Mission-Report

Laboratory expert mission from the SRL partner to Nepal 2017

Nepal

June 2017

Supranational Reference Laboratory Munich-Gauting

Kuratorium Tuberkulose in der Welt .V.

Experts:

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1. Abbreviations

CO	Country office
DST	Drug susceptibility testing
EP-TB	Extra-pulmonary TB
FQ	fluoroquinolones
GENETUP	German Nepal Tuberculosis Project
HQ	Head quarter
LPA	Line probe assay
MDR	Multi-drug-resistant corresponding to resistance toward INH and RIF
MoH	Ministry of health
NTC	National TB center Timi
NTP	National TB program
pre-XDR	Pre-extensive drug resistance corresponding to MDR-TB plus resistance toward FQ or SLID
RR	Rifampicin resistance
SLID	second line injectable drug
SRL	Supranational Reference Laboratory
TB	tuberculosis
WHO	World health organization
XDR	extensive drug resistance corresponding to MDR-TB plus resistance toward FQ and SLID
yoa	Years of age

2. Background:

- *Epidemiological situation*: Nepal has an estimated annual 44,000 incident cases (estimates from 2015) corresponding to an incidence rate of 156 (137–176) TB cases per 100,000 population. The number of notified TB cases was 34'122 in 2015 corresponding to a notification rate of 77.5% with a slight annual decline over the last 3 years. The total estimated incidence of RR/MDR-TB is around 1'500 cases per year. Of those, 451 cases were laboratory-confirmed in 2016 and 379 were started on MDR/RR-TB treatment. The rate of pre-XDR-TB (defined by resistance either to fluoroquinolones or to SLIDs) among all RR/MDR-TB cases was 20% in the last DRS with an increasing tendency. Currently, approximately 40% of all RR/MDR-TB isolates recovered at both NRL departments NTC and GENETUP are classified as pre-XDR-TB. There were seven XDR-TB patients who were put on treatment in 2015.
- With technical assistance from Paul Nunn, the teams from WHO-HQ and -CO, and the SRL partner Munich-Gauting, the Nepalese NTP has drafted an NSP in 2017 which has been endorsed by the MoH in August 2017 after translation into Nepalese language. During implementation of the NSP, laboratory diagnostics plays a key role in order to improve case notification.
- This present mission was conducted on behalf of WHO supported by SRL Gauting. The major objectives being:
    - To revise/prioritize Laboratory Strategic Plan and recheck/revise projections in line with NSP
    - Prioritization of the laboratory components of the National Strategic Plan for implementation,

- Development of a roadmap for the implementation of the laboratory components of the NSP.
- To develop infrastructure restructuring for both National Reference Laboratories (NTC and GENETUP/NATA) for quality service delivery.
- Provide technical assistance
  - to the NTC laboratory team
    - with improving line probe assay diagnostics in order to reduce indeterminate results and cross-contaminations with DNA,
  - to GENETUP
    - with further QMS development
    - with the DST in MGIT

3. Findings:

3.1. *LPA diagnostics at the NTC:*

- Both LPAs, Genotype MTBDR*plus* and Genotype sl version 2, are implemented in routine diagnostics at the NTC department of the NRL. They are performed directly from clinical specimens as well as from culture material. The NTC laboratory performs more than 1'500 LPAs per years.
- The staff works with a good sense of responsibility and a high degree of reliability and accuracy. Both, positive and negative controls are performed with all runs. In general, they properly perform the work.

3.2. Infrastructure of the NTC laboratory

- An overview of the room plan is displayed in **Figure 1**.
- The NTC laboratory has undergone refurbishment over the last years.
- A new room has been added to the NRL ("no function) which has been recently reserved for MGIT diagnostics (**Figure 2**). In this room, a basic ventilation system has been installed. This allowed to move the MGIT machine from the assembly of smaller rooms in the right upper corner of the sketch to the comparably spacious MGIT room.

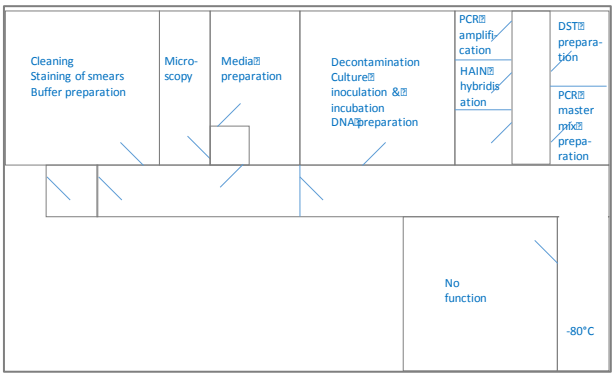


Figure 1: Overview of rooms and functions of the NTC laboratory

- Instead, the pre-amplification room was relocated into the previous MGIT room ("PCR master mix preparation") because this room has a closable door and ceiling high-walls.

3.3. QMS

- *Genetup*
  - The QMS of the GENETUP department of the NRL covers almost all tests and techniques applied for TB diagnostics. Since the recent mission of Mrs von Rudno it has significantly developed. Drafted SOPs have been endorsed, new documents have been developed and partly endorsed. Staff has been trained according to QMS documents. The actual list of QM documents is displayed in **ANNEX 2**.
  - The QMS commissioner Bijendra is highly motivated to further develop the system.
- *NTC laboratory*

- Several QM documents are available in the NTC. The staff is interested in the implementation of a more comprehensive QMS.
- Mr. Krishna Adhikari has been appointed as QM commissioner (QMC) at the NTC. He will closely collaborate with the QMC of GENETUP for further development and harmonization of both QMS.

3.4. NSP – Diagnostic algorithm

- Previously, up to six diagnostic algorithms were used for different types and categories of patients. Now, the have been replaced by a single quite comprehensive diagnostic algorithm which has been developed within the NSP with technical assistance from WHO experts (**Figure 3**). The algorithm is based on risk stratified Xpert MTB/RIF diagnostics categorizing patients in three risk groups: (i) particularly vulnerable patients such as e.g. children or PLHIV, (ii) patients at risk of MDR-TB such as e.g. previously treated patients, non-converters, MDR-TB contacts or diabetics, and (iii) all others. The diagnostic algorithm shall further develop towards universal access to Xpert MTB/RIF diagnostics over the next five years.

3.5. Calculations of consumables and reagents for the implementation of the NSP

- Numbers of tests, consumables and reagents required for TB diagnostics have been calculated for the years 2015 – 2020 based on the new diagnostic algorithm taking into consideration a development towards universal access to Xpert MTB/RIF.
- For those calculations, a comprehensive Excel-file has been used which was based on the WHO – TB planning and budgeting tool. The calculations emanate from epidemiological data and key information on the diagnostic algorithm of the country.
- As result, the tool provides numbers of test kits, Xpert cartridges etc. and calculates total costs using GDF cost templates or local costs if available.

3.6. NSP priorities and roadmap development

- See extra document following soon

3.7. MGIT training

- GENETUP has reactivated the Bactec MGIT 960 machine for DST.
- Procurement of material and reagents has started. Some missing materials have been provided by the SRL partner in Gauting.
- The upgrade of the emergency generator with an automated switch-on system is planned.

3.8. General observations

- Both departments of the NRL, work on a high quality level. All required tests and techniques are implemented. The staff of both laboratories is motivated and eager to learn new techniques, skills and knowledge. Guidelines about major laboratory issues are available.
- The GENETUP laboratory provides major services for the NTC performing more than 50% of cultures, DSTs and high numbers of PCR and smear microscopies for the National TB Program. It is fully integrated in the NTP and integral part of both National TB laboratory services and clinical TB patient management.
- Reagents, test-kits, and consumables of both NRL departments are procured by the NTC. Actual needs of materials are submitted by the GENETUP department to the NTC department of the NRL and from there forwarded to the procurement department of the NTC which then submits the order list of required materials to the GFATM procurement department which finally procures it.

4. Challenges: Major challenges identified are…

4.1. Line probe assay diagnostics at the NTC:

- Several cases of contaminations were reported from previous missions and identified when looking through the documentation files LPAs.
- Only successful runs with minor problems have been documented and filed. When asked, technicians reported of complete runs which were discarded and not documented because results were not interpretable due to technical problems such as poor quality of LPA signals or contamination of the negative control.

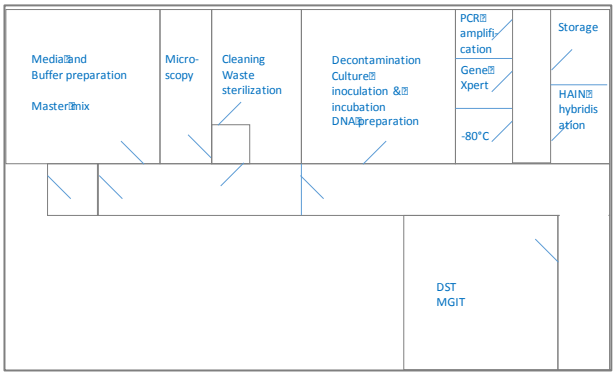


Figure 2: Recommended re-arrangement of rooms and functions of the NTC laboratory. The previous cleaning room should become a clean room for media-, buffer- and master mix preparation

4.2. Infrastructure of the NTC laboratory

- While the equipment of the NTC laboratory has well developed over the recent years and became quite modern, the furniture remained the same over decades. Now, most of laboratory furniture is old and spoiled. Surfaces are damaged and expose macerated wood. Door hinges of cabinets are partly damaged so that they cannot be closed any more.
- As a consequence, surfaces can neither be properly cleaned, disinfected nor decontaminated from DNA which unavoidably leads to contamination problems of microbiological and molecular biological assays.
- The new post-amplification room (HAIN hybridization) is equipped with a supply air outlet at the height of the work bench. This unescapably blows DNA snippets from the hybridization process towards the glass wall of the new pre-amplification room. This one is equipped with an exhaust air suction creating under-pressure of several Pascal in the room. When opening the door, DNA polluted air will automatically be sucked into the room baring the risk of contaminating LPA reagents.

