**DRAFT**

Updated Research Agenda on the Programmatic Management of Drug-Resistant TB

Authors: Members of Former research subgroup, MDR Working Group of Stop-TB Partnership, GDI Research Task Force, RESIST-TB, others

**Abstract**

**Introduction**

**Methods**

*Development of research questions*

The research agenda was prepared by members of the former Research Subgroup of the MDR-TB Working Group of the Stop-TB Partnership, RESIST-TB (Research Excellence to Stop TB Resistance), and the Global Drug-Resistant TB Initiative. The group first reviewed the 2008 research agenda on PMDT to determine whether the priorities published there had been resolved, partially resolved or unresolved [[1](#_ENREF_1)]. In addition, other relevant resources including publications, guidelines, documents, and websites published before August 2013 (See Table 1) were identified by literature search and suggestion, and reviewed to identify knowledge gaps. Group members split into five teams based on the focused research areas in the 2008 research agenda on PMDT [[1](#_ENREF_1)]. The knowledge gaps were then translated into research questions. A survey the relative priority of the research questions was distributed by email to PMDT research stakeholders.

*Format of survey*

The survey was split into two sections: 1) Main category selection and ranking and 2) Subcategory ranking. Participants were instructed in the first section to select 5 priority research questions among those in each main category (range ? to ? questions) and then to rank the 5 selected research questions from 1-5, with 1 being the greatest priority. Participants were asked to do this in each of the focused research areas identified in the 2008 research agenda on PMDT, referred to here as “Main categories” [[1](#_ENREF_1)]. In the second segment, participants were instructed to select and rank 5 knowledge gaps, referred to here as “Subcategories.”

*Analysis of survey*

For each main category, we determined N as the subset of the 133 participants who selected at least one research question, and then found the proportion who selected each individual question. Selected, unranked questions were re-coded at the intermediate value of 2.5, and any questions that were unselected by a participant were imputed to 6, to reflect their priority as lower than the lowest possible ranking for a selected research question. We then determined the mean rank for each research question, on a scale of 1 as the highest priority to 6 as the lowest priority. (See Figures 2 – 6). As a sensitivity analysis, we coded unselected questions to missing and weighted the mean by response rate [specify formula].

For the Subcategory ranking section, we included responses from individuals who completed this section close to correct, ranking 4, 5, or 6 ranked subcategories. Because some individuals ranked far more than the instructed 5 subcategories, their answers could not be included in this analysis. The Subcategory ranking presents categories that correspond to the earlier individual research questions and thus present an opportunity to assess internal consistency. Additionally, they provide participants the chance to prioritize not only within a Main category but *across* Main categories.

Again, participants had the option to rank 1 as the highest priority and 5 as the lowest priority, or to mark questions as unranked. Unranked subcategories were re-coded at the intermediate value of 2.5, and any subcategories that were unselected by a participant were re-coded as 6, to reflect their priority as lower than the lowest possible ranking for a selected subcategory. We determined the mean ranking value for each subcategory, on a scale of 1 as the highest priority to 6 as the lowest priority. (See Figure 7).

**Results**

Surveys were distributed through email to contact lists of relevant organizations including RESIST-TB, Treatment Action Group, TB CARE I, TB TEAM, and the Stop TB Partnership’s New Diagnostics Working Group and MDR-TB Working Group. Of over 500 recipients of the survey, 133 completed at least one question. The number of participants declined progressively for each category so Ns are presented for each (Figure 1). A full list of research questions that correspond to the figures below is located in Annex 1.

In the Laboratory Support Main category, nearly 70% of 132 participants selected the questions “Do results of new diagnostic tests improve patient-relevant outcomes OR treatment outcomes?” and “How can we reliably identify forms of tuberculosis that are not easily diagnosed by examination of sputum sample (e.g., meningitis, pediatric TB, TB in HIV-coinfected persons)?” as priorities (see Figure 2a). Among those ranked, these two were also the top ranked with scores of 3.32 and 3.66 respectively (Figure 2b). These were selected to the exclusion of questions that focused more on refining drug-susceptibility testing (DST), markers of fitness, and evaluating treatment response.

