

# Report on workshop on epidemiological studies of determinants for drug resistance

Held on

6-7 October 2010,

at

KNCV Tuberculosis Foundation, The Hague, The Netherlands

Co-hosted by

Center for Poverty-related Communicable Diseases (CPCD), Amsterdam  
Medical Center, The Netherlands

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**Stop TB Partnership**



## Workshop rationale

Globally, nearly half a million new cases and an additional 1–1.5 million prevalent cases of drug-resistant tuberculosis (DR-TB) were present globally in 2006. The disease is transmissible and deadly, and represents a public health emergency. Treatment for DR-TB is complex, expensive and of limited efficacy, therefore prevention of DR-TB is paramount for its control. There are substantial gaps in our understanding of the conditions that promote acquisition, amplification and transmission of DR-TB at the global level as well as in specific settings. Filling these gaps is one of the research priorities in order to successfully scale up Programmatic Management of Drug-resistant TB.

The Stop TB Partnership's MDRTB Research Subgroup recently issued a concept paper aimed at increasing awareness of the DR-TB problem, and at promoting the design and implementation of epidemiological and other studies to identify its determinants as a basis for enhanced prevention of DR-TB worldwide. This paper recognizes that current data (e.g. from the Global Project on TB DR Surveillance) are only accessible for cross-country and cross-setting analyses in aggregated form, thereby limiting their interpretation. It therefore outlines how DR survey and surveillance data can be used to study these determinants across countries and settings on an individual patient basis. Apart from analysis of existing data it proposes prospective, systematic, individual patient-based collection of data from routine DR surveillance as the backbone for multi-country studies, making optimal use of the planned introduction of routine DR surveillance in many countries as recommended by WHO for (primarily) retreatment patients. Added onto this backbone can be focused prospective or retrospective sub-studies to elucidate the role of specific risk factors in specific settings (e.g. nosocomial transmission).

Such prospective studies and analyses require collaboration of several countries, coordinated and systematic data collection, and funding. As a first step, study protocols need to be developed with clear and relevant objectives, study questions and designs, in order to lay the groundwork for subsequent advocacy for funding and involvement of countries.

Therefore a workshop was held, bringing together experts in the field of DR surveillance and research, to develop outlines for study protocols for epidemiological multi-country studies to identify determinants tuberculosis drug resistance in various settings and outline strategies for their funding and implementation.

## Workshop summary

Below is a summary of the presentations and discussions during the workshop.

### Objectives

Einar Heldal (Norwegian Association of Heart and Lung Patients, Norway) presented the objectives of the workshop: to develop outlines for epidemiological multi-country studies aimed at identifying determinants of tuberculosis drug resistance in various settings, with clear and relevant objectives, study questions and designs, in order to lay the groundwork for subsequent advocacy for funding and involvement of countries, as a basis for enhanced prevention of DR-TB worldwide. He identified a number of challenges:

- Lack of data;
- How to select countries/areas that can be contrasted because of their different courses of the DR epidemic;
- The political/emotional controversies that some of the potential risk factors may raise, e.g. type and quality of first-line treatment supervision, use of rifampin in the continuation phase of the Category 1 regimen; and drug quality;
- Implementation of new control strategies lagging behind at country/local level;
- Often weak functioning of NTP central units' basic (DOTS) functions, such as supervision, recording & reporting, and drug stock-outs, which may create MDR-TB;
- Limited (operational) research capacity in most NTPs;
- Research findings often have limited policy consequences (weak "policy transfer");
- Limited use of routinely collected data for management/decision making, much reliance on surveys.

### Discussion paper

Frank Cobelens (AMC/AIGHD, Netherlands) presented the discussion paper on the need and prospects for studies into the main drivers of the DR-TB epidemic prepared by the Research Subgroup of the Stop-TB MDRTB Working Group. While much is known *in general* on how DR in TB is generated and propagated, there is little knowledge of the relative contribution of causative factors ("drivers") in *specific settings*. It is important to understand the major drivers of the DR epidemic in order to effectively target control interventions globally, regionally and in specific settings, as well as to monitor interventions for their impact on the DR situation. Obstacles to understanding the epidemiology of DR-TB include the long generation time of the TB epidemic; limited availability and/or quality of drug resistance data; limited quality of routine TB statistics; and coexistence and interaction of several risk factors. Recently new opportunities for studying the epidemiology of DR-TB have arisen: the availability and scale-up of molecular assays for drug susceptibility testing; the recent revision of the WHO DR surveillance guidelines to include routine surveillance of DR in high risk groups, including retreatment patients; the increasing availability of analytical tools of multilevel data; and the increase in funding opportunities. These allow collection and analysis of individual patient-level data, which had thus far not been possible at a large scale. Some of the "drivers" of interest will be historical in nature, and require analyses of existing databases spanning several years. Others operate at the moment and require prospective ("concurrent") collection and analysis of data, for which the routine surveillance programs may offer excellent opportunities. Investigation of "hot spots" identified by routine surveillance can offer important insights of direct relevance to control of DR-TB.

