

Is deployment of diagnostic test alone enough? Comprehensive package of interventions to strengthen TB laboratory network: three years of experience in Burkina Faso

Riccardo Alagna (✉ alagna.riccardo@hsr.it)

Ospedale San Raffaele <https://orcid.org/0000-0002-8768-8180>

Adjima Combarry

National Tuberculosis Programme of Burkina Faso

Elisa Tagliani

IRCSS San Raffaele Scientific Institute

Léon Tinnoga Sawadogo

National Tuberculosis Programme of Burkina Faso

Tandaogo Saouadogo

National Tuberculosis Programme of Burkina Faso

Souba Diandé

National Tuberculosis Programme of Burkina Faso

Francis Ouedraogo

National Tuberculosis Programme of Burkina Faso

Daniela Maria Cirillo

IRCSS San Raffaele Scientific Institute

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Abstract

Backgrounds

Laboratory plays a critical role in tuberculosis (TB) control by providing testing for diagnosis, treatment monitoring, and surveillance at each level of the health care system. Weak accessibility to TB diagnosis services still represents a big concern in many limited resources' countries. Here we review the experience of Burkina Faso in implementing a comprehensive intervention packages to strengthen TB laboratory capacity and diagnostic accessibility.

Methods

Interventions lasted from October 2016 to December 2018 and focused on two main areas: i) development of strategic documents and policies; ii) implementation of TB diagnostic technology. National TB laboratory data were collected over 2016–2018, stratified according to five programmatic TB laboratory indicators: i) Percentage of notified new and relapse TB cases with bacteriological confirmation; ii) Percentage of notified new and relapse TB cases tested with a WHO-recommended rapid diagnostic test (WRD); iii) Percentage of notified, bacteriologically confirmed TB cases with DST results for rifampin; iv) Percentage of notified MDR-TB cases; v) Smear/Xpert ratio. We evaluated the following indicators between 2016-2017 and 2016-2018

Results

From 2016 to 2018 the number of bacteriologically confirmed cases increased of 4%. The number of new and relapse TB cases notified tested with a WRD increase of 27% compared to 2016 and the number of bacteriologically confirmed cases with an available DST result for rifampicin increased from 27% of 2016 to 66% in 2018. The number of MDR-TB cases notified over the number of estimated MDR-TB cases in 2018 increase of 35% compared to 2016. In 2018, the ratio between the number of smear microscopy and Xpert MTB/RIF test decreased from 53 in 2016 to 21 to 2018.

Conclusion

We demonstrated that implementation of comprehensive package of laboratory strengthening interventions had a positive effect on the evaluated indicators and external assistance has played a fundamental role in speeding up the TB laboratory system improvement process

Background

The laboratory represents an integral part of the continuum of care since centuries by providing evidence for decision making in clinical practice. Despite its vital contribution to healthcare, it is estimated that only 60–70% of all patient care decisions are based on laboratory results [1]. In addition, the diagnostic gap is a common issue for many infectious diseases, but it is much higher for tuberculosis (TB) [2].

Globally, the case detection rate of TB is only 56% with a gap of approximately 3.6 million TB cases in 2018. The missed cases are either not diagnosed or diagnosed but not reported [3]. Despite the promising development of new TB diagnostic tests aimed at reducing access barrier and provide rapid and accurate detection of TB and drug resistance, poor accessibility to health care is still a big concern in many settings [4, 5]. Years of experiences on field implementation have demonstrated that diagnostic tests alone may fail to meet the expected impact on the TB care cascade if not implemented within the context of a strengthened health system [6].

In the context of a strengthened laboratory system, one of the key missions of National TB Programmes (NTP) to improve accessibility of diagnostic services, is to keep updating national policy and strategies in line with global policy issued by the World Health Organization (WHO) [7–10]. Development of new TB diagnostics, treatment and prevention tools has increased substantially over the last decades, leading to more than 20 new or updated WHO guidelines on different aspects of TB care [8, 9]. Already, since 2010 the NTPs had to respond to a number of WHO policy updates on TB laboratory strengthening.