4.3. QMS

- The QMS's of NTC and GENETUP are not yet harmonized.
- In GENETUP, SOPs for tests, methods and equipment are well advanced. Most managerial SOPs (e.g. staff-, warehouse-, equipment-, contract-, complaint-, error-, or risk-management, procurement, infrastructure etc.) are however missing.
- In the NTC, several SOPs for tests, methods and equipment are still missing and the QMS does not yet follow a systematic structure.

4.4. NSP – Diagnostic algorithm

- Although impressively complex and considering most clinical situations, the diagnostic algorithm does not reflect certain patient groups such as e.g. young children or follow-up cases.
- Certain ambiguities have been identified in the algorithm. Those are:
  1. Migrants & prisoners are missing in the list of risk groups although considered in the NSP calculations.
  2. The algorithm seems to suggest Xpert testing after treatment with FLD.
  3. For "MTB (+) RIF indeterminate or no results" the algorithm recommends to „follow algorithm to interpret result" but does not clarify which algorithm to follow in such cases.

4. The algorithm requests to "repeat Xpert and follow 2nd result" but does not specify what to do if Rr is confirmed with the 2nd test. It guides the user back to the exact same point where he was since the patient is still at low risk of MDR-TB.
5. In reality, results from molecular resistance testing are much more complex than delineated in the algorithm. The following constellations occur but are not reflected by the algorithm:
    - LPA indeterminate / Culture negative
    - LPA indeterminate / DST FQ & SLID susceptible
    - LPA indeterminate / DST FQ or SLID resistant
    - LPA WT / DST FQ and|or SLID resistant
    - LPA missing wildtype but no mutation signal / DST FQ & SLID susceptible
    - LPA missing wildtype but no mutation signal / DST FQ & SLID resistant
    - LPA mutation signal / DST FQ & SLID susceptible
6. The NSP calculations do not only consider patients with abnormal CXR but also clinical suspects for Xpert diagnostics while the diagnostic algorithm recommends only to test patients with "abnormal CxR". Diagnostic algorithm and NSP calculations need to be harmonized.

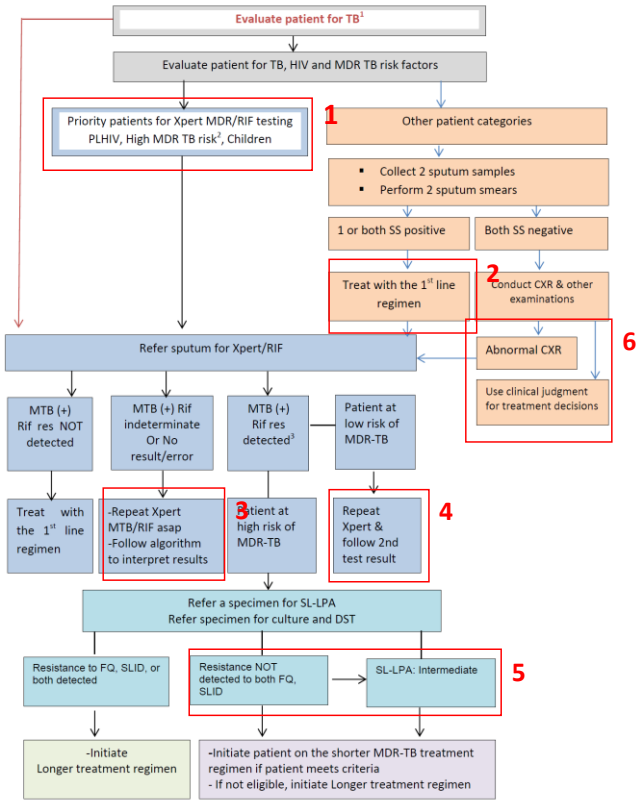


Figure 3: Diagnostic algorithm as foreseen in the NSP. Numbers indicate idenfied weaknesses and refer to respective explanations in the text in chapter 4.3

4.5. Calculations of consumables and reagents for the implementation of the NSP

- Identified and potential weaknesses in the data are reflected in the figures A1.1 – A1.5 of ANNEX 1.
- **Figure A1.1:** *Epidemiology data*
    - *Missing data points*
        - Previously treated cases: Number of previously treated children 0-14 years of age are missing and should be approximately 158.
    - *Potential inconsistencies*
        - Rate of 10% of previously treated cases (n=3'421) seems rather low. In previous years rates of 15% have been observed.
        - Incident cases: How is the decline of more than 10% over 2-3 years substantiated? Even under optimal control conditions, a measurable drop of incidence is only expected with minimum two years delay. Provided that incidence remains more or less stable until 2020, the number of total cases will be rather 47'087 (and not 41'920).
    - *Confirmed inconsistencies*
        - Childhood TB:

        - a realistic proportion of children among all TB cases would be approximately 15% (e.g. Helen & Cohen, Background document: Estimating the incidence of childhood TB and MDR-TB). Given about 47'000 cases in 2020, seven thousand children with TB are expected. With the envisaged notification of 10% childhood TB cases, 4'700 TB children would be found (67%) but **2'300 missed**. Given the 87% notification of all TB cases, 6'100 of 47'000 cases will be missed. Of those, almost 40% would be children. Those goals do not seem ambitious enough.
        - Given the 6'100 missed cases and 2300 missed childhood TB cases, there will be only 3'800 (= 8 % of all cases) missed adult cases. Is a notification rate of 92% realistic for adults in a country with such remote areas, poor logistical systems and a not yet well developed laboratory network?
    - The "number of total new cases 0-14 years of age" is too low. It would be calculated as "total cases 0-14 years of age" minus "previously treated" and "extra-pulmonary cases" and would result in approximately 1'420 cases for 2016 (before above explained corrections of the incidence rates) and would require correction for all years 2016 - 2020.
- **Figure A1.2**: *Resistance data*
    - The estimate of having 80% FLD resistance data by 2019 is not in line with the diagnostic algorithm which is based on risk group stratification If planned to fade out the risk stratification within two years, it should be clarified in a foot-note to the algorithm that it shall only be an interim approach until all patients receive RIF testing with Xpert. However: How realistic is it to reach this goal by 2020?
    - The term FLD resistance data should be replaced by "RIF susceptibility data" since only a minority of patients will receive FLD-DST.
    - Currently, 40% of all isolates tested for SLD resistance at both NTC and GENETUP have either FQ or SLID resistance. This rate is steadily and rapidly increasing since years. The indicated 109 cases corresponded to less than 25% of the number which might occur if the 40% will turn out to be more realistic.
    - Is it practically possible to identify 95% of MDR-TB cases and to put them under treatment when only 87% of all TB cases are notified?
- **Figure A1.3:** *Calculation of numbers of Xpert cartridges*
    - The number of cartridges would be too high when using the risk group stratification of the diagnostic algorithm. Was the number calculated for all suspects? If so, the algorithm instructs only to test patients with changes in the CxR with Xpert MTB/RIF.
    - The total number of tests indicated in the green line "Diagnosis: Molecular (Xpert)" is the sum of only the two lines below which are
        - "Presumptive TB passive case finding, smear negative" and
        - "Presumptive TB passive case finding, radiologically suspected"

      How are all other patient categories considered?
    - The number of calculated tests is not feasible with the number of machines planned to implement until 2020.
- **Figure A1.4:** *TB & HIV*
    - The figures of "HIV positive people eligible for TB testing" and "HIV in care with presumptive TB" seem semantically identical but differ by 3'174 cases. Where did the authors of the NSP calculations see the difference of those two patient groups?

- **Figure A1.5:** *Culture diagnostics*
  - Numbers of cultures of patients on MDR-TB treatment are far too low:
    - According to the actual NSP calculations, 676 MDR-TB patients, 270 pre-XDR or XDR-TB patients will be on treatment in 2018.
    - 12 follow-up cultures per patient = 8'112 cultures
    - plus 18 follow-up cultures per pre-XDR and XDR-patient = 4'812 cultures
    - **TOTAL: >12'000 cultures in 2018.**
  - EP-TB is not considered for culture calculations (n=0) although EP-TB is an important indication for diagnostic TB-cultures. Fifteen to 25% of all incident TB cases suffer from EP-TB corresponding to a minimum of 11.000 EP-TB cases.

4.6. NSP priorities and roadmap development

- See extra document following soon

4.7. MGIT training

- One drawer of the Bactec MGIT 960 machine was not functional during the training.
- Only the head of the laboratory is currently fully trained and experienced in MGIT DST.
- The upgrade of the emergency generator with an automated switch on system is still pending.
- MGIT tubes, reagents and drug powder need to be renewed. Respective order-lists have been submitted a while ago to the NTC but procurement seems to be pending between NTC and GFATM.