The vision is to come to one or more coordinated multi-country projects based on routine DR screening with systematic use of surveillance data to gain insight into course and main drivers of the DR epidemic and to inform national and regional DR-TB control policies, with add-on studies to answer specific questions. For this, consensus is needed on need, policy relevance and main study questions; the usefulness of historical and/or concurrent data; designs, including add-on studies; minimum datasets and formats (surveillance); need and options for coordination; and options for funding.

### Systematic review into determinants of MDR TB

Laura Podewils (CDC, USA) presented the preliminary results of a systematic review into determinants of MDR TB. By means of a meta-analysis she aims to quantify the relative contributions of several demographic, social, behavioral, genetic and clinical determinants at the patient level. Provisionally, 131 articles will be included in the review. She notes that this

comprehensive review will provide valuable information on the associations between patient-level factors and MDR TB risk, but cannot provide estimates of the relative contribution of patient-level factors compared to organism-specific, programmatic, cultural, environmental, and geo-political factors.

#### Design and practical lessons in the PETTS study

Peter Cegielski (CDC, USA) presented the design and practical lessons learned from the Preserving Effective TB Treatment Study (PETTS). The aim of PETTS is to assess whether applying high standards of MDR TB treatment with second line drugs (SLD), prevents acquirement of additional resistance. In 13 Green Light Committee (GLC) approved MDR TB treatment sites (in 5 countries) and 15 other MDR TB treatment sites (in 4 different countries), initial resistance in patients enrolled in 2005-2008 is measured as well as (risk factors for) acquired resistance, plus its effect on patient outcomes. For this, monthly sputum culture isolates are sent to CDC for DST and genotyping. Peter presented practical lessons that need to be considered in any study but are even more challenging in big, prospective multi-center, multi-country studies; these relate to complex sampling strategies, informed consent, collection and categorization of meaningful variables including comparability across sites, ownership and stewardship, need for continuous data-monitoring, and continuous funding.

#### Modeling opportunities (Ted)

Ted Cohen (Harvard, USA) discussed the role of mathematical modeling. Areas covered thus far have included Within-host models, both qualitative (mechanisms of appearance of multiple drug resistance during combination drug treatment) and quantitative (predicting the risk of such appearance); and population-level models, also both qualitative (identification of determinants of trends: intrinsic and extrinsic factors) and quantitative (predicting DR TB trends over time, projecting effects of diagnostic tools and interventions, and cost-effectiveness analysis). It is questionable whether there is such a thing as a MDR epidemic, or whether it is the same phenomenon of DR acquisition and local spread that occurs in many places at the same time. Therefore, the scale of analysis is important. Data from Vietnam and Ukraine were presented showing that by meaningful aggregation of clinics or survey clusters localized "outbreaks" or hot spots become apparent. Such hot spots can be explored for their geographic and temporal variability, such as is being done in Peru.

New opportunities include identifying transmission clusters using molecular epidemiological data, contact tracing and spatiotemporal information; and rapid detection of resistance. Retrospective analyses have been done to identify risk factors for fingerprint clustering of MDR-TB cases, as well as to reconstruct the evolution of drug resistance in particular strains throughout their treatment and transmission histories. New data have been used to estimate the transmission fitness DR strains and the contribution of transmission to the spread of DR-TB. Issues to be considered are how to structure surveillance (and analysis of surveillance data) to detect outbreaks and inform local response; how to incorporate new diagnostic tools; and is there a role for mathematical modeling?

#### Program relevance and policy transfer

Gillian Mann (LSTM, UK) first summarizes what the program relevance is of studies on determinants for DR TB. Program managers need to know the scale of the problem (prevalence, incidence) including among geographical and socio-economic groups, the interaction with other diseases (e.g. HIV, diabetes) and with other risk factors (e.g. malnutrition), and what is the relative contribution of transmission and acquisition of DR TB. They need this information for planning and implementation of the TB control program including diagnosis, treatment, follow-up, and patient support.

