means that some countries use algorithms that establish rapid molecular test production for priority groups, until that can be implemented as universal tests.

There was an expansion of laboratories that make Xpert MTB/RIF and available units, but its underuse means that SM remains the primary diagnostic method in most NTBLNs. As a result, any NTBLN planning must consider strategies for transitioning into rapid method diagnosis as a starting test.

Only in 41% of the countries, the GeneXpert equipment is exclusively used for TB. In the rest, the platform is optimized mostly for COVID-19 and HIV diagnosis, but also for hepatitis, chlamydia, mycoplasmas, and other STDs.

The Stop TB Strategy places universal access to DSTs as one of its key components, establishing as a goal for 2020 that 100% of reported, bacteriologically confirmed cases should have at least a DST for D. In this study, the proportion of DSTs that were made to reported, bacteriologically confirmed cases was within the range 1,3%-69% in 10 countries

Among the goals of every NTBP, under the "Stop TB" Strategy, is that of securing universal access to high quality care for all TB patients to end the TB epidemic by 2055. Ensuring early case detection using quality bacteriological tests remains a necessary step for recovery. Therefore, A NTBLN that provides diagnosis with a high level of quality is essential for TB elimination. Availability of guidelines in the form of manuals is critical to manage laboratory quality. 35% of countries still have no manuals for quality management.

Technical manuals for the development of the different laboratory tests are convenient for country reference and guidance providing the guidelines and standards for its proper execution. On this subject, there are still countries that are bereft of SM, culture, DST o Xpert MTB/RIF manuals.

By and large, all NRLs have diagnostic technique SOPs, but in some countries, they are still not implemented in all intermediate of local lever laboratories. Such differences are even greater regarding biosecurity SOPs, as they are neither available in six countries' NRLs or in intermediate level laboratories from 10 countries and local level laboratories from 11 countries.

Only four countries' NRLs have gained certification for ISO 15 189 or 17 025 standard and those four laboratories succeeded in certifying some technique.

SM external quality assessment is implemented in the NTBLNs from all the countries, at least in one of its recommended variants. However, 76% of the countries failed to put it into effect during 2020, and 54% had a coverage below 60%, which match the findings observed in 2016. Each method has different benefits and downsides, along with

different resource requirements. However, it is advisable to design an expansion plan for the EQA program to increase coverage, since it has not grown since 2016. In 60% of the countries, SM panel submission has not been implemented. While not effective to assess routine work quality, but only reading quality, this method is still helpful to assess quality in a large number of services as compared to the re-reading form, which could help to improve coverage in the region's network

Culture medium quality was examined in just 47% of the countries during 2020, generally with good coverage in the assessed laboratories and an acceptable quality in most laboratories of the network.

As for EQA for DSTs, it was implemented in only 59% of the countries in 2020. The percentage of DST-producing locations that have shown competence in external quality control was 83-100%, but it should be highlighted that in countries that have other DST laboratories besides the NRL, coverage failed to reach 30%. Only 30% of countries make EQA for LPAs, while most of them (82%) implement EQA for the Xpert MTB/RIF test.

By monitoring quality regularly through the performance indicators that are assessed by laboratories in the course of internal quality control, unconventional technical procedures can be detected that could impact on SM, culture and DST quality and consequently the network diagnostic quality. It is also a vital supply for planning technical visits, training, and resource procurement. 76% of countries uses any of the performance indicators for SM and culture evaluation, but a low proportion has implemented them for DST (12%), Xpert MTB/RIF (50%) and none for LPA. As to the culture contamination percentage, while being used by National Network Laboratories, this data is not known to all the NRLs, as it is not systematically compiled at central level in all the countries of the region.

The response time indicator for diagnostic tests is assessed in only 30% of the countries, plus the value of this indicator is not systematically retrieved by all the NRLs. By monitoring result delivery time, some laboratory procedures can be optimized (for example, efficient rapid molecular method and rapid culture application, and elimination of unjustified delays). It also helps identify challenges that are associated with NTBP algorithms, workflow in each lab, information systems and report systems, in order to improve diagnosis, clinical management and patient treatment.

A large proportion of countries have no working information system in the NTBLN that enables efficient and timely management of laboratory information. Only 47% of

countries have an online information system, despite its growth since 2016. 12% of the countries make use of an electronic report system from the GenXpert units for real-time notification of results. This low percentage hinders optimization of the Xpert MTB / RIF assay for TB diagnosis, that would allow physicians to take right decisions on a TB patient's course of treatment.

Operational information analysis is essential for location quality evaluation and case bacteriological confirmation. In Pan-American networks, the majority of countries compile information. However, compilation systems range from paper records and Excel electronic records to web platforms for online information registry, and no major advance was accomplished since 2016. Information sources have a variety of structures, so delivery, reception, consolidation and analysis processes may cause delays when it comes to strengthening all the country information.