4.8. General challenges:

- Although staff of both NRL departments (GENETUP & NTC) is of highest importance for the achievement of the NSP goals, very little has been done in the past to further train and motivate the staffs. Particularly the GENETUP team – although it is strongly supporting the NTC and is fully integrated in the NTP – has never received funding from the NTP for training or education.
- Although both NRL departments are supporting the NTC and are integrated in the same national TB program, little direct collaboration and inter-action is observed. No staff meetings were held in the past.
- Although GENETUP provides a major part of laboratory and clinical services on behalf of the NTP, it receives quite little support from the national program with regard to
  - Staffing: only two staff units of the laboratory are financed by GFATM through the NTC although at least seven specialist would be required to perform the work. In 2016 financing of staff was interrupted for several months for unknown reasons although GENETUP specialists continued to provide the same services as before.
  - Training: The NTP has not financed and given little support for the training of GENETUP specialists over the last years. As GENEUP provides its services exclusively for the NTP, respective training from the national program would be required.
  - Infrastructure and maintenance: No financial budget plan is available on the national level to support maintenance of infrastructure such as e.g. ventilation systems or equipment.
- Actual salaries of GENETUP staff seem to be comparably lower than those of the NTC due to a recent introduction of a 25% risk bonus for TB lab workers in the NTC.
- The quite complicated procurement mechanism regularly leads to delays in delivery or even stock-outs at the GENETUP department of the NRL.

5. Activities

5.1. Line probe assay diagnostics at the NTC:

- Expert KH followed the staff during the LPA procedures and identified several strengths and weaknesses. She provided practical tips and recommendations how to improve the workflow and how to reduce contaminations.
- Expert HH discussed important changes in the room plan in order to prevent spread of DNA and in order to reduce contaminations. Those will be presented with the second topic of the mission.

5.2. Infrastructure of the NTC laboratory

- Together with the complete laboratory team, potential re-arrangements of the room functions and re-organisation of the workflows were discussed and played through. As result, a new room plan was developed and agreed upon with the NTC lab team.
- The importance and potentials of new furniture for all laboratory rooms with modern and intact surfaces was discussed with the team. An action plan with time line was agreed upon with the head of the lab and the team in order to enable the team to profit from a GFATM grant for financing new furniture.
- The expert HH explained the urgent need of new furniture to the GFATM country office. Provided that a concrete procurement list is submitted to the GFATM by August 2017, the need could be considered in the negotiations for re-allocation of unused funds. The urgency of the matter has been reported to the head of the NTC laboratory and the NTC director.

5.3. QMS

- The developments of the GENETUP QMS since the recent mission have been reviewed. Incomplete documents have been finalized and drafted documents pending endorsement have signed and implemented. Questions and next steps have been discussed with the QMS commissioner and the head of the laboratory.
- The necessity, advantages and chances of QMS implementation have been discussed with the NTC laboratory team. A QMS commissioner (QMC) candidate has been assigned by the head of the laboratory and proposed for official assignment to the NTC director. Tasks and responsibilities of the QMC have been explained. Further steps have been discussed with the laboratory team.
- The necessity and chances of a unified QMS of both NRL departments (GENETUP & NTC) have been discussed with both heads of the laboratories and the NTC director. Next steps towards implementation of a common QMS have been agreed upon by both lab managements.

5.4. NSP – Diagnostic algorithm

- The diagnostic algorithm has been extensively discussed with the NTC director, TB doctors, the NTC controller, the laboratory team and WHO country TB officer and all identified weaknesses have been explained. Together with the local experts, amendments have been developed as proposed under key recommendations.

5.5. Calculations of consumables and reagents for the implementation of the NSP

- Identified shortcomings and potential miss-calculations have been extensively discussed with the NTP manager, the controller of the NTC, the haed of the NTC-laboratory and their teams.
- In a telephone conference in mid July 2017, the described strengths and weaknesses of the NSP calculations have been presented to WHO HQ.

5.6. NSP priorities and roadmap development

- See extra document following soon

5.7. MGIT training

- Practical refresher training has been provided over two days to the GENETUP team in
  - Use and maintenance of the MGIT machine,
  - Registering, entering and taking-out MGIT cultures and DSTs,
  - DST in MGIT,
  - Basic trouble-shooting.
- The head of the GENETUP laboratory has called the BD representative who has meanwhile repaired the broken drawer.

5.8. General activities:

- The great importance of continuous and strong support of both laboratory teams (GENETUP and NTC) has been discussed and agreed upon with the NTP manager. He admitted that support of NRL staff was far too little in the past and that particularly international trainings and funding of international exposure was almost exclusively given to clinical staff. SRL experts and NTP management agreed that in future both NRL departments should profit from stronger support.
- The importance of close collaboration between both NRL departments has been discussed with both NRL laboratory teams. It has been agreed by both NRL heads that at least bi-monthly team-meetings should be provided, i.e. three times per year in GENETUP and three times per year in the NTC.
- The procurement mechanism has been analyzed and possibilities to facilitate the procedure have been discussed and identified together with the heads of both NRL departments and the GFATM procurement experts.

6. Key recommendations:

6.1. Line probe assay diagnostics at the NTC:

- Document and file all runs and all LPA results no matter what the outcome of the run is and how the controls are. Set-up standards for and perform trouble shooting after each unsuccessful run and plan short-, mid- and long-term improvements all with technical assistance from the SRL partner.
- Technically:
  - Immediately upon opening a new LPA kit, prepare aliquots of all reagents suitable for the average daily work load. This will prevent contamination of a whole kit.
  - Shortly spin down reagent vials after incubation in water baths in order to prevent spread of fluid sticking to the lids of the vials.
  - Change the water of water baths at least on a weekly basis.
  - Regularly decontaminate the following items with Sodium-hypochloride and rinse afterwards with water and 70% ethanol:
    - Hybridization tub, PCR racks and stands daily after usage,
    - GT Blot 48 at least every second week
  - Clean all thermal cyclers with 70 % Ethanol at least

6.2. Infrastructure of the NTC laboratory

- Re-arrange the laboratory rooms as displayed in **Figure 2**. The previous cleaning room should become the room for the “preparation of media, buffer and master mix”. This would ensure sufficient distance from the amplification and post-amplification rooms. Due to its distance from all potentially contaminating activities, the risk of contaminations would be minimized for both PCR and LPA.

- Re-locate post-amplification activities to the current pre-amplification box ("HAIN hybridization" in **Figure 2**). The under-pressure in this room would prevent DNA from spreading in other parts of the laboratory.
- Plan new furniture for all rooms in August 2017 and submit the list of furniture to the GFATM with the request to consider the procurement with the re-allocation of left-over funds. Make sure that all surfaces are robust, cleanable and disinfectable. Work-bench surfaces should preferentially be made from Trespa TopLab or equivalent quality. All other surfaces should be of ≥2mm Trespa material of ≥3 mm melamin.
- Finalize procurement and installation of the new furniture before March 2018 i.e before the end of the current GFATM funding period.

6.3. QMS

- Implement identical QMS in both departments of the NRL. Use the already existing QMS of GENETUP and implement identical documents with the identical system structure in the NTC. The QMC of GENETUP should share all currently QM documents with the NTC. With technical assistance from the SRL partner those documents should be implemented in the NTC laboratory.
- Further develop the QMS in close collaboration of NTC, GENETUP and the SRL partner.
- Officially assign a QMC in the NTC laboratory and make sure he/she has sufficient capacities, time and resources to further develop the QMS in the NTC together with the QMC of GENETUP.
- Plan international training of both QMCs (NTC and GENETUP) in 2018 and allocate respective budget for the training e.g. in one of the WHO endorsed SLPTA training courses or – if more advanced training is required - in one of the FIND SLMTA trainings.

6.4. NSP – Diagnostic algorithm

- Develop new and special diagnostic algorithms for childhood-, extra-pulmonary-TB and follow-up cases.
    - Children: Xpert MTB/RIF is weak in detecting TB in young children. Estimated sensitivity rates are far below 50%, thus more than half of children below 5 years of age remain undiagnosed with this tool. TST, CXR and clinical assessment play much stronger roles.
    - Xpert MTB/RIF is not used for follow-up of TB cases under treatment.
- Minimize ambiguities in the diagnostic algorithm in order to prevent misunderstandings in its application. Concretely, consider the following recommendations for amendment:
    - Migrants & prisoners should be considered as risk groups for both TB and MDR-TB in the diagnostic algorithm and routinely receive Xpert diagnostics. This should also be considered in the calculations of reagents and consumables.
    - For the junction highlighted with **red box 2 in figure 3** from treatment with FLD to Xpert testing it should be clarified whether Xpert MTB/RIF shall be performed simultaneously with prescription of FLD treatment or after the treatment.
    - At the junction highlighted with the **red box 3 in figure 3** interpretation and consequences from test results should be specified.
    - In order to prevent that the command highlighted with **red box 4 in figure 3** leads to paradox circles the command "Patient at high risk of MDR-TB" should be complemented by "…or RIF resistance confirmed by second test".
    - The junction highlighted with **red box 5 in figure 3** should be re-arranged taking all different results of SL-LPA into consideration.