Two pathways on activities and evidence flow into, and out of, policy and practice can be distinguished as ways to integrate research results and programs (see: Parkhurst J, Weller I, Kemp J. Lancet Vol 375 April 24, 2010):

- GROP: Getting research out of practice. The GROP track provides areas for research development, particularly on hypothesis development, improved operational research on implementation and scale up of complex interventions and process evaluation, and on outcome evaluation. The GROP track focuses on mainstreaming methodologies which can evaluate ongoing interventions as they are implemented. This track is particularly relevant where there are evidence gaps or where issues/responses are context specific.
- GRIPP: Getting research into policy and practice. The GRIPP track focuses on using evaluation data as input for policies. Barriers for this track are amongst others that a lot of evidence

### Laboratory issues and possibilities

Armand van Deun (Union) presented on the requirements and difficulties of performing drug resistance surveillance. In the new WHO guidelines, the standard for retreatment cases is continuous surveillance. Drug resistance surveillance among retreatment cases is a proxy for recent NTP performance, although acquired and transmitted DR TB cannot be distinguished with surveillance on DST results at diagnosis only. Therefore, surveillance is mainly meant to monitor trends. Armand reflected on requirements for DR surveillance in terms of representative sampling (otherwise need to correct for incomplete sampling of certain retreatment groups), consistency over time, denominators not based on samples or population size but based on patients (but how to deal with successive retreatment regimens?), etc. Within retreatment patients, failure cases have the highest priority for DR surveillance. He also presented long-term results from the Damien Foundation in Bangladesh.

Dick van Soolingen (RIVM) presented preliminary results from a European project on molecular surveillance of MDR TB, showing that a large proportion of the MDR strains imported into the European Union region belong to the Beijing genotype family.

### Determinants of transmission and acquisition of drug resistance

In two groups, relevant determinants with regard to transmission and acquisition of drug resistance were defined.

For **acquisition**, the following determinants, relevant categorizations and related factors were specified:

- Retreatment regimen
- Treatment adherence
  - Separately during intensive and continuation phase
  - Whether treatment is directly observed (DOT) and if so, which type of DOT
  - Inpatient versus outpatient treatment
- Drug quality
  - Categories: using drugs from WHO prequalified suppliers, drugs approved with in-country quality control, other/unknown.
- Extent of uncontrolled access to TB drugs, including in private sector
- Extent of deviations from standardized treatment regimens
- Use of fixed dose combinations
  - No
  - Yes. If yes, which ones and when were they introduced
- Extent of drug supply problems
  - Number of days of stock-out (to be derived from GDF/GLC mission reports)
  - Comparison quantity of drugs given out versus number of reported cases at different levels (national to district)
  - Regulations in place/enforced
  - Quality of recording and reporting: categorize by means of data from international monitoring missions; need for routine monitoring data (one option mentioned was the TBNET tool for MDRTB)
- Proportion of cases (per treatment category) in public, public-private mix (PPM), and private sector (note: this proportion is most difficult to measure). Take into account:
  - Cases can switch between public and private sector during diagnosis/treatment
  - Regimens in use per sector
  - TB guidelines available and used per sector
  - Source of drugs used
  - Costs/access per sector of diagnosis and treatment. Ways to measure costs mentioned are: % of international median price; number of days of work needed against minimum wages to afford full regimen

For all determinants, availability and quality/reliability of data and how to measure them on a meta-level, is an important issue.

For **transmission**, the following determinants and relevant categorizations and related factors were defined:

- Socio-economic status
- HIV

- Delays in diagnosis of DR TB, both patient and health care system delays including turnaround time of diagnostics
- Delays in starting effective (SLD) treatment
- Congregate settings: hospitalization, incarceration, waiting areas in clinics
- Prevalence of chronic cases. There is no uniform definition of chronic cases but here we define them as those that are not treated with appropriate SLD regimens for whatever reasons (e.g. untreatable due to resistance profile, related to expectation towards adherence in socially vulnerable groups)

Ways to study the contribution of these determinants are to:

- Assess time trends
- Assess the incidence of (DR) TB in HCW compared to the general population
- Use contact management data sources
- Making use of simple genotyping methods

Which factors are the main determinants for transmission can be investigated through studies on group-level comparison (e.g. clinic or region). These studies should focus on smear-positive cases (data can be extrapolated to estimate data including smear-negative cases). Group-level or meta-data that can be used to study whether transmission is a major driver include:

- MDR prevalence/incidence in new/retreatment patients
- MDR prevalence/incidence in children
- Geographic clustering of MDR TB

Noted was that local knowledge on the potentially most relevant determinants is available, and is to be used as the basis for investigations. Data on health seeking behavior could be useful to estimate local duration of infectiousness and establish which places are expected to be the most important places for transmission to take place.