For information and indicator analysis, quality data collection is critical, which is why it is vital to ensure high coverage in notification. There is a 30% of countries who have a coverage below 50%, while other have none at all.

Sample reference systems make a huge difference, since they can efficiently boost access to diagnosis in areas where tests are not available, prevent the need for and costs associated with patient travel and lead to equity in access to health. A robust sample reference system can be more profitable than to contract personnel, purchase, and equipment maintenance to make tests at lower levels. To reliably send samples, a system is needed including not only the necessary sample transport mechanisms for a safe sample delivery, but also logistics, result information, qualified staff, data management, monitoring and evaluation, a policy framework, SOPs, a comprehensive plan with sufficient funding and adequate governance. Only 24% of the countries have a comprehensive strategic national laboratory plan that features among its components the sample reference system.

There can be a variety of sample reference mechanisms in a country, and the often remain unknown to NRLs/Network coordination, which may result in inefficiencies, replications, needless expenses in sample transport. A technical group formation for coordination of the reference system may boost efficiency and reconcile and integrate the different systems. In complex systems, local or regional teams may need to be created to interact with focal people at each establishment. Only in 17% of the countries there is a technical working group in the MH that is responsible for sample referral-related issues, while in 40% a contact person is made responsible of the NTBLN. Sample reference systems

are found not just in the MH, but also in other systems like the correctional, police and military systems.

Patient information confidentiality must be kept throughout the process of sample referral, from its collection and transport to its return. 65% and 75% of the countries enforce national policies and procedures to manage laboratory data security and patient data confidentiality.

Mapping sample reference systems can become simpler with the use of the Geographic Information System (GIS). Software programs are available that can make use of these supplies to streamline and optimized systems. In very few countries this geographic information is available.

Only 40% of the countries possess a definite structure of the sample reference system, and 30%-40% have someone in charge of the sample referral system at central and intermediate level, respectively. There are wide-ranging transport types and modes, being taken over chiefly by workers from health establishments and/or the private mail and/or a courier service.

In 82% of the countries a guide is available with information about transport, packing, transit and response time SOPs, but only 65% of the countries reported that the laboratory personnel are trained in those contents.

In 65% of the countries, diagnosis request forms are standardized for every test and applied at all levels. In relation to a three-layer package use for international-scale sample transport, it is in use in most of the countries, while at the local level it's used by very few.

For sending back results, a large proportion of the countries use paper and/or electronic format. It is a shortcoming that 30% still does not use electronic delivery

Most of these countries possess no system to allow them to monitor sample journey from the referring laboratory to the testing laboratory, and monitor result delivery, sample quality, rejections and missing results. They do not compile information about on the response time that elapses from collection until result delivery, the number of referred samples and sent samples for which the result was returned. Monitoring and evaluating the sample reference system is key to examine system performance and should include monitoring performance indicators. Monitoring makes it easier to detect problems and enables the start of corrective actions in order to make sure that samples arrive to testing locations at the right time and results are promptly delivered.

There are successful experiences in the sample reference system from countries like Indonesia, Bangladesh, Nigeria. After interventions to this system, access to diagnosis and rapid test use optimization (Xpert) increased, and response time for results dropped, allowing doctors to take sound decisions about patient treatment, especially when the test is not widely available

Difficulties are experienced for implementing and spreading rapid techniques (Xpert MTB/RIF, LPA, ICL), BACTEC MGIT 960/320 and universal access to DST for all TB patients. The main barriers remain the same as those of 2016: insufficient budget, lack of infrastructure/biosecurity in labs and shortage in human resources. Moreover, for the use BACTEC MGIT 960/320, bureaucratic hold-ups in the procurement/importation processes added up significantly to the difficulties in implementing this method.

The main strengths of the NTBLN as reported by the countries were: training, personnel experience and commitment, structures and organized laboratory network and wide availability of diagnostic techniques.

The main weaknesses of the NTBLNs as reported by the countries, which remain consistent in relation to the study from 2017, are directly connected to government health policy ¿design and implementation. They were insufficient budget, personnel shortage and/or deficient training, inadequate laboratory infrastructure and an inefficient information system. Overcoming these barriers is a hard enterprise, but it is the future challenge to improve access to health, equity and service quality.

Health policies that focus on achieving greater equity are constrained by history, culture, politics, economy and the social foundations of the context they are applied to. If we consider this complexity and its interdependence, achieving significant benefits in health will not only require a modification of the present outlook in health policies, systems, and services, but also tackling the challenge of the new ways of governance in the State and society, which is a topic that goes beyond the health sector.

Conclusions

This study is a valuable component to design an improvement plan in high-priority areas that were identified during this situational diagnosis and enable the strengthening of the NTBLNs in the Region.