As a result of these rapid change, countries have experienced different level of progress in adopting and fully implementing TB laboratory policies and strategies [11]. In this context, among its several mandates, the WHO play a crucial role in directing and coordinating the international public health efforts through assistance to countries, partnerships, and initiatives with the aim to facilitate translation of policy into practice. The TB Supranational Reference Laboratory Network (SRLN) is a key WHO technical resource in supporting the strengthening of laboratory capacity in high TB burden countries [12].

The Emerging Bacterial Pathogens Unit (EBPU) of the Fondazione Centro San Raffaele part of San Raffaele Scientific Institute of Milan, Italy, was appointed as SRL and as WHO Collaborating Centre for TB laboratory strengthening (ITA-98) in 2006 and 2013, respectively. Between 2016 to 2018, the EBPU-SRL Milan, through the United States Agency for International Development (USAID) financial support, has served as technical partner to the WHO Global TB Program providing support to selected countries, including Burkina Faso, specifically on strengthening the TB diagnostic capacities and to support Drug-Resistance Surveillance (DRS) activities in the country.

The objective of the present study is to determine the impact of implementing comprehensive intervention packages on the TB laboratory capacity and accessibility in Burkina Faso.

Methods

Setting

In 2016, the Burkina Faso's TB three-tier laboratory network consisted of a National Reference Laboratory (NRL), 13 regional laboratories and 97 peripheral laboratories. Both fluorescence and conventional light microscopy are the main TB diagnostic method used. In October 2016, three 4-module GeneXpert instruments with Xpert MTB/RIF testing (Cepheid, Sunnyvale CA) became available in the country: one

was installed at the NRL, and two in two regional laboratories. Solid culture, phenotypic and genotypic drug susceptibility testing (DST) for first-line anti-TB drugs were only available at the NRL.

Routine TB examination consisted of clinical evaluation, sputum smear microscopy, and chest radiography. Patients at high-risk of multidrug-resistant TB (MDR-TB), children and people living with HIV (PLHIV) were tested for Xpert MTB/RIF and patients with rifampin resistance results were referred to the NRL for phenotypic and genotypic testing for first-line anti-TB drugs.

Intervention Strategy

Under the WHO- Global TB Programme coordination and support, the EBPU-SRL Milan provided extended and highly specialised technical assistance (TA) to the National TB Programme (NTP) and NRL of Burkina Faso. The TA lasted a total of 27 months (October 2016 - December 2018), and focused on two main areas: i) development of strategic documents and policies; ii) implementation of TB diagnostic technology (Fig. 1).

Development of strategic documents and policies

The development of strategic documents and policies has been primarily guided by a comprehensive assessment of the country TB laboratory network together with the conduction of an anti-TB drug-resistance surveillance study (DRS). The National TB Laboratory network assessment led to the identification of strengths and weaknesses of the overall system, whereas the DRS study provided information on national anti-TB drug resistance prevalence. Altogether, these information guided the NTP in the development of targeted public health measures to control the causes and to prevent the further expansion of drug resistant TB. In addition, they allowed to determine priority actions to be implemented, and constituted the foundations for developing new or revising existing national policies and strategic plans such as the five-years National Strategic Plan (NSP) 2018–2022 (REF). Diagnostic algorithms had also been revised to move toward the END TB Strategy goals of universal access to rapid diagnostics and DST [13]. To this purpose, the SRL Milan supported the NTP in the development of an Xpert MTB/RIF operational plan for the years 2018–2022 to strengthen the national GeneXpert network. Special attention had also been paid to the sample referral and transport system to enable the timely diagnosis for patients living in the countries remote areas.