In the Treatment Main category, more than 80% of 126 participants identified “How do we efficiently develop more effective, shorter and safer M/XDR-TB treatment regimens that may be used for special populations (e.g., pregnant/lactating women, children, HIV-coinfected individuals)?” and “What are the optimal combinations and duration of treatment to prevent the emergence of anti-TB drug resistance?” as priority questions (Figure 3a). These were ranked as the top two questions (scores: 2.72, 2.80) in the treatment-strategy category (Figure 3b), while, “Is the 9 month "Bangladesh" MDR-TB treatment regimen effective in countries with high prevalence of resistance to second-line drugs (SLDs)? What modifications would be necessary?” was selected by 80% and was virtually indistinguishable from these two at 2.84. Least popular in this category were questions related to optimization and further individualization of treatment with 2nd-line drugs (with or without ART) and toxicity.

In the Programmatically Relevant Research Main category, the only clear “winner” was “What are options for short-course treatment and how can it be used to expand MDR-TB treatment?” selected by nearly 60% of 119 participants (Figure 4a). Selected by 40-60% were the questions: “Which groups of patients with increased proportion of MDR-TB should be targeted for DST in the context of limited resources and which diagnostic algorithms should be used to identify patients within risk groups?”, “What are barriers to treatment initiation and completion?” and “What infection control measures exist with proven evidence to reduce transmission?”. These were all ranked in the top 5 by those who ranked at least one question as was, “Operationally, what are the best methods to ensure optimal treatment, including guidelines; reliable drug supply; staff appropriately trained; adequate health facilities?” (Figure 4b). These topics were preferred over those that would inform integration of new technologies, equity, and donor engagement.

The Epidemiology Main category had 115 participants of whom 70% selected the question “What interventions (e.g., household contact tracing; early, routine DST for all TB cases) are effective at reducing nosocomial infection? What is the impact of these interventions?” More than 40% also selected “In countries without current, representative data on the burden of drug-resistant TB, what is the burden? (How) can non-representative data be used to improve estimates of DR-TB?” and “What ecologic or population-level characteristics predict resistance incidence, acquisition and/or amplification, transmission, outcomes: regimens; population burden of other diseases (e.g., HIV); degree of public-private mix in TB control; geography or socio-economic status?” (Figure 5a) These were all ranked in the top 5 (Figure 5b). The topics with the fewest selections & lowest rankings included the role of strain and resistance patterns as predictors of epidemiologic indicators.

Lastly among 113 participants to the Management of Contacts Main category, more than 80% selected, “What are optimal drugs, combinations, and durations for LTBI in known contacts of MDR-TB patients?” as a priority (Figure 6a). Additionally, more than 60% identified, “What biomarkers can be used to distinguish infection from disease?” and “Are there biomarkers markers that can identify who, among infected contacts, is most likely to develop active disease?” and “What are the best methods for preventing household transmission?“. In addition to these four, “How can vaccines be developed to prevent infection?” was ranked among the top five in this category (Figure 6b, scores 3.17-4.01). In contrast, topics on post-exposure vaccines, averting nosocomial transmission, and individualization of prophylactic treatment were lower priorities.

In the final part of the survey, which asked participants to select across Subcategories of the Main categories (Lab Support, Treatment Strategy, Programmatically Relevant Research, Epidemiology and Management of Contacts), the top choice was short regimens (3.29), including in heavily exposed populations (5.15); prevention and identification of secondary cases (through treatment, prophylaxis, vaccines and casefinding, improved diagnostics for difficult-to-diagnose populations); as well as implementation research (Figure 7).