- NSP calculations should be re-calculated according to the diagnostic algorithm which means that Xpert would only be required for patients with abnormal CXR but not for clinical suspects with normal CxR. Diagnostic algorithm and NSP calculations should be harmonized.

6.5. Calculations of consumables and reagents for the implementation of the NSP

- Carefully re-check the epidemiology figures of the NSP calculations following the list of potential miss-calculations presented under 4.4.
- Re-calculate number of previously treated and total number of children 0-14 years of age.
- Re-check whether percentage of only 10% previously treated cases is in line with national data. Consider adjustment to local particularities particularly in the Kathmandu valley in order to prevent lack of lab reagents and test kits.
- Re-discuss the probability that incidence drops by 13 % (from 47'000 to 41'000 p.a.) until 2020 as taken as basis for calculation in the NSP.
- Re-check the literature and discuss how realistic a proportion of less than 10% children is among all TB cases compared to other countries with similar incidence rates and living conditions *(e.g. Helen & Cohen, Background document: Estimating the incidence of childhood TB and MDR-TB)*. If a rate of 15% would be regarded more realistic all figures should be recalculated.
- Discuss and consider to set more ambitious goals to fight childhood TB in Nepal. Children with TB have always been fairly neglected in Nepal. The NSP should plan a clear change in this attitude and plan with less than 25% of missed TB cases among children.
- Re-consider how realistic a notification of more than 92% is among adults by 2020 (see estimates under 4.4 Figure A1.1) in view of the poor infrastructure in most laboratories, the rudimentary logistical inter-connection in the laboratory network and only three years remaining.
- Re-check and harmonize correspondence of calculations and diagnostic algorithm. Be more consistent in the use of the diagnostic algorithm or adjust it to the real plans of developing diagnostic work-flows.
- Re-calculate the percentage of FLD resistance data by 2018ff if resistance data are intended to be available for all FLD or rather use the terminology *RIF susceptibility data* of only RIF resistance shall be of interest.
- Re-check whether a rate of less than 25% pre-XDR-TB is realistically reflecting the rapidly increasing numbers of pre-XDR-TB in Nepal. This rate has great impact on estimations of culture diagnostics.
- Solve the apparent contradiction in the NSP to identify 95% of MDR-TB cases when only 87% of all TB cases are notified?
- Solved the apparent contradiction of the diagnostic algorithm instructing to test only suspects with changes in CxR and the actual calculation intending to test all clinical suspects. If all suspects shall be tested: Re-discuss whether this can realistically be achieved by 2020 given the actual poor logistical and infrastructural situation.
- Re-calculate the number of Xpert cartridges by including all patient groups in the sum not only the upper two lines "presumptive TB, passive case finding, smear negative" and "presumptive TB, radiologically suspected".
- Re-plan the number of GeneXpert modules to be procured over the next years in order to meet the numbers of tests stipulated by the NSP for 2020.

- Re-check the definitions of *"HIV positive people eligible for TB testing"* and *"HIV in care with presumptive TB".* In case they mean identical types of cases check why figures in the table differ from each other.
- Re-calculate the numbers of cultures required to follow-up MDR-TB patients. Consider that at least 12 follow-up cultures are required per MDR-TB and 18 per pre-XDR- and XDR-case.
- After having set up diagnostic algorithms for EP-TB, calculate the number of diagnostic cultures required for its diagnosis.

6.6. NSP priorities and roadmap development

- See extra document following soon

6.7. MGIT analyses

- Upgrade the emergency generator with an automated switch-on system.
- Re-validate the DST in MGIT by testing five resistant and five susceptible MTB isolates in direct comparison to LPA and proportional method.
- Finalize and officially endorse the drafted MGIT equipment- and DST-SOPs and forms.
- When comparative testing yields identical results, the SOPs are officially endorsed and staff is trained, implement MGIT DST in routine diagnostics.
- Make sure all required materials for MGIT testing are delivered short-term to the GENETUP laboratory. The laboratory is currently experience shortage of MGIT materials and cannot directly profit from the actual trainings by short-term implementation of MGIT testing due to stock-out of required reagents.
- Organize and budget practical trainings of MGIT culture and MGIT DST for at least one expert per NRL department (NTC & GENETUP) on-site in Kathmandu or abroad in a laboratory where the technology is well established.

6.8. General recommendations

- Much stronger support trainings and international exposure of both NRL staffs in future. Make sure that both departments equally profit from the trainings by sending specialists to the training and by sharing newly learned skills and techniques with both departments in pre-organized meetings.
- Strengthen collaboration and interaction between both departments of the NRL, GENETUP and the NTC laboratory. Organize bi-monthly common staff meetings (alternating at NTC and GENETUP). During those meetings, address the following issues:
    - Present new SOPs and standards of the common QMS.
    - Discuss actual challenges of laboratory diagnostics such as problems with logistics and transportation, procurement, LOTs of reagents, EQA, difficult diagnostic cases, implementation or interpretation of diagnostic algorithms etc.
    - Use the opportunity to present current research or international standards found in papers or own operational research.
    - General organizational issues.
- Provide much stronger support to GENETUP in order to allow the center to further provide the services to the NTP in laboratory diagnostics and TB patient management on the same quality and quantity level as over the past years. The support should cover financing of at least six staff units in the laboratory and a respective number staff units in the outpatient clinic which has to be defined upon consultation with the chief doctor of the project. GENETUP staff should be integrated in all training plans and invited to trainings offered at the NTC.

- Facilitate the procurement mechanism of GENETUP by allowing direct submission of order lists to the GFATM and thus preventing delays or stock-outs and reducing unnecessary work-load to NTC staff. GENETUP significantly contributes to the success of the national TB program by testing many specimens and isolates with culture, molecular tests and DST but is relatively often experiencing delays in delivery of required materials of even stock-outs due to the highly complicated procurement procedure with quite many departments involved. A lean procurement mechanism would allow a direct submission of order lists by the head of the GENETUP laboratory to the GFATM procurement department and thus significantly reduce the work-load of the NTC with the procurement of materials for GENETUP. According to GFATM representatives this would be technically possible as soon as the official agreement of the NTC director is given to the GFATM to follow this procedure.

ANNEX 1: NSP calculations – comments and recommendations

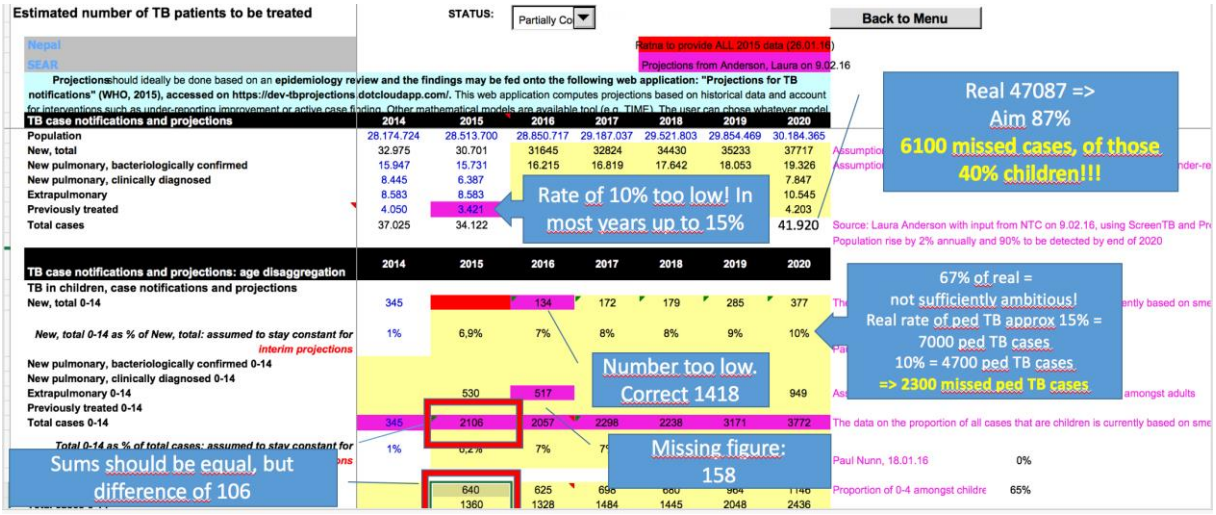


Figure A1.1: potential or confirmed inconsistencies and missing data points in the epidemiology section of the NSP calculations