This comprehensive package of strategic and operational plans facilitated the development of the concept note for the Global Fund grant cycle 2018–2020 to ensure the proper financing of the TB laboratory priorities.

Implementation of TB diagnostic technology

The development of strategic documents was interconnected with activities aimed at strengthening the TB national diagnostic services. By the end of 2016, the GeneXpert network was expanded with additional twelve 4-modules machines resulting in a total of 15 instruments covering all regions. A total

of 60 laboratory technicians were trained to operate the GeneXpert machines, and more than 200 clinicians were instructed on TB patients referral and initiation of appropriate treatment based on Xpert results. To ensure the effective introduction of Xpert MTB/RIF test within the diagnostic routine, a pilot operational research project financed by the STOP TB Partnership named “Applying a Standardized Approach to Strengthen Performances of GeneXpert Networks” (ASAP-GxNet) was started. In particular, the project aimed at strengthening the local managerial skills and at assessing in a standardised way the functionality of the GeneXpert network. Finally, the expansion of the GeneXpert network accompanied the strengthening of the diagnostic capacity at the NRL. The priorities focused on the implementation of Line Probe Assay (LPA) for second line drugs and on the development of a procurement plan for a Biosafety Level-3 (BSL-3) container laboratory to be used for liquid culture and DST.

Data Sources And Analysis

The National TB Programme provided the TB case notification data from the national TB electronic database from 2016–2018. Data included TB notifications among new and previously treated patients stratified for type of diagnosis (clinical or bacteriological), test type (Xpert MTB/RIF) and result.

Quantitative data per year were imported to Excel spreadsheet and stratified according to five programmatic TB laboratory indicators: i) Percentage of notified new and relapse TB cases with bacteriological confirmation; ii) Percentage of notified new and relapse TB cases tested with a WHO-recommended rapid diagnostic test (WRD); iii) Percentage of notified, bacteriologically confirmed (positive by smear microscopy, culture or WRD) TB cases with DST results for rifampin; iv) Percentage of notified MDR-TB cases; v) Smear/Xpert ratio.

TB notification outcomes were stratified following the five above-mentioned indicators and trends compared over a three years time-frame using a z-test for proportions. A two-tailed p-value less than 0.01 was considered statistically significant.

Results

Technical support started in 2016 with the identification of strengths and weaknesses of national TB laboratory network followed by development, validation and implementation of strategic initiatives in 2017 and 2018 as showed in Figure 1: i) implementation of twelve 4-modules GeneXpert machines by the end of 2016, ii) development, validation and implementation of TB diagnostic guidelines in 2017 and 2018. To evaluate the impact of TB diagnostic guidelines and the advantage of TA, we evaluated the following indicators between 2016-2017 and 2016-2018:

i) Notified new and relapse TB cases bacteriologically confirmation in 2016-2017 and 2018

A total of 5918 and 5839 new and relapse TB cases were notified in 2016 and 2017, respectively. Of them, 3993 (67%) and 4044 (69%) were bacteriologically confirmed through smear microscopy and/or

Xpert MTB/RIF (Figure 2). The difference between the number of bacteriologically confirmed cases between 2016 and 2017 was not statistically significant ($p= 0.037$). In 2018, out of the 6166 new and relapse TB cases notified, 4288 (71%) were bacteriologically confirmed through smear microscopy and/or Xpert MTB/RIF (Figure 2). The difference between the number of bacteriologically confirmed cases between 2016 and 2018 was statistically significant ($p < 0.00001$).

ii) Notified new and relapse TB cases tested with a WRD in 2016-2017 and 2018

The number of new and relapse TB cases notified tested with a WRD increased from 18% (1094/5918) in 2016 to 20% (1147/5839) in 2017, but this increase was not statistically significant ($p=0.756$) (Figure 2). The difference between the number of new and relapse TB cases notified tested with a WRD between 2016 and 2017 was not statistically significant ($p= 0.109$). The number of new and relapse TB cases notified tested with a WRD was 2826/6166 (46%) in 2018, showing a statistically significant increase of 27% compared to 2016 (1094/5918, 18%) ($p < 0.00001$).

