



EDCTP Stakeholder Meeting on tuberculosis and mycobacterial infections

Online Consultation Feedback

1 Introduction

In preparation for the meeting, EDCTP has set up an online consultation to gather views from stakeholders. Through this open consultative process, EDCTP is seeking views from a broad range of stakeholders from academia, industry, foundations, non-governmental organisations, civil society, governments and other interested parties working in the field of tuberculosis and mycobacterial infections

The comments and recommendations received will inform discussions and where appropriate contribute to EDCTP strategy in this field. The feedback from the online consultation is presented in this document as submitted by the contributors. The feedback will also feature in the final meeting report.

2 Online Consultation Feedback

Dr Eleni Aklillu

Karolinska Institute, Sweden

Current status of the field

Progress in responding to multidrug-resistant TB (MDR-TB) therapy remains slow and yet the number of new cases of MDR-TB in high MDR-TB burden countries is increasing. Treatment for MDR-TB is costly and can have serious adverse events. Treatment of extensively drug-resistant TB, or XDR-TB remains a major challenge. TB remains the most common opportunistic infections in HIV patients. Although effective therapy is available for both TB and HIV, concurrent treatment is complicated due to drug interaction and overlapping toxicities. Until recently, the optimal time to start antiretroviral therapy in TB-HIV coinfecting patients receiving therapy was not known. Recent studies including ours indicated early start of HIV therapy reduces mortality but this remains to be replicated. Similarly recent studies including ours in adult population indicated no need for efavirenz dose escalation during TB-HIV co-treatment in African population. However drug interaction studies between antiretroviral and anti-tuberculosis drugs in Children and infants remains to be investigated.

Future Directions

There is no effective vaccine to prevent TB in adults. Development of diagnostic test and effective vaccine against for TB and MDR-TB is indispensable. Research focused on optimization of TB and HIV/AIDS co-treatment in children is urgently needed.

The role of EDCTP

Providing fund for clinical trials to researchers.

**Dr Abraham Aseffa**

AHRI, Tanzania

Current status of the field

Lack or failure of:

- Point of care test for early and accurate diagnosis with drug sensitivity information
- Diagnosis and effective treatment of latent tuberculosis
- Blocking transmission with vaccination or sterilizing treatment

Challenges:

Still inadequate understanding of the basics of immune response in tuberculosis at tissue level (and still weak strategically designed research capacity in high burden countries and their institutions to address basic and applied research needs on site)

Inadequate understanding of and consideration of the diversity of tuberculosis strains in diverse populations in product development

Future Directions

- Systems approach to understand TB
- Encouraging progress in product development (particularly in diagnostics, drugs)
- Greater role and more intense participation of high burden countries in tuberculosis research and translation of knowledge into practice
- Encouraging signs of economic development in high burden countries

The role of EDCTP

- Continue to promote high quality and innovative research that targets key bottlenecks in TB control and prevention
- Strengthen and intensify international collaborative research in high burden country institutions with active participation of advanced European centers
- Engage local governments early and at all stages of TB research and consider their priorities in EDCTP consultations with advanced research centres in Europe and Africa
- Strengthen high standards of ethics in health research

Dr Kingsley Asiedu

World Health Organization

Current status of the field

My areas of interest relate to Buruli ulcer disease, a mycobacterial infection caused by *M. ulcerans*. The main challenges are late detection and treatment that includes injectable streptomycin and an oral rifampicin. Because of the injection, patients have to travel daily to nearest health facilities to receive care.

Buruli ulcer is a mycobacterial disease that causes chronic skin ulcers. Early detection is critical in preventing prolonged morbidity and disability. Most patients live in remote areas where health services are not available. Current challenge is mainly due to the late reporting of the disease and consequent complication in managing patients.

Future Directions

WHO is coordinating a clinical trial with the view to developing a regimen so that treatment can be given in the community under direct supervision. This will be a huge advance to simplify treatment and make it more accessible to patients. The study is expected to be completed by end of 2015.