**Internal validity and robustness**

The overlap between questions selected in the Subcategories and the priority ranking across Subcategories was substantial, suggesting strong internal consistency in the survey responses. Rare exceptions include that “vaccines as a strategy for management of contacts“ was selected as the 3rd-ranked Subcategory overall while the related questions were 4th and 6th within the Management of Contacts Main category. Similarly, access to MDR-TB diagnosis and treatment was selected as 4th in the Programmatically Relevant Research Main category while participants scored it 4th overall. Other top-ranked Subcategories comprised questions that were in the top 3 within the Subcategory rankings.

In addition to the imputation of unselected questions, weighting by response rate was also used to account for non-response. The results from the weighting were very similar to the imputation and are not presented.

**Discussion**

This third research agenda informing the programmatic management of drug-resistant TB is the result of a lengthy, multistep, systematic, and consultative approach to identify current research priorities. It builds on the pioneering efforts that led to publications in 2001 and 2008 [[1](#_ENREF_1),[2](#_ENREF_2)]. For the present effort, we added an extensive literature review and survey to the previous strategy of identifying and grouping priorities by the then Research Subgroup of the MDR-TB Working Group of the Stop-TB Partnership. Notwithstanding the limitations detailed below, the priorities presented here are the result of an exhaustive and inclusive process.

Certain priorities emerged consistently across categories while others were inconsistently favored. Shortened regimens, effective in a range of patient populations, were clearly perceived as a high priority within the treatment-strategy and programmatically relevant research categories as well as across categories. This topic was also highlighted in the 2008 document among components of treatment to be optimized. Reinforced interest may reflect the opportunities presented by the recent conditional approval of two new anti-TB drugs [[3](#_ENREF_3),[4](#_ENREF_4)] and significant recent activity in the development of shortened regimens for DR-TB, including the trial and observational studies beginning with the so-called Bangladesh regimen. [[5-7](#_ENREF_5)] Moreover, the TB Alliance is exploring indications for DR-TB for as many as 3 regimens (NC-005, Stand (NC-006), and NIX-TB). Additionally, groups such as the AIDS Clinical Trials Group (ACTG, DDI study and MARVEL) and Médecins Sans Frontières (through TB-PRACTECAL and with Partners In Health, endTB) are exploring shorter, simpler regimens that depend less on second-line drugs with extensive prior use. Interestingly, efficacy, rather than tolerability (or toxicity) emerged as the priority endpoint in this type of research.

Treatment of LTBI, among other measures to prevent or rapidly detect active disease—pre-exposure vaccines, averting nosocomial transmission, and case finding—was selected at several points among the priorities. In contrast to shorter, more efficacious regimens, there has been extremely limited activity in this domain since the 2008 publication, which also highlighted this topic as a priority. Exceptions include case series and observational studies of treatment of LTBI in household contacts, often children, with regimens containing fluoroquinolones [[8-12](#_ENREF_8)]

Changes from the 2008 research agenda are notable. These include a refinement of the priority placed on new DST methods; in the current version, the call is for better evidence around the impact of new methods on treatment outcomes and on methods that can diagnose difficult-to-diagnose TB (extrapulmonary or TB in HIV-coinfected or pediatric populations). The emphasis on programmatic research to select algorithms for screening sub-populations for MDR-TB persists, but as a lower priority in the area of programmatically relevant research. Since Xpert has been widely adopted in the last several years, and implemented according to (perceived) risks in a country, perhaps the urgency around data to support and guide its introduction has abated. Without supplanting an understanding of the variability in distribution of drug resistance, refinements have emerged: how to use non-representative data to better estimate the burden of DR-TB; what is the frequency of resistance to pyrazinamide, moxifloxacin, and injectables. The former reflects the reality that still a limited number of countries, especially in Africa, have national data from recent, representative surveys or ongoing surveillance of drug resistance. The absence of recent, representative data, it is understood, does not correspond to the absence of resistance [[13](#_ENREF_13)].