iii) Notified, bacteriologically confirmed (positive by smear microscopy, culture or WRD) TB cases with DST results for rifampin in 2016-2017 and 2018

The number of bacteriologically confirmed TB cases with an available DST result for rifampicin increased from 27% in 2016 (1094/3993) to 28% in 2017 (1147/4044) (Figure 3). This increase is not statistically significant ($p=337$). Notably, the number of bacteriologically confirmed cases with an available DST result for rifampicin increased from 27% of 2016 to 66% (2826/4288) in 2018. This 39% points increase was highly significant ($p < 0.00001$) (Figure 3).

iv) Notified MDR-TB cases in 2016-2017 and 2018

The number of MDR-TB cases notified over the number of estimated MDR-TB cases increased from 43% (58/136) in 2016 to 47% (63/134) in 2017, this increase was not statistically significant ($p=0.471$). The number of MDR-TB cases notified over the number of estimated MDR-TB cases was 102/131 (78%) in 2018, showing a statistically significant increase of 35% compared to 2016 ($p < 0.00001$).

v) Smear/Xpert ratio

To evaluate the use of Xpert MTB/RIF in routine practice, we calculated the ratio between the number of smear-microscopy and Xpert MTB/RIF test performed in 2016-2017. This ratio decrease from 53 (58510/1105) in 2016 to 51 (61755/1200) in 2017, this decrease was not statistically significant ($p=0.490$). In 2018, the ratio between the number of smear microscopy and Xpert MTB/RIF test decreased to 21 (59714/2826), showing a statistically significant decrease of 30% decrease compared to 2017 ($p < 0.00001$), and suggesting a robust replacement of smear microscopy with the Xpert.

Discussion

Translation of global laboratory policy into country customized strategies and action plans is a priority to ensure the optimal introduction of new diagnostic technologies [6]. In this paper, we isolated the effect of laboratory strategies and guidelines implementation to improve accessibility to diagnostic services. We demonstrated that the implementation of key strategies and guidelines is crucial to ameliorate accessibility to diagnostic services. This evidence is clearly supported by the variation of indicators across time. By the end of 2016, the country has experienced a 5-time increase in the number of 4-module GeneXpert instruments. That expansion was crucial to decentralize diagnostic capacity but still not sufficient to significantly improve evaluated indicators as demonstrated by the comparison between 2016 and 2017. We instead observed a significant increase in indicators in 2018 after the implementation of laboratory guidelines and strategies. This evidence suggests that broader access to diagnostic services require a comprehensive package of interventions that address multiple needs including diagnostic algorithms, sample referral system strategy, Xpert Operational Plan and financial estimantes. Nonetheless, while all of evaluated indicators showed a substantial variation over time, the overall number of new and relapse TB cases bacteriologically confirmed showed a small, but statistically significant, change between 2016 and 2018. The increase of GeneXpert use, as seen with the other indicators, demonstrates that positive trend of TB cases bacteriologically confirmed was modestly influenced by implementation of guidelines and strategies rather than simple implementation of new instruments. In addition, the reason why the overall number of new and relapse TB cases bacteriologically confirmed did not show a substantial increase over time, can be explained by the implementation of an interim diagnostic algorithm that limited access to Xpert MTB/RIF mainly, but not only, to smear positive patients such as those at high-risk of MDR-TB. This ensured the smooth and gradual move toward the universal DST and avoided possible overload of the network.

Consequently, as expected, the value of this strategic approach minimized the impact on reduction of TB cases clinically diagnosed over the all TB cases notified.

In addition, most of the impact in terms of notifications is observed on the MDR-TB category, where the implementation of the diagnostic algorithm lead to a significant increase in the notification toward the expected number of cases (Fig. 3, right panel).