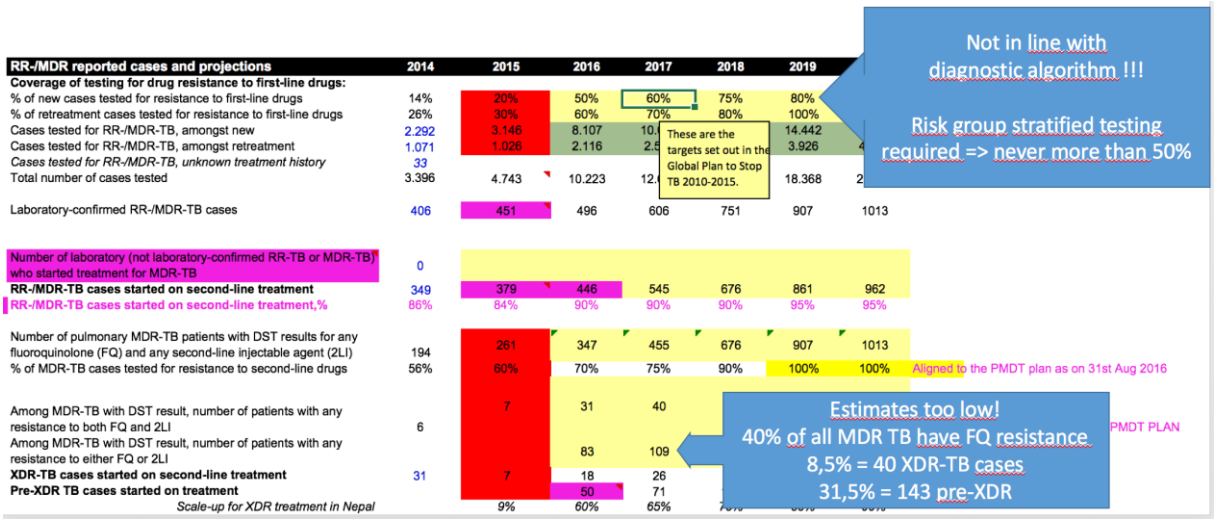
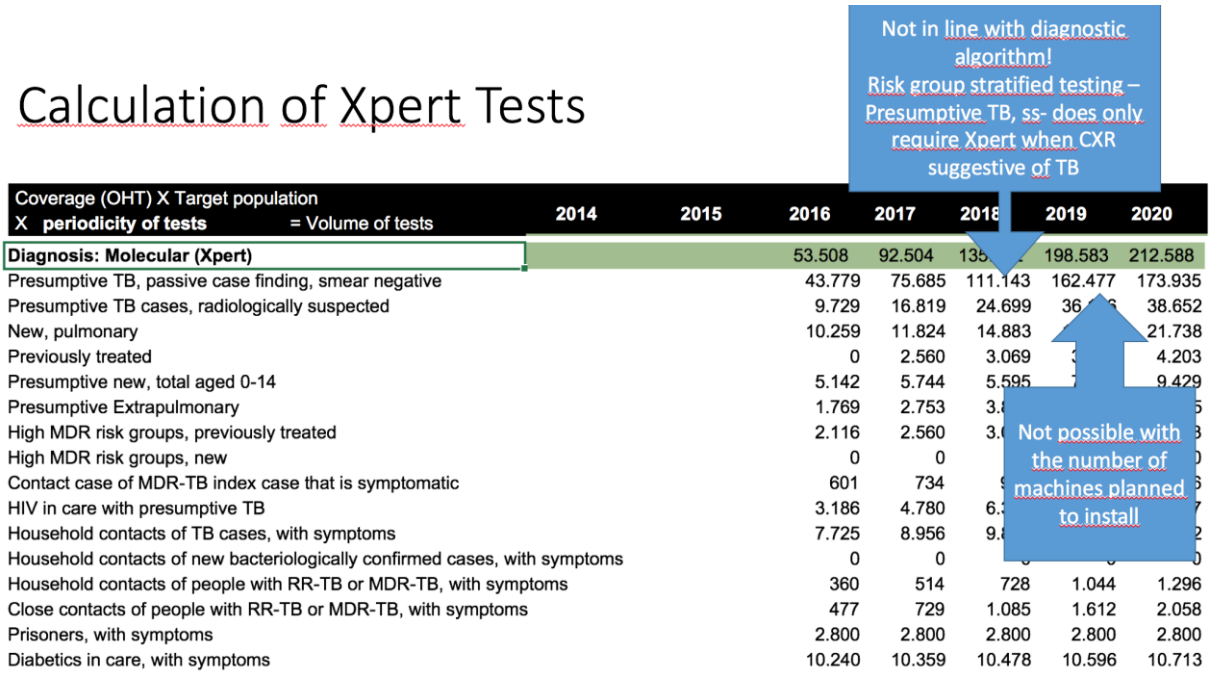
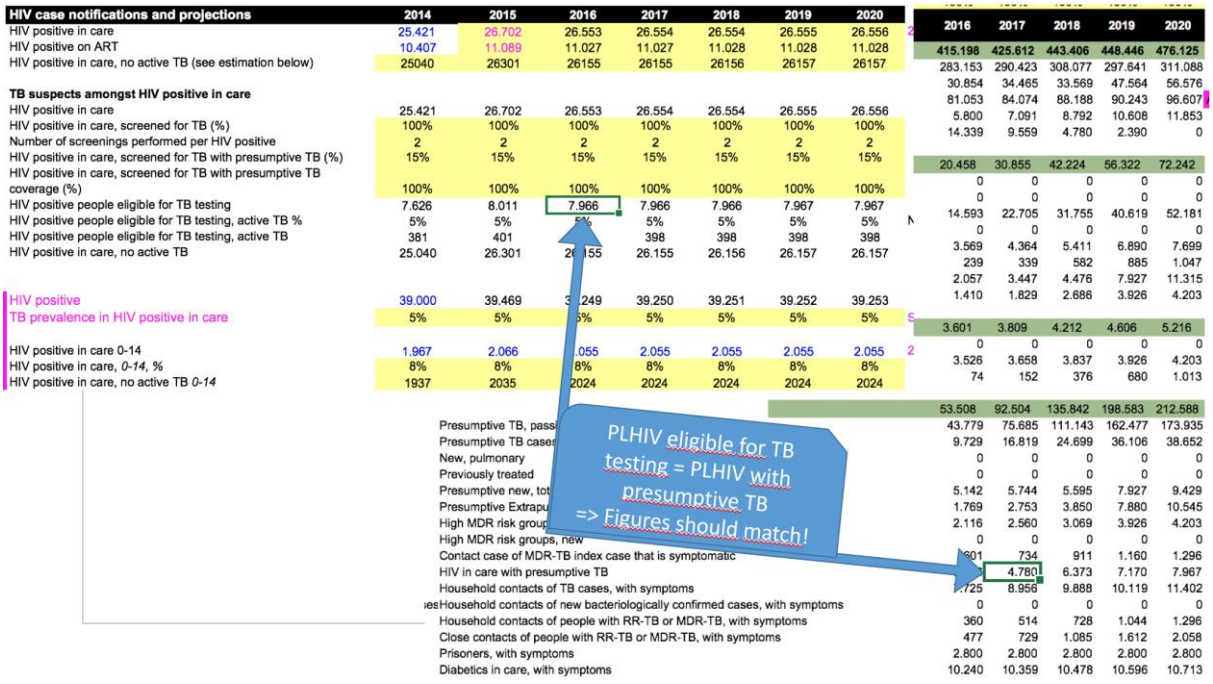


Figure A1.2: Potential or confirmed inconsistencies in the epidemiology section with regards to resistance testing and M/pre-X/XDR-TB



Coverage (OHT) X Target population X **periodicity of tests** = Volume of tests	2014	2015	2016	2017	2018	2019	2020
Diagnosis: Molecular (Xpert)			53.508	92.504	135	198.583	212.588
Presumptive TB, passive case finding, smear negative			43.779	75.685	111.143	162.477	173.935
Presumptive TB cases, radiologically suspected			9.729	16.819	24.699	36	38.652
New, pulmonary			10.259	11.824	14.883		21.738
Previously treated			0	2.560	3.069	3	4.203
Presumptive new, total aged 0-14			5.142	5.744	5.595	7	9.429
Presumptive Extrapulmonary			1.769	2.753	3.8		5
High MDR risk groups, previously treated			2.116	2.560	3.0		3
High MDR risk groups, new			0	0			0
Contact case of MDR-TB index case that is symptomatic			601	734	9		6
HIV in care with presumptive TB			3.186	4.780	6.3		7
Household contacts of TB cases, with symptoms			7.725	8.956	9.8		2
Household contacts of new bacteriologically confirmed cases, with symptoms			0	0			0
Household contacts of people with RR-TB or MDR-TB, with symptoms			360	514	728	1.044	1.296
Close contacts of people with RR-TB or MDR-TB, with symptoms			477	729	1.085	1.612	2.058
Prisoners, with symptoms			2.800	2.800	2.800	2.800	2.800
Diabetics in care, with symptoms			10.240	10.359	10.478	10.596	10.713

Figure A1.3: Potential or confirmed inconsistencies in the calculation of required Xpert Tests