*Implementation*

As noted, the changes in priorities since 2008 reflect, in part, exciting advances in rapid diagnostics and treatment options. Some changes also reflect a pragmatism about the current state of affairs—that there would be interest in developing methodologies for drawing inference from non-representative anti-TB drug resistance surveys, for example—and the limitations in resources for TB research [[14](#_ENREF_14)]. For the same reason, many of the 2008 priorities appear again as priorities six years later. Also influencing the implementation of research are the priorities of industry partners. Although this document highlights short, effective regimens as a top priority, *no trial of shortened regimens containing one or more new drugs has been initiated.* This is despite conditional approval of one drug (bedaquiline) in late 2012 and the other (delamanid) in 2013 based on their superiority in placebo-controlled trials. Continued advocacy around resources for research and accelerated testing of new interventions will be essential. To this end, the engagement of the new Global Drug Resistant TB Initiative and RESIST-TB, as well as activists, researchers, donors and policymakers will be essential to continued research advocacy.

*Limitations*

The systematic, transparent, and inclusive process that resulted in the present document represents a strength. The survey sought input from an extensive list of individuals that included clinical researchers, policy makers, clinicians and other service providers, activists, patients, and donors. The relatively low response rate, approximately 20%, and lack of information on the participants limit the extent to which we can assert that results are generalizable. We note, however, that the priorities identified represent progressions from those identified in the previous documents, and therefore, seem credible. We also note that the results may reflect a bias toward very applied research, which was introduced in the previous research agendas on which the current exercise was based.

**Conclusion**

**References**

1. Cobelens FG, Heldal E, Kimerling ME, Mitnick CD, Podewils LJ, et al. (2008) Scaling up programmatic management of drug-resistant tuberculosis: a prioritized research agenda. PLoS Med 5: e150.

2. Gupta R, Espinal M (2003) A prioritised research agenda for DOTS-Plus for multidrug-resistant tuberculosis (MDR-TB). Int J Tuberc Lung Dis 7: 410-414.

3. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, et al. (2014) Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 371: 723-732.

4. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, et al. (2013) Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J 41: 1393-1400.

5. Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, et al. (2010) Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 182: 684-692.

6. Nunn AJ, Rusen I, Van Deun A, Torrea G, Phillips PP, et al. (2014) Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials 15: 353.

7. Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, et al. (2014) Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 18: 1180-1187.

8. Seddon JA, Hesseling AC, Finlayson H, Fielding K, Cox H, et al. (2013) Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study. Clin Infect Dis 57: 1676-1684.

9. Thee S, Garcia-Prats AJ, McIlleron HM, Wiesner L, Castel S, et al. (2014) Pharmacokinetics of ofloxacin and levofloxacin for prevention and treatment of multidrug-resistant tuberculosis in children. Antimicrob Agents Chemother 58: 2948-2951.

10. Adler-Shohet FC, Low J, Carson M, Girma H, Singh J (2014) Management of latent tuberculosis infection in child contacts of multidrug-resistant tuberculosis. Pediatr Infect Dis J 33: 664-666.

11. Bamrah S, Brostrom R, Dorina F, Setik L, Song R, et al. (2014) Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012. Int J Tuberc Lung Dis 18: 912-918.

12. Williams B, Ramroop S, Shah P, Anderson L, Das S, et al. (2013) Management of pediatric contacts of multidrug resistant tuberculosis in the United Kingdom. Pediatr Infect Dis J 32: 926-927.

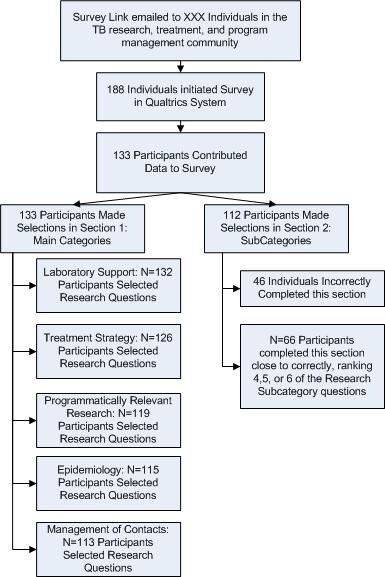
13. Zignol M, Sismanidis C, Falzon D, Glaziou P, Dara M, et al. (2013) Multidrug-resistant tuberculosis in children: evidence from global surveillance. Eur Respir J 42: 701-707.