After lunch the first day and part of the second day, the participants divided themselves over three groups to discuss:

1. which data from routine surveillance systems are available and can be used to determine the contribution of transmission and acquisition of drug-resistant TB?
2. which data from historical studies are available and can be used?
3. which data are to be collected with outbreak investigations and additional prospective studies (e.g. on nosocomial infections, drug quality)?

#### Routine surveillance on drug-resistant TB

After some discussion the following framework was proposed:

1. Emphasize the need for true surveillance of retreatment cases for DR (at least examination of rifampin resistance)
2. Emphasize the need for true surveillance of all failures of first line therapy for DR (at least examination of rifampin resistance)

These 2 activities will hopefully support infrastructure development to testing for DR and allow the patients in highest clinical need of second line drugs to be identified.

3. Offer efficient study designs for periodic testing of DR among new patients (this area was identified as a potential area for further research that might be fundable). One option discussed was lot quality assurance sampling (LQAS), but this needs to be further explored as a possibility given several methodological considerations including sample sizes and possibilities of limited geographical representativeness. Therefore, other efficient survey designs should also be explored.

These surveys should include the same basic data as the DR surveillance activities, but we would further emphasize the need for also measuring isoniazid resistance since isoniazid resistance may precede the emergence of MDR.

#### Historical studies

There was consensus that the examination of historical data offers the possibility of gaining fundamental insights into understanding why MDR has emerged in specific settings. The emphasis should be placed on

hypothesis-generating activities. Several issues were raised as we look for opportunities for retrospective analysis:

1. The first priority should be to identify historical datasets that are 'high-quality'.

This was a long discussion that didn't come to clear conclusions. All agreed that datasets in which consistency and reliability could be demonstrated should be preferred, but the methods for doing this 'certification' require further discussion. The involvement of local collaborators is obviously key to the success of this type of analysis. Priority should be placed on longitudinal data, but cross-sectional studies would be useful to analyze as well (see below). Case-based data should be prioritized over aggregated data, but data that are only available at aggregate level may still be useful if it is possible to analyze the data on less aggregated level (i.e. data reported on the country-level may be disaggregated into regional estimates if the proper data are available for such splitting). Particular areas where such data may be available include: former Soviet Union, South Africa, Brazil (members of these regions were contributing to this discussion).

## 2. Types of questions that might be asked of such data.

Longitudinal data: investigation of trends; Documenting changes in MDR distribution in specific settings over time; Documenting decreases in susceptibility among MDR strains over time; Documenting changes in lineage distribution over time. Cross-sectional data: investigation of variability (MDR variability by location or by patient type).

## 3. Funding.

We discussed the difficulty in finding funding to support these activities and thought it may be possible to fold these activities into our proposals to engage in prospective work. The justification for doing historical studies is that lessons learned from this type of analysis (which is relatively cheap compared with prospective studies) could generate plausible hypotheses to test prospectively.

### Outbreak investigations and prospective studies

"Hot spots" of (M)DR-TB as identified in routine DR surveillance should be investigated to obtain information on the most important causes in order to limit their further expansion or spread and to prevent such hot spots from emerging elsewhere. This can be done by adapting tools of classical outbreak investigation. There was consensus that investigations should start at "desk level", and then proceed to the level of clinics (or districts, or provinces, depending on the most useful level of aggregation) and finally to that of patients. For each, additional studies can be needed to verify or further detail the findings of the investigation.

#### 1. Desk study: the questions to be answered in this initial stage include:

- Is there an outbreak (incidence clearly in excess of the expected)? Could it be due to bias/errors in laboratory testing or reporting?
- Is it mainly due to DR acquisition or to DR transmission? Map cases by person, type of resistance, location and time (who, what, where, when).
- Have there been: drug stock-outs, changes in drug supplier, changes/lapses in treatment regimens or use of fixed-dose combination, problems with access to care in the treatment phase, major delays in the diagnosis-to-treatment chain?
- Who gets DST, which method used and where done, what is the quality assurance system and how are results reported to the clinician?