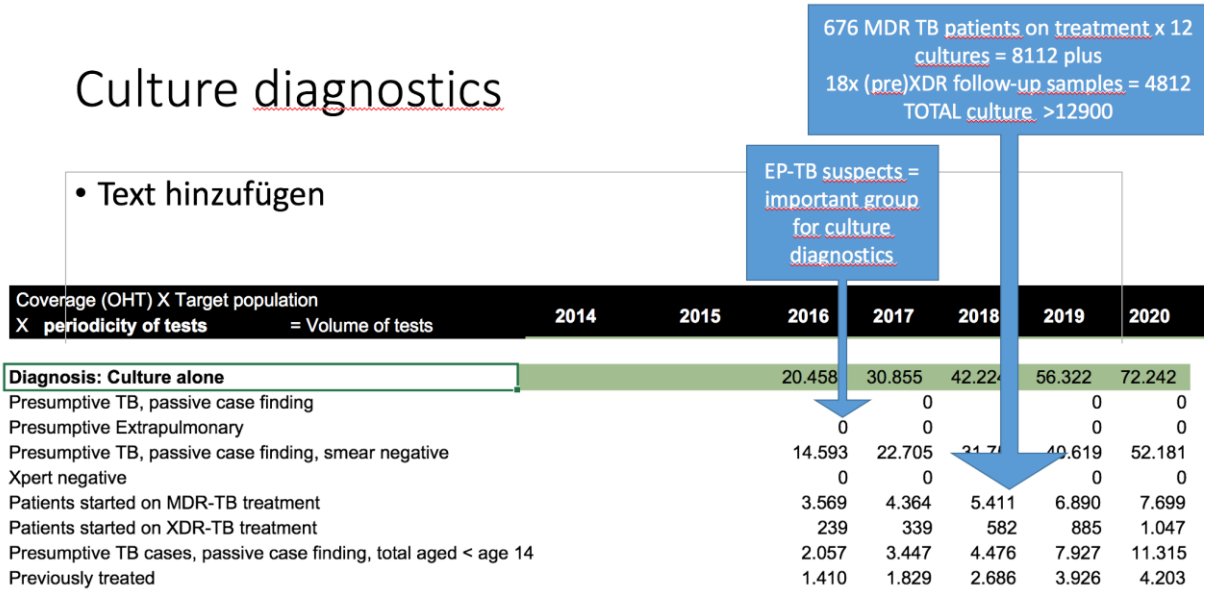


HIV case notifications and projections	2014	2015	2016	2017	2018	2019	2020
HIV positive in care	25.421	26.702	26.553	26.554	26.554	26.555	26.556
HIV positive on ART	10.407	11.089	11.027	11.027	11.028	11.028	11.028
HIV positive in care, no active TB (see estimation below)	25040	26301	26155	26155	26156	26157	26157
TB suspects amongst HIV positive in care							
HIV positive in care	25.421	26.702	26.553	26.554	26.554	26.555	26.556
HIV positive in care, screened for TB (%)	100%	100%	100%	100%	100%	100%	100%
Number of screenings performed per HIV positive	2	2	2	2	2	2	2
HIV positive in care, screened for TB with presumptive TB (%)	15%	15%	15%	15%	15%	15%	15%
HIV positive in care, screened for TB with presumptive TB coverage (%)	100%	100%	100%	100%	100%	100%	100%
HIV positive people eligible for TB testing	7.626	8.011	7.966	7.966	7.966	7.967	7.967
HIV positive people eligible for TB testing, active TB %	5%	5%	5%	5%	5%	5%	5%
HIV positive people eligible for TB testing, active TB	381	401	398	398	398	398	398
HIV positive in care, no active TB	25.040	26.301	26.155	26.155	26.156	26.157	26.157
HIV positive	39.000	39.469	39.249	39.250	39.251	39.252	39.253
TB prevalence in HIV positive in care	5%	5%	5%	5%	5%	5%	5%
HIV positive in care 0-14	1.967	2.066	2.055	2.055	2.055	2.055	2.055
HIV positive in care, *0-14*, %	8%	8%	8%	8%	8%	8%	8%
HIV positive in care, no active TB *0-14*	1937	2035	2024	2024	2024	2024	2024

2016	2017	2018	2019	2020
415.198	425.612	443.406	448.446	476.125
283.153	290.423	308.077	297.641	311.088
30.854	34.465	33.569	47.564	56.576
81.053	84.074	88.188	90.243	96.607
5.800	7.091	8.792	10.608	11.853
14.339	9.559	4.780	2.390	0
20.458	30.855	42.224	56.322	72.242
0	0	0	0	0
0	0	0	0	0
14.593	22.705	31.755	40.619	52.181
0	0	0	0	0
3.569	4.364	5.411	6.890	7.699
239	339	582	885	1.047
2.057	3.447	4.476	7.927	11.315
1.410	1.829	2.686	3.926	4.203
3.601	3.809	4.212	4.606	5.216
0	0	0	0	0
3.526	3.658	3.837	3.926	4.203
74	152	376	680	1.013

	2016	2017	2018	2019	2020
Presumptive TB, pass	53.508	92.504	135.842	198.583	212.588
Presumptive TB cases	43.779	75.685	111.143	162.477	173.935
New, pulmonary	9.729	16.819	24.699	36.106	38.652
Previously treated	0	0	0	0	0
Presumptive new, tot	0	0	0	0	0
Presumptive Extrapu	5.142	5.744	5.595	7.927	9.429
High MDR risk group	1.769	2.753	3.850	7.880	10.545
High MDR risk groups, new	2.116	2.560	3.069	3.926	4.203
Contact case of MDR-TB index case that is symptomatic	0	0	0	0	0
HIV in care with presumptive TB	601	734	911	1.160	1.296
Household contacts of TB cases, with symptoms	4.780	6.373	7.170	7.967	
Household contacts of new bacteriologically confirmed cases, with symptoms	725	8.956	9.888	10.119	11.402
Household contacts of people with RR-TB or MDR-TB, with symptoms	0	0	0	0	0
Close contacts of people with RR-TB or MDR-TB, with symptoms	360	514	728	1.044	1.296
Prisoners, with symptoms	477	729	1.085	1.612	2.058
Diabetics in care, with symptoms	2.800	2.800	2.800	2.800	2.800
	10.240	10.359	10.478	10.596	10.713

Figure A1.4: Potential or confirmed inconsistencies in the calculations of PLWHIV



Coverage (OHT) X Target population X **periodicity of tests** = Volume of tests	2014	2015	2016	2017	2018	2019	2020
Diagnosis: Culture alone			20.458	30.855	42.224	56.322	72.242
Presumptive TB, passive case finding			0	0		0	0
Presumptive Extrapulmonary			0	0		0	0
Presumptive TB, passive case finding, smear negative			14.593	22.705	31.74	40.619	52.181
Xpert negative			0	0		0	0
Patients started on MDR-TB treatment			3.569	4.364	5.411	6.890	7.699
Patients started on XDR-TB treatment			239	339	582	885	1.047
Presumptive TB cases, passive case finding, total aged < age 14			2.057	3.447	4.476	7.927	11.315
Previously treated			1.410	1.829	2.686	3.926	4.203

Figure A1.5: Potential or confirmed inconsistencies in the calculations of numbers of cultures required

ANNEX 2: Actual lists of QM documents at GENETUP (**green marks** = in work; **blue marks** = still to write; **red marks** = still to approve)

List of method SOPs

List SOP-M (Method)		in work since (Date)	Approved Released (Effective date)	in Revision (Date)	Archive (Date)
NEP-GEN-SOP-M-001.V01	Auramin staining		26.03.17		
NEP-GEN-SOP-M-002.V01	Preparation of LJ Media		26.03.17		
NEP-GEN-SOP-M-003.V01	**First and second line drugs susceptibility testing**	Bijendra/Hoffman			
NEP-GEN-SOP-M-004.V01	NaOH-NALC Decontamination Method		28.03.17		
NEP-GEN-SOP-M-005.V01	**MGIT**	Bhagwan			
NEP-GEN-SOP-M-006.V01	Ziehl Neelson Staining		30.03.17		
NEP-GEN-SOP-M-007.V01	**Speciment processing for culture**	Bhagwan			
NEP-GEN-SOP-M-008.V01	Maintenance of mycobacterial strains		28.03.17		
NEP-GEN-SOP-M-009.V01	REMA_Antibiotics working solutions	Bijendra			
NEP-GEN-SOP-M-010.V01	REMA_ Inoculum Preparation	Bijendra			
NEP-GEN-SOP-M-011.V01	REMA_Plate preparation-FLD	Bijendra			
NEP-GEN-SOP-M-012.V01	REMA_Plate preparation-SLD	Bijendra			
NEP-GEN-SOP-M-013.V01	REMA_Resazurin addition	Bijendra			
NEP-GEN-SOP-M-014.V01	REMA_Results	Bijendra			
NEP-GEN-SOP-M-015.V01	REMA_ Antibiotic stock	Bijendra			
NEP-GEN-SOP-M-016.V01	REMA_media & solutions	Bijendra			
NEP-GEN-SOP-M-017.V01	REMA_Resazurin addition	Bijendra			
NEP-GEN-SOP-M-018.V01	GeneXpert		02.05.17		
NEP-GEN-SOP-M-019.V01	empty				
NEP-GEN-SOP-M-020.V01	empty				
NEP-GEN-SOP-M-021.V01	Reading and interpretation of L-J culture Results		16.05.17		
NEP-GEN-SOP-M-022.V01	Line Probe Assay-DNA extraction		16.05.17		
NEP-GEN-SOP-M-023.V01	Line Probe Assay MTBDRplus DNA Amplification		16.05.17		
NEP-GEN-SOP-M-024.V01	Line Probe Assay MTBDRplus Hybridization		16.05.17		
NEP-GEN-SOP-M-025.V01	Reading and Interpretation MTBDRplus Result		16.05.17		
NEP-GEN-SOP-M-026.V01	Line Probe Assay MTBSRsl DNA Amplification		16.05.17		
NEP-GEN-SOP-M-027.V01	Line Probe Assay MTBDRsl Hybridization		16.05.17		
NEP-GEN-SOP-M-028.V01	Reading and Interpretation MTBDRsl Result		17.05.17		
NEP-GEN-SOP-M-029.V01	Internal Quality control of specimens decontamination by determination of contamination rates				
NEP-GEN-SOP-M-030.V01	Internal Quality control of MGIT and LJ culture Diagnostics				
NEP-GEN-SOP-M-031.V01	Handling and further analysis of positive MGIT cultures				
NEP-GEN-SOP-M-032.V01	Biochemical differentiation of mycobacteria and identification of MTBC	Bhagwan sir			
NEP-GEN-SOP-M-033.V01	Drug susceptibility testing in MGIT				
NEP-GEN-SOP-M-034.V01	Internal Quality control of Drug Susceptibility results by coorelation with				