14. Frick M (2014) Tuberculosis Research and Development: 2014 Report on Tuberculosis Research Funding Trends, 2005–2013. Treatment Action Group

Stop TB Partnership.

|  |
| --- |
| **Table 1:** List of documents, publications, and websites reviewed for research priorities |
| CDC Plan to Combat Extensively Drug Resistance Tuberculosis, Recommendations for the Federal Tuberculosis Task Force (2009) |
| NIAID Research Agenda: Multidrug Resistance and Extensively Drug Resistant Tuberculosis (2007) |
| MSF/PIH Manual- Tuberculosis: Practical Guide for Clinicians, Nurses, Laboratory Technicians and Medical Auxiliaries (2013) |
| WHO/Stop TB Operational Research Guide: Priorities in Operational Research to Improve Tuberculosis Care and Control |
| The Union: Guidelines for the Clinical and Operational Management of DR-TB |
| Global Plan to Stop TB (2011-2015) |
| ECDC Technical Report ERLN-TB Expert Opinion on the Use of the Rapid Molecular Assays for the Diagnosis of Tuberculosis and Detection of Drug Resistance |
| Guidelines for the Programmatic Management of Drug-Resistance Tuberculosis Emergency Update 2008 |
| Guidelines for the Programmatic Management of Drug-Resistance Tuberculosis 2011 Update |
| WHO and TDR-Priorities for Tuberculosis Research: A Report of the disease reference group on TB, leprosy and Buruli ulcer |
| STOP-TB Partnership: An International Roadmap for Tuberculosis Research |
| TB Alliance Website |
| Stop TB Working Group on New Drugs Website |
| New Diagnostics Working Group Website |
| NIH RePORTER |
| Articles citing the 2008 research agenda [[1](#_ENREF_1)] |

**Figure 1: Survey Response**



**Figure 2a: Selection of Lab Support research priorities**

**Figure 2b: Ranking of Lab Support research priorities**

**Figure 3a: Selection of Treatment Strategy research priorities**

**Figure 3b: Ranking of Treatment Strategy research priorities**

**Figure 4a: Selection of Programmatically Relevant Research research priorities**

**Figure 4b: Ranking of Programmatically Relevant Research research priorities**

**Figure 5a: Selection of Epidemiology research priorities**

**Figure 5b: Ranking of Epidemiology research priorities**

**Figure 6a: Selection of Management of Contacts research priorities**

**Figure 6b: Ranking of Management of Contacts research priorities**

**Figure 7: Subcategory average of priority ranking**

**Annex 1: Research questions and corresponding Subcategories**

**Laboratory Support**

|  |  |
| --- | --- |
| Variable | Complete Question |
| LS\_2 | Do results of new diagnostic tests improve patient-relevant outcomes OR treatment outcomes? |
| LS\_4 | How can we reliably identify forms of tuberculosis that are not easily diagnosed by examination of sputum sample (e.g., meningitis, pediatric TB, TB in HIV-coinfected persons)? |
| LS\_3 | What is the impact of new diagnostic tests on public health and programs? |
| LS\_1 | What is the performance of new diagnostic tests, compared to gold standards, across programmatic settings? |
| LS\_5 | How can current methods be improved or better interpreted to enhance clinical management of patients (whose TB is caused by a bacterial population) with the following characteristics: (1)low level INH resistance; (2) discordant RIF results between tests; (3) resistance results for only a subset of fluoroquinolones, rifamycins, aminoglycosides/polypeptides? |
| LS\_10 | How can we develop better biomarkers, including non-bacteriological markers, to accelerate new TB drug/regimen research and development and improve clinical and programmatic ability to assess treatment response? |
| LS\_6 | What is the correlation of individual mutations with phenotypic drug susceptibility and with the clinical outcomes of these isolates? |
| LS\_8 | What factors allow MTB strains to efficiently cause transmission and increase virulence? |
| LS\_7 | How can we develop new rapid tests that are correlated to specific mutations and patient outcomes for second line drug susceptibility? |
| LS\_9 | How can we improve the understanding of host factors that contribute to the development of drug resistance, e.g. key molecular features of host/pathogen interactions including immune system characteristics that differentiate latent vs. active disease and those that enhance host susceptibility and progression to active disease? |