Additional evidence might suggest that also TA played an important role in speeding up the process toward a better diagnostic accessibility. The smear/Xpert ratio has been used as an approximate index of Xpert market penetration, however, trend of this indicator is also well suited to observe how country move in regard to Xpert use when compared to other contexts [11, 14]. According to WHO guidelines, countries are recommended to move toward universal use of Xpert MTB/RIF for all TB suspect before 2020. Between 2017 and 2018, Burkina Faso showed a decrease of 73% of its smear/Xpert ratio, resulting in a more and more Xpert MTB/RIF tests instead of microscopy. Definitely, much faster than other African countries with more experience on Xpert implementation like Mozambique, Uganda, DR Congo, and Zimbabwe [14].

We recognize that demonstrating causal relation between provision of TA and strengthening of laboratory system is challenging due to its complexity to isolate the differential effects of TA service deliver. Ideally, randomized or quasi-randomized controlled studies have the potential to assess implementation fidelity for different types and dosages of TA [15]. However, it is undoubtedly that interventions had a positive effect on the evaluated indicators and external assistance has played a fundamental role in speeding up the TB laboratory system improvement process. Other factors not taken into account and possibly contributing to the positive effects observed are country's ownership and commitment that ensured the achievements of results

Conclusion

The experience in Burkina Faso suggests that laboratory guidelines adoption and implementation are absolutely needed to rapidly advance on provision of TB laboratory services. However, several lessons learnt can be captured for use by other NTPs that aim to achieve concrete goals in strengthening their national TB laboratory networks. Overall, one of the key lessons was to build a roadmap of priority interventions guided by a comprehensive analysis that included country's epidemic, context, country's unique approach to laboratory service deliver, and availability of financial, human and other resources. Timing played a crucial role, as Burkina Faso was able to achieve most of its results by conducting this comprehensive analysis and development of key operational plan the year before the Global Fund grant development. This allowed to secure funding to implement priority activities. Absolutely, these results cannot be achieved without a strong national commitment. It represents a sine qua non condition in order to ensure that planned activity have a continuum on national TB control strategy. External assistance contributed to the adoption of guidelines; however, further studies are needed to evaluate the direct impact of TA in strengthening TB laboratory system. In this context a TA model that integrate into an existing donor-recipient system and country needs is essential to maximize external aid outcomes.

Declarations

Ethics approval and consent to participate

'Not applicable'

Consent for publication

'Not applicable'

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to data protection requirements but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests"

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Authors' contributions

RA led the design of the study, advised on data analysis and interpretation and drafted the manuscript. AC participated in the design of the study, advised on data analysis and interpretation, and drafted manuscript. SLT, ST, DS, OF the process of data analysis, participated on data interpretation, and drafted the manuscript. ET participated in the interpretation of the data and writing the manuscript. DMC advised on data analysis, participated in data interpretation and writing of the manuscript. All authors read and approved the final manuscript.

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References

1. Regan M, Forsman R. The impact of the laboratory on disease management. *Dis Manag.* 2006;9(2):122-30. Epub 2006/04/20. doi: 10.1089/dis.2006.9.122. PubMed PMID: 16620198.
2. Arinaminpathy N, Dowdy D. Understanding the incremental value of novel diagnostic tests for tuberculosis. *Nature.* 2015;528(7580):S60-7. Epub 2015/12/04. doi: 10.1038/nature16045. PubMed PMID: 26633767.
3. World Health Organization. Global Tuberculosis Report 2018. Available from: <http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?ua=1> . Geneve: WHO,2018.
4. Zumla A, Abubakar I. Improving access to multi-drug resistant tuberculosis diagnostic and health services for refugees and migrants. *BMC Med.* 2018;16(1):221. Epub 2018/12/01. doi: 10.1186/s12916-018-1218-0. PubMed PMID: 30497477; PubMed Central PMCID: PMC6267830.
5. Lin HH, Dowdy D, Dye C, Murray M, Cohen T. The impact of new tuberculosis diagnostics on transmission: why context matters. *Bull World Health Organ.* 2012;90(10):739-47A. Epub 2012/10/31. doi: 10.2471/BLT.11.101436. PubMed PMID: 23109741; PubMed Central PMCID: PMC3471051.
6. Albert H, Nathavitharana RR, Isaacs C, Pai M, Denkinger CM, Boehme CC. Development, roll-out and impact of Xpert MTB/RIF for tuberculosis: what lessons have we learnt and how can we do better?