List of equipment SOPs

List SOP-E (Equipment)	Name	in work since (Date)	Approved Released (Effective date)	in Revision (Date)	Archive (Date)
NEP-GEN-SOP-E-001.V01	Use and Maintenance of BSC class II		26.03.17		
NEP-GEN-SOP-E-002.V01	**Bactec**	Bhagwan			
NEP-GEN-SOP-E-003.V01	**Autoclave**	Bhagwan			
NEP-GEN-SOP-E-004.V01	Maintenance of Genexpert		02.05.17		
NEP-GEN-SOP-E-005.V01	hot air sterilizer		15.06.17		
NEP-GEN-SOP-E-006.V01	internal control of autoclave and hot air sterlizer				
NEP-GEN-SOP-E-007.V01	microscopes		15.06.17		
NEP-GEN-SOP-E-008.V01	inspissator				
NEP-GEN-SOP-E-009.V01	precision balance				
NEP-GEN-SOP-E-010.V01	nephelometer / Mac Farland measure				

List of general SOPs and QM documents

List SOP-G (general)	Name	in work since (Date)	Approved and Released (Effective date)	in Revision (Date)	Archive (Date)
NEP-GEN-SOP-G-001.V01	Waste Management		27.03.17		
NEP-GEN-SOP-G-002.V01	Safety rule for laboratory workers		29.03.17		
NEP-GEN-SOP-G-003.V01	Document controll		27.03.17		
NEP-GEN-SOP-G-004.V01	Use of desinectand		29.03.17		
NEP-GEN-SOP-G-005.V01	Personal Education and Training		29.03.17		
NEP-GEN-SOP-G-006.V01	Laboratory meetings and breifings				
NEP-GEN-SOP-G-007.V01	validation and verification of laboratory tests and methods				
NEP-GEN-SOP-G-008.V01	Reporting of Monthly report and Quarterly Reports				
NEP-GEN-SOP-G-009.V01	handling and management of dangerous chemical and reagents				
NEP-GEN-SOP-G-010.V01	management of biohazards				
NEP-GEN-SOP-G-011.V01	sterilization of solid and liquid wastes				
NEP-GEN-SOP-G-012.V01	sterilization of buffers and liquid media				
NEP-GEN-SOP-G-013.V01	sterilization of solid materials				
NEP-GEN-SOP-G-014.V01	good laboratory practice and general behaviour in laboratory rooms				
NEP-GEN-SOP-G-015.V01	Preparation and workflow of registration workplace	Bijendra			
NEP-GEN-SOP-G-016.V01	Preparation and workflow of decontamination/ inoculation workplace	Bijendra			
NEP-GEN-SOP-G-017.V01	Preparation and workflow of smear microscopy workplace	Bijendra			
NEP-GEN-SOP-G-018.V01	preparation and workflow of culture reading workplace	Bijendra			
NEP-GEN-SOP-G-019.V01	Preparation and workflow of drug susceptibility testing workplace	Bijendra			
NEP-GEN-SOP-G-020.V01	Preparation and workflow of Molecular diagnostic workplace	Bijendra			
NEP-GEN-SOP-G-021.V01	Preparation and workflow of recording and reporting workplace				
NEP-GEN-SOP-G-022.V01	Preparation and workflow of media preparation				
NEP-GEN-SOP-G-023.V01	Preparation and workflow of cleaning room				

List of forms and short SOPs

List SOP-F (Forms)	Name	in work since (Date)	Released an approved (Effective date)	in Revision (Date)	Archive (Date)
NEP-GEN-SOP-F-001.V01	Emergency in TB-Laboratory		11.03.17		
NEP-GEN-SOP-F-002.V01	Temperature control deep freeze (-80oC)		11.03.17		
NEP-GEN-SOP-F-003.V01	Temperature control Refigerator (2-8°)		11.03.17		
NEP-GEN-SOP-F-004.V01	Temperature control deep freeze (-35oC)		11.03.17		
NEP-GEN-SOP-F-005.V01	Temperature control Incubator		13.03.17		
NEP-GEN-SOP-F-006.V01	Short Guide for DNA Isolation		14.03.17		
NEP-GEN-SOP-F-007.V01	Results Assessment for Auramine Staining Microscopy		13.03.17		
NEP-GEN-SOP-F-008.V01	Handling in Reception		16.03.17		
NEP-GEN-SOP-F-009.V01	Short Guide for Auramine Fluorescent Staining		14.03.17		
NEP-GEN-SOP-F-010.V01	Organogram		14.03.17		
NEP-GEN-SOP-F-011.V02	Short guide for Genexpert Assay Preparation		29.03.17		
NEP-GEN-SOP-F-012.V01	Training courses		13.03.17		
NEP-GEN-SOP-F-013.V01	General equipment maintenance		13.03.17		
NEP-GEN-SOP-F-014.V01	Algorithm of laboratory test at GENETUP NRL	approve by Dr. Hoffman			
NEP-GEN-SOP-F-015.V01	GenoType® Mycobacterium CM, MTBC, MTBDR, and MTBDRsl Kits:pre-amplification and amplification steps		14.03.17		
NEP-GEN-SOP-F-016.V01	Short Guide for DNA Hybridization Step using GenoType®		14.03.17		
NEP-GEN-SOP-F-017.V01	Urine Decontamination		14.03.17		
NEP-GEN-SOP-F-018.V01	Cerebrospinal Fluid (CSF) Decontamination				
NEP-GEN-SOP-F-019.V01	Screening test for Pulmonary Tuberculosis of lab Staffs		04.11.17		
NEP-GEN-SOP-F-020.V01	Decontamination of Biopsy tissue samples		14.03.17		
NEP-GEN-SOP-F-021.V01	Preparation of Working Solutions for the NaOH-NALC Decontamination Procedure		14.03.17		
NEP-GEN-SOP-F-022.V01	Quality Control of Prepared Auramine Reagent		14.03.17		
NEP-GEN-SOP-F-023.V01	Preservation and Maintenance of mycobacterial strains		30.03.17		
NEP-GEN-SOP-F-024.V01	Logbook of the BSC air flow checking		14.03.17		
NEP-GEN-SOP-F-025.V01	Short Guide Nitrat Reduction test		14.03.17		
NEP-GEN-SOP-F-026.V01	Laboratory Cleaning		14.03.17		
NEP-GEN-SOP-F-027.V01	Documentation Laboratory cleaning - daily work sheet **excel**		15.03.17		
NEP-GEN-SOP-F-028.V01	DRplus report form		14.03.17		
NEP-GEN-SOP-F-029.V01	Gene Xpert Log Book		14.03.17		
NEP-GEN-SOP-F-030.V01	genexpert maintenance log sheet **excel**		14.03.17		
NEP-GEN-SOP-F-031.V01	Short guide How to operate Gene Xpert Test		14.03.17		
NEP-GEN-SOP-F-032.V01	Reading and interpretation of Drug Susceptibility Testing results		14.03.17		
NEP-GEN-SOP-F-033.V01	Lab suplies for NATA **excel**		14.03.17		
NEP-GEN-SOP-F-034.V01	DOTS PLUS LABORATORY LOG BOOK		14.03.17		
NEP-GEN-SOP-F-035.V01	Ziehl Neelson Staining Short Guide		27.03.17		
NEP-GEN-SOP-F-036.V01	AUTOCLAVE WORKSHEET(PANASONIC)		14.03.17		
NEP-GEN-SOP-F-037.V01	LPA Log Sheet		14.03.17		
NEP-GEN-SOP-F-038.V01	Maintenance log sheet		14.03.17		
NEP-GEN-SOP-F-039.V01	Reagent Autoclave check List		14.03.17		
NEP-GEN-SOP-F-040.V01	Reagent Log sheet		14.03.17		
NEP-GEN-SOP-F-041.V01	MTBDRsl report form		14.03.17		
NEP-GEN-SOP-F-042.V01	PNP media		14.03.17		
NEP-GEN-SOP-F-043.V01	Preparation of Macfarland standard		12.03.17		
NEP-GEN-SOP-F-044.V01	Preparation of Phosphate Buffer		13.03.17		
NEP-GEN-SOP-F-045.V01	empty				
NEP-GEN-SOP-F-046.V01	xpert report from		12.03.17		
NEP-GEN-SOP-F-047.V01	preparation of L-J media Short guide		15.03.17		
NEP-GEN-SOP-F-048.V01	preparation ot first line drug solutions Short guide		15.03.17		
NEP-GEN-SOP-F-049.V01	preparation of second line drug solutions Short guide		15.03.17		
NEP-GEN-SOP-F-050.V01	Short guide BSC		16.03.17		
NEP-GEN-SOP-F-051.V01	Logbook of the BSC air flow checking		16.03.17		
NEP-GEN-SOP-F-052.V01	Media Preparation Date documentation		17.03.17		
NEP-GEN-SOP-F-053.V01	Quality Control of Prepared Reagent Ziehl Neelson		17.03.17		
NEP-GEN-SOP-F-054.V01	Ziehl Neelson Stain Preparation Short guide		17.03.17		
NEP-GEN-SOP-F-055.V01	Preparation of control slides for smear microscopy		27.03.17		
NEP-GEN-SOP-F-056.V01	Sample collection Clinic Storage and Transport of specimen		27.03.17		
NEP-GEN-SOP-F-057.V01	Internal quality control of L-J media		27.03.17		
NEP-GEN-SOP-F-058.V01	Quality Control Monitoring of MGIT Culture		28.03.17		
NEP-GEN-SOP-F-059.V01	Quality Control of MGIT Culture		28.03.17		
NEP-GEN-SOP-F-060.V01	Cleaning and disnfection Centrifuge		30.03.17		
NEP-GEN-SOP-F-061.V01	Maintenance of Genexpert Instrument		29.03.17		
NEP-GEN-SOP-F-062.V01	Auramine Stain preparation Short guide		30.03.17		
NEP-GEN-SOP-F-063.V01	Request and reporting form for TB culture and Drug Susceptibility Test (DST)		02.04.17		
NEP-GEN-SOP-F-064.V01	Request and reporting form for TB culture and Second Line Drug Susceptibility		02.04.17		
NEP-GEN-SOP-F-065.V01	Quality control of first-line drug media with the reference strain *M. tuberculosis* H37Rv		02.04.17		
NEP-GEN-SOP-F-066.V01	Quality control of second line drug-containing media using the reference strainM. tuberculosis H37Rv		02.04.17		
NEP-GEN-SOP-F-067.V01	Handling of drugs powder		02.04.17		
NEP-GEN-SOP-F-068.V01	Checklist for monitorig and supervision Programm		03.04.17		
NEP-GEN-SOP-F-069.V01	Egg Logbook		04.04.17		
NEP-GEN-SOP-F-070.V01	IQC INH medium				
NEP-GEN-SOP-F-071.V01	IQC EMB medium	Bijendra/Hoffmann			
NEP-GEN-SOP-F-072.V01	IQC RIF medium	Bijendra/Hoffmann			
NEP-GEN-SOP-F-073.V01	IQC SM medium	Bijendra/Hoffmann			
NEP-GEN-SOP-F-074.V01	IQC LFX medium	Bijendra/Hoffmann			
NEP-GEN-SOP-F-075.V01	IQC KM medium	Bijendra/Hoffmann			
NEP-GEN-SOP-F-076.V01	IQC CM medium	Bijendra/Hoffmann			
NEP-GEN-SOP-F-077.V01	empty				
NEP-GEN-SOP-F-078.V01	Gentup culture log book		16.05.17		
NEP-GEN-SOP-F-079.V01	DOTS PLUS LABORATORY CULTURE LOG BOOK		16.05.17		
NEP-GEN-SOP-F-080.V01	Short Guide for DNA extraction for Line Probe Assay		16.05.17		
NEP-GEN-SOP-F-081.V01	Microbiology Lab Negative Pressure Monitoring		29.05.17		
NEP-GEN-SOP-F-082.V01	Microscope Maintenance log sheet		15.06.17		
NEP-GEN-SOP-F-083.V01	Maintenance of MGIT		15.06.17		
NEP-GEN-SOP-F-084.V01	Hot air Sterilization log sheet		15.06.17		
NEP-GEN-SOP-F-085.V01	Lot control Sheets		15.06.17		