**Treatment Strategy**

|  |  |
| --- | --- |
| Variable | Complete Question |
| TS\_1 | How do we efficiently develop more effective, shorter and safer M/XDR-TB treatment regimens that may be used for special populations (e.g., pregnant/lactating women, children, HIV-coinfected individuals)? |
| TS\_7 | What are the optimal combinations and duration of treatment to prevent the emergence of anti-TB drug resistance? |
| TS\_3 | Is the 9 month "Bangladesh" MDR-TB treatment regimen effective in countries with high prevalence of resistance to second-line drugs (SLDs)? What modifications would be necessary? |
| TS\_4 | How do we prevent toxicity from SLDs and optimally mitigate serious adverse events (SAEs) in DR- and XDR-TB treatment regimens? (especially in special populations e.g., pregnant/lactating women, children, HIV-coinfected individuals) |
| TS\_6 | How can we optimize the use of SLD combinations, and SLD with antiretrovial therapy, through evidence accumulated in drug-drug interactions and other pharmacokinetic studies? |
| TS\_2 | What are the precise pharmacological characteristics, efficacies and toxicities and interactions of group 5 drugs both in MDR- and XDR-TB treatment combinations? |
| TS\_5 | How does pathogen and host interaction affect management of DR-TB? |

**Programmatically Relevant Research**

|  |  |
| --- | --- |
| Variable | Complete Question |
| PRR\_2 | What are options for short-course treatment and how can it be used to expand MDR-TB treatment? |
| PRR\_3 | What are barriers to treatment initiation and completion? |
| PRR\_1 | Which groups of patients with increased proportion of MDR-TB should be targeted for DST in the context of limited resources and which diagnostic algorithms should be used to identify patients within risk groups? |
| PRR\_18 | Operationally, what are the best methods to ensure optimal treatment, including guidelines; reliable drug supply; staff appropriately trained; adequate health facilities? |
| PRR\_4 | What infection control measures exist with proven evidence to reduce transmission? |
| PRR\_9 | How do we study key barriers to delivery of services for TB and DR-TB diagnosis and treatment initiation? |
| PRR\_11 | What is the impact of new interventions and technology on case-finding and treatment initiation? |
| PRR\_8 | How can data be used more actively to identify barriers to PMDRTB scale up and to identify topics for operational research? |
| PRR\_7 | What is the quality of routinely captured data, including on the programmatic management of drug resistant tuberculosis (PMDRTB), and what interventions are required to improve data capture & quality? |
| PRR\_16 | What strategies support integration of TB control activities into health care systems? |
| PRR\_12 | What is relative contribution of public- and private-sector providers? How can use of new tools be integrated, correctly and effectively in private sector, to enhance contribution to TB control? |
| PRR\_17 | How do we integrate (and modify) social determinants to improve TB control? |
| PRR\_10 | How do new interventions and technologies become adapted and integrated into NTPs? |
| PRR\_15 | (How) do rapid molecular test affect treatment outcome and long-term endpoints? |
| PRR\_5 | What current tests are available to assess potential for transmission? |
| PRR\_13 | What resources are needed to ensure equitable access to care? |
| PRR\_6 | How do gaps in infection control vary across settings? |
| PRR\_14 | What commitments are necessary from donors and how can they be held accountable? |