- Eur Respir J. 2016;48(2):516-25. Epub 2016/07/16. doi: 10.1183/13993003.00543-2016. PubMed PMID: 27418550; PubMed Central PMCID: PMC4967565.
7. Nasser SM, Cooke G, Kranzer K, Norris SL, Olliaro P, Ford N. Strength of recommendations in WHO guidelines using GRADE was associated with uptake in national policy. *J Clin Epidemiol.* 2015;68(6):703-7. Epub 2015/01/13. doi: 10.1016/j.jclinepi.2014.11.006. PubMed PMID: 25578218.
 8. Brigden G, Nhung NV, Skrahina A, Ndjeka N, Falzon D, Zignol M. Advances in clinical trial design for development of new TB treatments-Translating international tuberculosis treatment guidelines into national strategic plans: Experiences from Belarus, South Africa, and Vietnam. *PLoS Med.* 2019;16(10):e1002896. Epub 2019/10/19. doi: 10.1371/journal.pmed.1002896. PubMed PMID: 31626628; PubMed Central PMCID: PMC6799896.
 9. Lienhardt C, Nahid P. Advances in clinical trial design for development of new TB treatments: A call for innovation. *PLoS Med.* 2019;16(3):e1002769. Epub 2019/03/23. doi: 10.1371/journal.pmed.1002769. PubMed PMID: 30901322; PubMed Central PMCID: PMC6430361.
 10. WHO Global tuberculosis report 2019 https://www.who.int/tb/publications/global_report/en/
 11. Cazabon D, Suresh A, Oghor C, Qin ZZ, Kik SV, Denkinger CM, et al. Implementation of Xpert MTB/RIF in 22 high tuberculosis burden countries: are we making progress? *Eur Respir J.* 2017;50(2). Epub 2017/09/02. doi: 10.1183/13993003.00918-2017. PubMed PMID: 28860268.
 12. Gilpin C, Mirzayev F. Tuberculosis Supranational Reference Laboratories: A Global Approach. *Clin Chest Med.* 2019;40(4):755-62. Epub 2019/11/17. doi: 10.1016/j.ccm.2019.07.005. PubMed PMID: 31731982.
 13. The End TB Strategy <https://www.who.int/tb/strategy/end-tb/en/>.
 14. Cazabon D, Pande T, Kik S, Van Gemert W, Sohn H, Denkinger C, et al. Market penetration of Xpert MTB/RIF in high tuberculosis burden countries: A trend analysis from 2014 - 2016. *Gates Open Res.* 2018;2:35. Epub 2019/09/25. doi: 10.12688/gatesopenres.12842.2. PubMed PMID: 30234198; PubMed Central PMCID: PMC6139378.2.
 15. Ruprah I, Marcano L. Does technical assistance matter? An impact evaluation approach to estimate its value added. *Journal of Development Effectiveness.* 2009;1(4):507-28. doi: 10.1080/19439340903370451.