ANNEX 3: Experts on Mission

Expert	Title	Function	Mission period
Katja Haslauer	Medical Laboratory Technician	QMS audit, implementation, technical assistance	Fr June 3rd, 2016 – Fr June 17th, 2016
Dr. Harald Hoffmann, MD, PhD	Microbiologist	Director of WHO SRL Munich Gauting & President of KTW	Su June 12th, 2016 - Fr June 17th, 2016

ANNEX 4: Mission Itinerary and Agenda

DAY	TIME	LOCATION	INT. EXP.	NEP. EXP.	TOPIC
Sat 10th	14:00	departure	K & H		Qatar airways flights 58 & 652
Sun 11th	10:45	arrival	K & H		
	13:00	Dalai La Hotel, Thamel	K & H		Check-in & refreshement
	15:30	GENETUP	K & H		Actual developments and achievements at GENETUP
Mon 12th	9:00	**WHO**	K & H	Ashish Shresta,	Briefing of WHO partners Priorities of mission
	10:00	**NTC**	K & H	G. Ghimire	Meeting with Gokarna Ghimire Briefing agreement of schedule of the week, Planning topics for each day,
	11:00	NTC	H	NTP Director Dr. Sarat C. Verma	Meeting with NTP manager. Presentation of plans for the week. Brain-storming on priorities of NSP implementation.
			K	NTC Lab team	LPA: trouble shooting of high contamination rates
	13:00	NTC	K & H	NTC Lab team	Visit of laboratory. Identification of potential causes of LPA contamination. Review of infrastructure
	14:00	NTC	K	NTC Lab team	Practical training of lab team in LPA
			H	G. Ghimire	Planning improvement of infrastructure of NTC lab in order to prevent further LPA contamination
	16:00	NTC	K & H	G. Ghimire	Summary oft he day Planning of next day
	17:00		K & H		Team debriefing
Tue 13th	9:00	NTC	H	G. Ghimire and NTC lab team	Priorities of NSP implementation. *Expected result:* Drafted list of Priorities
		GENETUP	K	Bijendra. Roy. Bhagwan Mah.	QM audit. Progress since recent intensive TA in QM implementation by E.v.R.
	13:00	NTC	H	G. Ghimire NTC lab team	Priorities of NSP implementation
		GENETUP	K	Bijendra. Roy. Bhagwan Mah.	TA with QM Identified gaps, list of priorities, plan of further QM development
	16:00				Summary oft he day in NTC and GENETUP Planning of next day
	17:00		K & H		Team debriefing

DAY	TIME	LOCATION	SRL	NEP. EXP.	TOPIC
Wed 14th	9:00	NTC	H	NTP controling	Review oft he NSP calculations and plans
		GENETUP	K	Bijendra. Roy. Bhagwan Mah.	Finalization and endorsement of drafted QM documents
	13:00	NTC	H	NTP controling	Review oft he NSP calculations and plans
		GENETUP	K	Bijendra. Roy. Bhagwan Mah.	Finalization and endorsement of drafted QM documents
	16:00				Summary oft he day Planning of next day
	17:00		K & H		Team debriefing
Thu 15th	9:00	GENETUP	K	Lab teams of NTC & Genetup	Common training for NTC & GENETUP specialists in infection control, disinfection, sterilization, bio-hazard management
	12:00	GENETUP			Lunch
	13:00	Save the Children / GFATM	H	Sarala Malla G. Ghimire	Plans and challenges of the GFATM plan Potential synergies and collaboration with • NSP implementation, • NTC laborartory refirbishment, • New GENETUP premises / BSL-3 lab, • Staff trainings, • General lab issues.
		GENETUP	K	Bijendra. Roy. Bhagwan Mah.	Internal quality controls
	16:00				Summary oft he day Planning of next day
	17:00		K & H		Team debriefing
Fr 16th	9:00	GENETUP	K & H	Bijendra. Roy. Bhagwan Mah.	Yearly internal staff trainings: plan & forecast
	11:00	GENETUP	K	Bhagwan Mah. & Dheena	MGIT DST
	13:00	GENETUP	H	Bhagwan Mah. Babhana Shr. NATA	Review of plans of potential new BLS-3 laboratory premises for GENETUP
	16:00				Summary oft he day Planning of next day
	17:00		K & H		Team debriefing
Sat 17th	9:00 – 16:00	Hotel	H		Sick leave
			K		Day off

DAY	TIME	LOCATION	SRL	NEP. EXP.	TOPIC
Sun 18th	9:00	NTC	H	Ashish Shresta, G. Ghimire, NTC controlling	Discussion of findings
		GENETUP	K	Bhagwan, Bijendra, GENETUP lab team	MGIT training
	11:00	NTC	H	NTC Director, WHO TB CO, NTC manage-ment, NTC Controller, Dr. B. Shresta, both NRL lab teams	Debriefing, presentation of all findings, challenges and recommendations, Presentation of major findings within calculations for NSP. Priorities & roadmap of NSP implementaiton
		GENETUP	K		Debriefing, major findings & recommendations of GENETUP team
	17:00	Departure	K		Quatar airlines
Mon 17th	9:00	NATA	H	Bhagwan Mah. Babhana Shr. NATA president	General issues of construction plan
	11:00	NATA	H	NATA management and architect	Discussion of construction plans. Adjustment of planst o current national guidelines and standards. Budget estimation
	14:00	NATA	H	Mr Pradhan	Legal and contract issues of infrastructure project
	15:00	NATA	H	NATA management	Debriefing of findings and recommendations for GENETUP. Planning and priorities of further collaboration
	17:00	WHO CO	H	Dr. Vandelaer, Dr. A. Shresta	Debriefing at WHO CO
	18:30	Departure	H		Quatar airlines

K = Katja Haslauer

H = Harald Hoffmann