**Epidemiology**

|  |  |
| --- | --- |
| Variable | Complete Question |
| E\_13 | What interventions (e.g., household contact tracing; early, routine DST for all TB cases) are effective at reducing nosocomial infection? What is the impact of these interventions? |
| E\_1 | In countries without current, representative data on the burden of drug-resistant TB, what is the burden? (How) can non-representative data be used to improve estimates of DR-TB? |
| E\_2 | What is the frequency of resistance to PZA, moxifloxacin, and injectables? |
| E\_12 | What ecologic or population-level characteristics predict resistance incidence, acquisition and/or amplification, transmission, outcomes: regimens; population burden of other diseases (e.g., HIV); degree of public-private mix in TB control; geography or socio-economic status? |
| E\_4 | What is the frequency of MDR-TB, XDR-TB, resistance to PZA, and moxifloxacin among important subgroups: children, migrants/internally displaced persons, people living with HIV? |
| E\_10 | Do different health-facility characteristics (e.g., access, quality of care, supervision, support) predict incidence? Drug resistance acquisition/amplification? Transmission? And outcomes? |
| E\_9 | Do individual-level demographic, behavioral, clinical characteristics predict incidence? Drug resistance acquisition/amplification? Transmission? And outcomes? |
| E\_6 | What are the consequences for the probability of transmission of multiple infections with different strains different types of drug resistance within a single host? |
| E\_5 | Do other components of fitness vary by genotype, strain? Does transmission frequency vary by strain & genotype, and is this variation modified by resistance? Does such strain-dependent transmissibility vary by setting, i.e., hospitals, prisons, mines? |
| E\_7 | Do strain/genotype predict incidence? Drug resistance acquisition/amplification? Transmission? And outcomes? |
| E\_3 | What is the variability of drug resistance within countries or regions? |
| E\_8 | Do different resistance patterns (mono, combinations) predict incidence? Drug resistance acquisition/amplification? Transmission? And outcomes? |
| E\_11 | Does source of transmission (i.e., nosocomia) predict incidence? Drug resistance acquisition/amplification? Transmission? And outcomes? |

**Management of Contacts**

|  |  |
| --- | --- |
| Variable | Complete Question |
| MC\_7 | What are optimal drugs, combinations, and durations for LTBI in known contacts of MDR-TB patients? |
| MC\_5 | What are the best methods for preventing household transmission? |
| MC\_3 | What biomarkers can be used to distinguish infection from disease? |
| MC\_1 | How can vaccines be developed to prevent infection? |
| MC\_4 | Are there biomarkers markers that can identify who, among infected contacts, is most likely to develop active disease? |
| MC\_2 | How can we develop a post-exposure vaccine that can prevent active disease in infected contacts? |
| MC\_6 | What are best methods to assure HCW implementation of measures known to reduce risk of nosocomial transmission? |
| MC\_8 | Should duration and combination be individualized according to risk factors for development of active disease and/or DST of presumed index case? |