#### 2. Clinic-based investigations:

- Design: comparison of units (clinics, districts or provinces, depending on the relevant level of aggregation) with increased (M)DR rates (cases) to units without increased (M)DR rates (controls), between and within geographical areas. Match case and control units on time since DOTS implementation and coverage of DST.
- Compare for potential determinants of acquisition as above: drug stock-outs, changes in drug supplier, changes/lapses in treatment regimens or use of fixed-dose combination, problems with access to care in the treatment phase.
- Compare for potential determinants of transmission: local prevalence of chronic TB; turnaround times of DST results, availability of and delays in second-line treatment, level of infection control, number and percentage of HIV-positive TB patients (DS and DR TB); number and percentage of internal/external migrants among the patients.

#### 3. Individual patient-based data

- Design: comparison of patients within units, comparing MDR patients (cases) to patients who were tested but have no MDR (controls). Match case and control patients by diagnostic category (new, failure, return after default, relapse).
- Collect data from cases and controls by extracting patient records and/or interviewing patients.
- Compare case patients with control patients for potential determinants of acquisition: adherence to treatment, use of rifampin before current treatment, previous treatments (where, what, interrupted, switched, access to care, etc.).
- Compare case patients with control patients for potential determinants of transmission: HIV status; history of hospitalization, frequent outpatient clinic attendance, incarceration, IV-drug use, homelessness, and alcohol use; country/region of origin.

#### 4. Additional studies.

Depending on the likely cause(s) of the (M)DR hot spot and the need for further verification, the following additional studies were identified.

| If likely cause is:  | Then do:   |
|--|--|
| Uncontrolled use of TB drugs   | Pharmacy surveys, in public and private sector                               |
| Nosocomial transmission, weak infection control  | IC risk assessment; molecular epidemiology studies, prospective              |
| Transmission in other congregate   | Molecular epidemiology studies, prospective                                  |
| Transmission from untreated chronic cases  | Molecular epidemiology studies, prospective                                  |
| Transmission due to long delays to diagnosis and appropriate treatment of other (M)DR patients | Molecular epidemiology studies, prospective                                  |
| Lapses in drug quality   | Treatment outcomes in units where these were used; test batches of drugs     |
| Use of alternative regimens  | Treatment outcomes in units where these were used                            |
| Low quality treatment in private sector/hospitals  | Studies on role of private practitioners, pharmacies, general hospitals etc. |

#### Conclusions and recommendations

The workshop concluded that:

1. There is a need for better understanding of the drivers of the (M)DR-TB epidemic in various settings and of the variation in (M)DR levels between settings;
2. Continuous surveillance of (M)DR among TB patients should be the backbone of data collection for this purpose, and better use should be made of surveillance data to inform policy;
3. Important information can be obtained by investigating local "hot spots";
4. Multi-country coordination would be desirable in order to get internationally comparable data.

A potential funding opportunity is the USAID-funded TB CARE programme. Most parties in the TB CARE 1 consortium were represented at this workshop. At the end of the meeting, it was agreed to submit a proposal for a TB CARE Core Project on guidelines/tools for 1) implementation of DR TB surveillance, 2) surveillance for action on M/XDR TB, 3) analysis and interpretation of DR TB surveillance data, followed by piloting of these guidelines including training of staff on the use of it. The tools will be tailored to the conditions of resource-poor settings including human resources and laboratory capacity (Frank Cobelens and Susan van den Hof will take the lead in this).

Other funding opportunities will be explored as they come along, and parties represented in the workshop will be invited to participate in proposals for multi-country projects. The Research Subgroup of The MDR-TB WG will coordinate further activities.