Figures

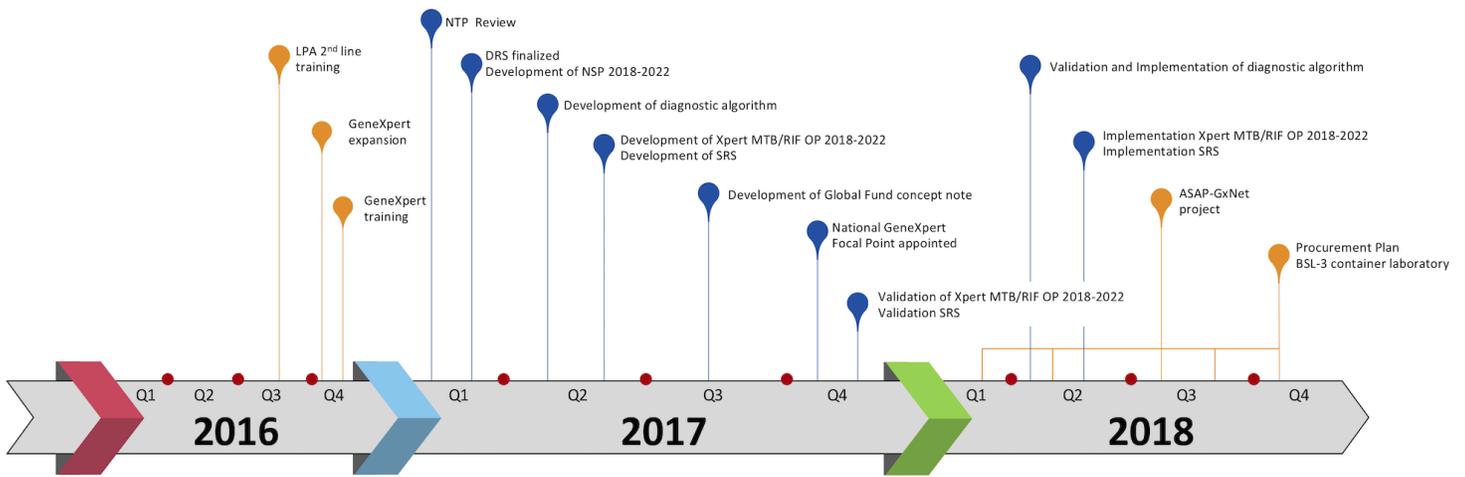


Figure 1

Timeline of TA activities carried out between October 2016 to December 2018. Orange dots represent the implementation of TB diagnostic guidelines and technology; Blue dots represent the development of strategic documents and policies. Line Probe Assay (LPA); National TB Programme (NTP); Drug-resistance Survey (DRS); Operational Plan (OP); Sample Referral Strategy (SRS); Biosafety Level-3 (BSL-3)

■ N° cases notified bacteriologically confirmed
 ■ N° cases notified
 ■ N° cases notified tested with WRD