Treatment of Buruli ulcer consists of a combination of rifampicin and streptomycin given for 8 weeks. A shift to complete oral therapy would simplify treatment and allow community treatment of the disease. A WHO sponsored clinical trial is in progress in Ghana and Benin to achieve this. The study is expected to be completed by end of 2015 but this target is likely to



be missed as recruitment has been slow. In addition to the development of improved treatment, there are efforts to develop a point-of-care diagnostic test.

The role of EDCTP

Partner with WHO and others to expand case-finding, strengthen institutions and build research capacity of staff involved in the clinical trial.

Dr Gemeda Abebe Ayana

Jimma University

Current status of the field

Unavailability of rapid and affordable diagnostics, emergence of drug resistant TB, HIV and other co-infections and limited research capacity.

Future Directions

The development of tests that could be used as point-of-care testing. With this regard, customization of GeneXpert with more detection level and additional probes could be considered. Moreover, the development of new drugs like Bedaquiline could bring advances in the field.

The role of EDCTP

EDCTP could contribute by organizing training, providing funds for researchers and institutions in Africa. The key players are the academic and research institutions in Africa along with related ministries

Mr Thomas C. Barrett

European Investment Bank

Current status of the field

The absence of new TB vaccines is one of the most crucial.

Future Directions

Prospects are good, provided that international collaboration on vaccine development and field-testing is strengthened materially.

The role of EDCTP

EDCTP's support through testing for a portfolio based approach to vaccine development could be of considerable importance in reducing the time and cost of developing new vaccines.

Dr David Barros

GSK

Current status of the field

Early prediction of resistant profile. Compliance and adequate dosing Biomarkers

Future Directions

New clinical studies: from EBA to more informative trials New combination treatments that include new INDs

The role of EDCTP

The entire field requires funding for the implementation of new regimes and for the essential support to implement new units to perform the trials which will be essential for small drug and vaccine development



Dr F. Xavier Blanc

CHU de Nantes

Current status of the field

Prevention: should isoniazid preventive therapy (IPT) in HIV-infected patients be administered only to TST+ patients? Added value of IGRAs in this context ??? And how long should we give IPT?

Control: alternatives to Xpert MTB/RIF? Need for point-of-care tests.

Treatment:

- Role of empirical TB treatment in HIV-infected patients?
- Options to dramatically reduce the duration of treatment for MDR or XDR-TB?
- Treatment of severe forms of TB (e.g. disseminated): alternatives to the current regimen?

Future Directions

Urine LAM.

New generations of automated PCR to better detect TB and resistance to TB drugs.

High dose of RIF.

The role of EDCTP

Interaction with the French ANRS could be useful for HIV-infected patients (children & adults).

Dr Catharina Boehme

FIND

Current status of the field

- Progress made wrt TB incidence reduction, but targets likely to not be met. Still very high burden of disease; Drug resistance spread very concerning
- Significant advances in diagnostics over the last 5 years with WHO recommendations for 5 new tools; Xpert MTB/RIF most transformative. Potential to maximize its impact with the help of m-health solutions
- However, very little progress wrt a true point of care test.

Future Directions

- Next generation molecular tools; with expanded drug resistance detection menu
- POC approaches: AB, AG based
- Lab strengthening and quality management remains key.

The role of EDCTP

- Clinical trial platform and trial standardization essential to facilitate the path to WHO (players: WHO/GLI; FIND; rather few strong trial sites for diagnostics in SSA: UCT, MMRP, MRC The Gambia); Trial coordination will be key to make sure that the right data are collected required for WHO expert review and recommendation;
- There are major funding gaps right now especially for late stage trials that are key to determine how to best roll out a new test, and how to maximize its impact.
- Quality assurance and lab strengthening remain significantly underserved areas with a very limited number of players (players: ASLM; CDC, USAID, FIND); longer-term mentorship programs needed
- Availability of specimens remains a main bottleneck for assay development.