**Subcategories**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Complete Question | Corresponding Individual Questions | Ranking in Main Category |
| Sub\_TS\_1 | Treatment Strategy-Better, Safer Treatment | TS\_1 | 1 |
| Sub\_LS\_1 | Laboratory Support-Clinical and programmatic value of drug-susceptibility testing | LS\_2  LS\_3  LS\_1  LS\_5  LS\_6  LS\_7 | 1  3  4  5  7  9 |
| Sub\_MC\_1 | Management of Contacts-Vaccines | MC\_1  MC\_2 | 4  6 |
| Sub\_PRR\_10 | Programmatically Relevant Research-Access to MDRTB: diagnosis, delivery and care management | PRR\_18 | 4 |
| Sub\_E\_8 | Epidemiology-Effectiveness and Impact of Interventions | E\_13 | 1 |
| Sub\_LS\_2 | Laboratory Support-New diagnostics for manifestations other than smear-positive, pulmonary disease in immunocompetent adults | LS\_4 | 2 |
| Sub\_TS\_3 | Treatment Strategy-Standardized, short regimen in settings with prior exposure to second-line drugs | TS\_3 | 3 |
| Sub\_PRR\_1 | Programmatically Relevant Research-Case finding | PRR\_1 | 3 |
| Sub\_PRR\_2 | Programmatically Relevant Research-Treatment delivery | PRR\_2  PRR\_3 | 1  2 |
| Sub\_TS\_7 | Treatment Strategy-Prevention of MDR-TB | TS\_7 | 2 |
| Sub\_LS\_5 | Laboratory Support-Biomarkers | LS\_10 | 6 |
| Sub\_MC\_2 | Management of Contacts-Preventing spread from source to contact | MC\_5 | 2 |
| Sub\_MC\_4 | Management of Contacts-Treating LTBI | MC\_7  MC\_8 | 1  8 |
| Sub\_PRR\_9 | Programmatically Relevant Research-Health system strengthening | PRR\_16  PRR\_17 | 10  12 |
| Sub\_E\_1 | Epidemiology-Burden of DR-TB: Geographic areas | E\_1  E\_2  E\_3 | 2  3  11 |
| Sub\_E\_3 | Epidemiology-Transmission dynamics of DR-TB | E\_6  E\_5 | 8  9 |
| Sub\_PRR\_8 | Programmatically Relevant Research-Novel methodologies | PRR\_15 | 14 |
| Sub\_LS\_3 | Laboratory Support-Epidemiological impact of bug and host factors | LS\_8 | 8 |
| Sub\_E\_7 | Epidemiology-Multi-level risk factors for DR-TB (with regard to incidence, drug resistance acquisition/amplification, transmission and DR-TB treatment outcomes): Community/Population Level | E\_12 | 4 |
| Sub\_E\_5 | Epidemiology-Multi-level risk factors for DR-TB (with regard to incidence, drug resistance acquisition/amplification, transmission and DR-TB treatment outcomes): Person | E\_9 | 7 |
| Sub\_LS\_4 | Laboratory Support-M. tuberculosis growth and persistence | None? |  |
| Sub\_TS\_4 | Treatment Strategy-Toxicity and serious adverse event treatment and management | TS\_4 | 4 |
| Sub\_E\_6 | Epidemiology-Multi-level risk factors for DR-TB (with regard to incidence, drug resistance acquisition/amplification, transmission and DR-TB treatment outcomes): Health facility/services- program | E\_10  E\_11 | 6  13 |
| Sub\_PRR\_4 | Programmatically Relevant Research-Recording and reporting, use of routine NTP data | PRR\_8  PRR\_7 | 8  9 |
| Sub\_TS\_6 | Treatment Strategy-Pharmacokinetics of present second line drugs and drug-drug interactions of second line drugs with ARVs | TS\_6 | 5 |
| Sub\_PRR\_5 | Programmatically Relevant Research-Implementation and dissemination | PRR\_9  PRR\_11  PRR\_10 | 6  7  13 |
| Sub\_E\_2 | Epidemiology-Burden of DR-TB: Subgroups | E\_4 | 5 |
| Sub\_PRR\_7 | Programmatically Relevant Research-Funding and commitment | PRR\_13  PRR\_14 | 16  18 |
| Sub\_TS\_2 | Treatment Strategy-Group 5 Drugs | TS\_2 | 6 |
| Sub\_MC\_3 | Management of Contacts-Health care training | MC\_6 | 7 |
| Sub\_TS\_5 | Treatment Strategy-Germ and host interaction | TS\_5 | 7 |
| Sub\_PRR\_3 | Programmatically Relevant Research-Infection control | PRR\_4  PRR\_5  PRR\_6 | 5  15  17 |
| Sub\_PRR\_6 | Programmatically Relevant Research-Coordination | PRR\_12 | 11 |
| Sub\_E\_4 | Epidemiology-Multi-level risk factors for DR-TB (with regard to incidence, drug resistance acquisition/amplification, transmission and DR-TB treatment outcomes): Organism | E\_7  E\_8 | 10  12 |