As compared to the 2016 study, in 2020 an almost twofold growth was observed in the proportion of countries that use LED lamp fluorescence microscopy, a decrease in the proportion of countries that use LJ and Stonebrink medium, and the proportion of countries that use automated methods remained stable.

The number of Xpert units and the number of laboratories equipped with Xpert units increased, but the equipment application was low and its decentralization in some countries was scarce. If we compare 2020 in connection with 2016, the increase in automated reading liquid media implementation for DST was 120%, the rise of Xpert MTB/RIF execution was 71%, and that of LFIA application for *M. tuberculosis* Complex identification was 17%. LPA availability increased in 120%.

The proportion of DSTs that is made to reported, bacteriologically confirmed cases was in the range of 1.3%-69% in 10 countries, which is far from universal coverage values.

35% of countries still have no manuals for quality management and there are countries that have no manuals on SM, culture, DST of Xpert MTB/RIF.

Only four countries' NRLs have gotten their certification for the standard ISO 15 189 or 17 025 and the same four countries succeeded in certifying a technique.

SM external quality assessment is implemented in the NTBLNs from all the countries, at least in one of its recommended variants. However, 76% of the countries failed to put it into effect during 2020, and 54% had a coverage below 60%, which match the findings observed in 2016.

Culture medium quality was examined in just 47% of the countries during 2020, generally with good coverage in the assessed laboratories and an acceptable quality in most laboratories of the network. As for EQA for DSTs, they were implemented in just 59% of the countries in 2020.

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The majority of countries compile information, but compilation systems range from paper records and Excel electronic records to web platforms for online information registry, and no major advance was accomplished since 2016.

Only 24% of the countries have a comprehensive strategic national laboratory plan that features among its components the sample reference system. In 17% of the countries there is a technical working group in the MH that is responsible for sample referral-related issues, while in 40% a contact person is made responsible of the NTBLN.

In 50% of the countries, all health institutions possess SOTs for sample collection, preservation and transport, while in the remaining 50% only it is only available in some institutions.

In relation to a three-layer package use for international-scale sample transport, it is in use in most of the countries, while locally is hardly ever used.

Most of these countries possess no system to allow them to monitor sample journey from the referring laboratory to the testing laboratory, and monitor result delivery, sample quality, rejections and missing results. They do not compile information about on the response time that elapses from collection until result delivery, the number of referred samples and sent samples for which the result was returned.

Difficulties are experienced for implementing and spreading rapid techniques (Xpert MTB/RIF, LPA, ICL), BACTEC MGIT 960/320 and universal access to DST for all TB patients. The main barriers remain the same as those of 2016: insufficient budget, lack of infrastructure/biosecurity in labs and shortage in human resources.

Recommendations

For a transition towards rapid method diagnosis strategies such as baseline test should be considered because SM still prevails as the first diagnostic test. It is also necessary to get further decentralization of rapid diagnostic test availability, strengthening the local level

It should be secured that 100% of NTBLNs have a written activity plan that is agreed on with the NTBP.

GeneXpert equipment performance should be enhanced to speed up case diagnoses, while reducing disease transmission, and diagnosed TB cases should be guaranteed to have

at least one DST for R. Countries that still make DST for top-priority groups should transition into a universally provided Anti-TB drug DST.

Every country that uses MGIT960/320 for anti-TB DST should incorporate the CC new recommendation of de 0.5 mg/L for R.

Progress is critical in the implementation of a formal quality management system with the goal of having the NRLs certified for compliance with international standards so that they can provide assistance to local and intermediate level laboratories to also get certification.

It is important that the national network operational evaluation by the NRLs/Network coordinators includes the systematic collection and analysis of all diagnostic test performance indicators, in order to implement actions of continuous improvement when needed.

A technical group formation for coordination of the reference system may boost efficiency and reconcile and integrate the different systems, as well as dealing with any barrier and set up processes to guarantee that resources are efficiently used. In complex systems, local or regional teams may need to be created to interact with focal people at each establishment.

All the health staff that is involved in the sample reference system circuit form its collection should be trained and sensitized. Physicians must get training on sample, test and test request form requirements. Laboratory staff should know procedures for sample collection, labelling, preservation, packing, reference form completion and transport organization. Relevant information on biosecurity needs to be provided to clinical, laboratory and transport staff.

Sensitization, recognition, and identification of the sample reference system as a major barrier in access to diagnosis is a must for laboratory network managers and healthcare officers that are tasked with decision making, who should consider it as a critical component to TB control.

Advocacy should be made before governments and donors to gather resources directed to overcome the main weaknesses that were reported by the networks: insufficient budget, deficient infrastructure, lack of an online information system and/or connectivity issues, personnel shortage and trouble for sample transport.

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