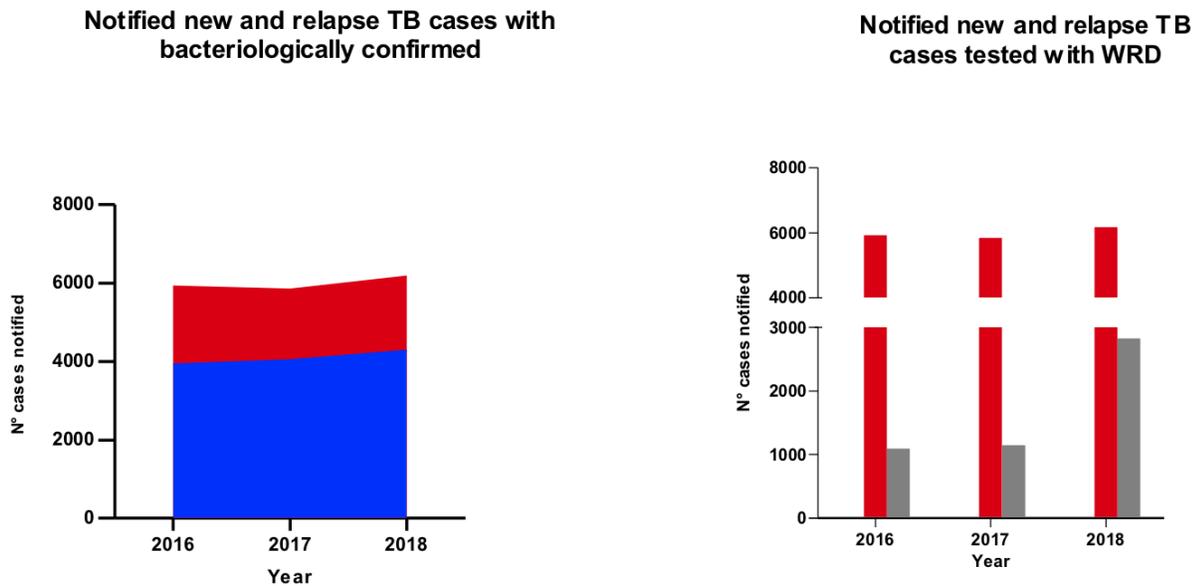
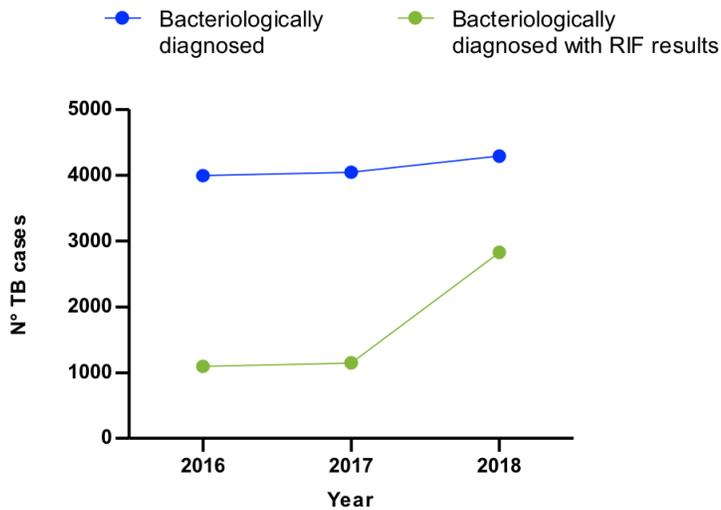


Figure 2

Laboratory indicators I and II. On the left, trend of number of new and relapse TB cases notified between 2016 to 2018 stratified for type of diagnosis. On the right, the absolute number and percentage of new and relapse TB cases notified between 2016 to 2018 tested with WRD; in red notified cases clinically diagnosed, in blu notified cases WRD diagnosed.

Notified, bacteriologically confirmed TB cases with DST results for rifampicin



MDR-TB cases

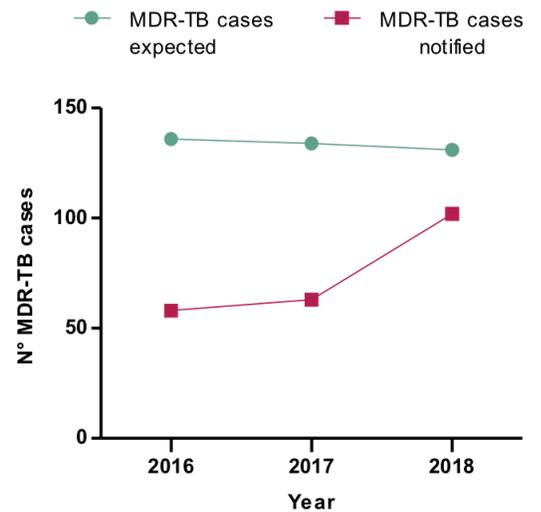


Figure 3

Laboratory indicators III and IV. On the left, number of notified bacteriologically confirmed TB cases compared to the number of bacteriologically confirmed TB cases with rifamicin result. On the right, number of MDR-TB cases notified over the number of estimated MDR-TB cases.