**Prof Martin Boeree**

Radboud University Nijmegen Medical Centre

Current status of the field

Key issues:

- Treatment of TB should be shorter of duration and less toxic. Such regimen lead to better compliance and less emergence of resistance.
- These regimen should also be possible in HIV coinfecting patients.
- Rapid diagnosis of TB and resistance
- Surrogate markers to monitor treatment response
- Improved and sustainable capacity to perform research in these fields

Future Directions

Remarkable progress in drug treatment research has been made already with better use of old compounds and new compounds. This should be extended in phase II and investigated in phase III. Promising: higher doses of rifampicin, rifapentin, moxifloxacin, bedaquilin, clofazimin, sutezolid, delamanid. In surrogate marker research the development of rapid markers of bacterial load is promising such as the MBL (rRNA) assay

The role of EDCTP

- Fund successful African European trial networks
- Strengthen capacity in this field
- Strengthen capacity in biomarker research
- Strengthen capacity in pharmacokinetic research in interaction with HIV infection

Key players: existing research institutes in Africa and Europe with well established track record. National involved governments, TB alliance for Drug Development, the BMG Foundation, pharmaceutical industries with TB drug development programs

Dr Maryline Bonnet

MSF-Geneva

Current status of the field

Not adequate treatment regimen: too long for susceptible tuberculosis and ineffective for drug resistance tuberculosis.

No effective diagnostic tools for tuberculosis in children.

No rapid, sensitive and easy to use point of case diagnostic test suitable to low level of health facility (primary health care).

Future Directions

Development of oral, short and well tolerated drug regimen for multidrug resistance tuberculosis based on the new and existing drugs (bedaquiline, delamanid, clofazimin, linezolid and fluroquinolons).

Non sputum based point of case diagnostic tests for children and HIV advanced infected patients.

The role of EDCTP

Through funding of collaborative research projects between European and African research institutions.

**Dr Maria Caldas**

Medical Doctor, Ministry of Health, Angola

Current status of the field

Involvement of HR (quantity and quality) / HR development plan of the peripheries, access to diagnostic laboratories (service coverage). Management of logistics on the ground, capacity building and community involvement in the fight against TB and Leprosy.

Future Directions

Strengthening DOTS in the community. Reinforce health surveillance including notification of TB cases and coordination at all levels.

The role of EDCTP

EDCTP should work as a partner with focal points within the country and initiate a planning process for improving indicators, after a realistic analysis of the situation in each area.

Dr Jeremiah Chakaya

KEMRI

Current status of the field

Weak health care systems limiting the effective delivery of TB services ; inadequate utilization of routinely collected data to inform policy recommendations; a poor understanding of the drivers of the TB epidemic in specific geo - spatial situations leading to a homogenous application of a package of interventions when in fact the epidemic is heterogeneous, the continuing problem of HIV influencing the TB epidemic; the emerging threat of drug resistant TB

Future Directions

There is an increasing focus on systems with health service delivery research likely to better define how to provide TB services, progress in diagnostic research and new diagnostics is promising to deliver better and faster TB diagnostics with the potential to detect cases early to stop TB transmission and to reduce TB morbidity and mortality.

The role of EDCTP

EDCTP can more strongly support health system and health services research, which provide some of the biggest challenges to TB care and control in Africa. EDCTP should also support the development of new diagnostic tools especially the search for a game changing point of care TB diagnostic test. Continuing to build capacity for high quality clinical trial capacity in Africa is also critical. Some of the key players in these areas include the American NIH, CDC, FIND and the Global Fund (for systems research). By supporting a mechanism similar to the now moribund TB Research movement EDCTP can help to provide a platform in which key players in this field can interact.

Dr Duncan Chanda

Institute for Medical Research & Training (IMReT)-UTH

Current status of the field

One of the main challenges in making progress lack of government buy-in in TB related research and lack critical evaluation of programmatic interventions. Governments are not dedicating enough resource to the fight against TB-making TB research a purely research agenda. Governments & National TB Programmes should put in place resources to support research including translating findings into tangible products that may help fight the epidemic.



Future Directions

The last 10 years has seen significant progress into TB biomarker research; and though few, a number of promising drugs products have progressed through various development process. EDCTP has provided a good opportunity for networking and sharing scientific & technical knowledge both in North-South & South-South collaboration. Personally I think there is likely to emerge novel diagnostics for TB and LTB arising from discoveries in the last 10 years and concerted collaborations across research institutions and biotech companies.