## Workshop agenda

| Date/Time                     | Session  |  |
|-------------------------------|--|--|
| <b>Wednesday, October 6</b>   |  |  |
| 08.45 - 09.00                 | Arrival at KNCV TF headquarters office                         |  |
| 09.00 - 09.30                 | Welcome and self-introduction of participants                  |  |
| 09.30 - 09.45                 | <b>Presentation on background and workshop</b>                 | Einar Heldal                           |
| 09.45 - 10.45                 | <b>Presentation on discussion paper</b>                        | Frank Cobelens                         |
| 10.45 - 11.00                 | Coffee and tea break   |  |
| 11.00 - 11.30                 | <b>Presentation and discussion on</b>                          | Laura Podewils                         |
| 11.30 - 12.00                 | <b>Presentation on design and lessons</b>                      | Peter Cegielski                        |
| 12.00 - 12.30                 | <b>Presentation on modeling opportunities</b>                  | Ted Cohen                              |
| 12.30 - 13.30                 | Lunch  |  |
| 13.30 - 15.00                 | <b>Discussion on:</b>  | All                                    |
| 15.00 - 15.15                 | Coffee and tea break   |  |
| 15.15 - 16.30                 | <b>Group work</b>  |  |
| 16.30 - 17.30                 | <b>Feedback conclusions from groups to plenary and discuss</b> | All                                    |
| 18.30 - 21.30                 | Dinner   |  |
| <b>Thursday, October 7</b>    |  |  |
| 09.00 - 09.15                 | <b>Presentation and discussion on policy</b>                   | Gillian Mann                           |
| 09.15 - 09.30                 | <b>Presentation on laboratory possibilities</b>                | Armand van Deun,<br>Dick van Soolingen |
| 09.30 - 12.30                 | <b>Group work per protocol to describe:</b>                    | All                                    |
|                               | - <b>objectives</b>  |  |
|                               | - <b>population</b>  |  |
|                               | - <b>settings</b>  |  |
|                               | - <b>methodology</b>   |  |
|                               | - <b>relation to programs</b>                                  |  |
|                               | - <b>budget estimate</b>                                       |  |
| (with coffee break at 10.45h) |  |  |
| 12.30 - 13.30                 | Lunch  |  |
| 13.30 - 14.30                 | <b>Feedback discussion points to plenary</b>                   | All                                    |
| 14.30 - 15.15                 | <b>Group work continued</b>                                    | All                                    |
| 15.15 - 15.30                 | Coffee and tea break   |  |
| 15.30 - 16.15                 | <b>Discussion on funding opportunities</b>                     | All                                    |
| 16.15 - 17.00                 | <b>Discussion on way forward</b>                               | Frank Cobelens &<br>Susan van den Hof  |
|                               | <b>Closure</b>   |  |

## Participant list

| <i>Family name, given name</i> | <i>Organization</i>   |
|--------------------------------|---|
| <b>Aung, Kya Jai Maug</b>      | Damien Foundation Bangladesh  |
| <b>Cegielski, Peter</b>        | Centers for Disease Prevention and Control                                  |
| <b>Cobelens, Frank</b>         | Amsterdam Medical Center - Center for Poverty-Related Communicable Diseases |
| <b>Cohen, Ted</b>              | Harvard University  |
| <b>Dadu, Andrei</b>            | WHO Europe  |
| <b>Deun, Armand van</b>        | Institute for Tropical Medicine, Belgium / The Union                        |
| <b>Heldal, Einar</b>           | Norwegian Association of Heart and Lung Patients (LHL)                      |
| <b>van den Hof, Susan</b>      | KNCV Tuberculosis Foundation  |
| <b>Hoffner, Sven</b>           | The National Institute for Infectious Disease Control, Sweden               |
| <b>Hu, Yi</b>                  | Fudan University, Shanghai  |
| <b>Keravec, Joel</b>           | Management Sciences for Health Brazil                                       |
| <b>Lienhardt, Christian</b>    | WHO Geneva  |
| <b>Mann, Gillian</b>           | Liverpool School of Tropical Medicine                                       |
| <b>Ohkado, Akihiro</b>         | Research Institute of Tuberculosis, Japan                                   |
| <b>Podewills, Laura</b>        | Centers for Disease Prevention and Control                                  |
| <b>Pool, Robert</b>            | Barcelona Centre for International Health Research                          |
| <b>Rieder, Hans</b>            | The Union   |
| <b>Sanchez, Elisabeth</b>      | Epicentre   |
| <b>Sandgren, Andreas</b>       | European Centre for Disease Prevention and Control                          |
| <b>van Soolingen, Dick</b>     | National Institute of Public Health and the Environment, The Netherlands    |
| <b>Victor, Tommie</b>          | University of Stellenbosch, South Africa                                    |
| <b>Viiklepp, Piret</b>         | National Institute for Health Development, Estonia                          |
| <b>Zignol, Matteo</b>          | WHO Geneva  |