The role of EDCTP

EDCTP has made tremendous efforts in getting scientist to work together and form synergistic alliances. However national governments from sub-Saharan Africa need to be engaged further if we are to maximise our outputs from EDCTP efforts. National governments need to put clearly defined funding mechanisms for health research which could then be complementary. However EDCTP funding mechanism with emphasis on capacity building remains critical in generating and supporting a critical mass of health research scientists that is critical to generating new ideas and products.

Prof Gavin Churchyard

Aurum Institute

Current status of the field

1. Sub-optimal implementation of TB control activities, largely due to weak health systems
2. Coverage of antiretroviral therapy is poor and ART still started too late
3. Laboratory diagnostic services inadequate. Reliance of sputum smear microscopy in a high HIV prevalence settings misses a lot of TB cases
4. Poor implementation of isoniazid preventive therapy, infection control and intensified case finding

Future Directions

1. Doing the basics of TB control better through health system strengthening in order to detect TB among those presenting to the health service with symptoms, start treatment as soon as possible and ensure cure
2. Scaling up antiretroviral therapy and starting earlier (CD4 count < 500)
3. Strengthening TB diagnostic services and appropriate introduction of Xpert MTB/RIF
4. Scaling up continuous isoniazid preventive therapy, infection control and intensified case finding. IPT for high-risk HIV-uninfected persons should be considered
5. Scale up household contact tracing with integrated TB/HIV counselling, testing and referral for treatment and care
6. Introduction and scaling up of new treatment shortening regimens if shown to be effective, including use of host directed therapy for TB.

The role of EDCTP

EDCTP can support research activities through

1. Funding of (i) clinical trials of new diagnostics, drugs and vaccines and (ii) implementation research to maximise impact of existing and new technologies
2. Supporting capacity building of young researchers and infrastructure.
3. Establish clinical trial networks for the evaluation of new drugs, diagnostics and vaccines

Key role players include

1. Researchers in Africa and Europe
2. Regulators
3. Product development partners, pharma
4. Ministries of health



Collaboration with other similar entities is important in order to harmonize efforts, such as NIH/DAIDS funded HVTN, ACTG, IMPAACT, HPTN, MTN

Mrs Isabelle Cieren-Puiseux

Sanofi

Current status of the field

With regards to prevent TB need to have more education training on the need to treat.

Future Directions

Lobbying to Authorities in order to facilitate and harmonize process for registration and product import

Prof Frank Cobelens

Amsterdam Institute for Global Health and Development

Current status of the field

1. Failing integration of TB and HIV services. While there is consensus about the control strategy (intensified case finding, isoniazid preventive therapy, early start of ART, infection control), these elements need to be combined in optimal health care delivery packages
2. Lack of accurate diagnostics that are both affordable and accessible. The advent of Xpert MTB/RIF is a revolutionary improvement but financial and technical limitations will limit access for patients
3. Lack of an effective, short and safe (preferably oral) treatment regimen for MDR-TB hampers its effective control
4. Lack of an effective and shortened one-for-all regimen that contains neither rifampicin nor isoniazid and can be used for MDR as well as drug-susceptible TB
5. Lack of an effective vaccine.

Future Directions

Integration of TB and HIV services: the control strategy elements (intensified case finding, isoniazid preventive therapy, early start of ART, infection control) are basically known, there is now need to show how they should be applied and integrated to achieve optimal effectiveness and impact on the TB-HIV epidemic.

Fast followers of Xpert as next-generation assays that can improve access are coming onto the market and need to be evaluated in real-life settings for their impact on case finding, treatment outcomes as well as cost-effectiveness. In addition, triage algorithms in which symptomatic patients are first screened by a cheap and simple assay that is highly sensitive but not necessarily highly specific need to be considered and evaluated. Biomarkers that are promising candidates to be used for triage have been identified and need to be evaluated for this purpose in patient populations where they should be applied.

Bedaquiline and delamanid, already past phase 2b, are likely candidates for a more effective and shortened MDR-TB regimen although with the possibility of added toxicities. Other candidates that are likely to pass 2b in the coming years, such as sutezolid, need to be considered as well, opening the way to a 6-month MDR regimen.

At the same time these and other new drugs (such as PA-824) need to be considered and evaluated for a shortened regimen (ideally down to 2 months) that is effective against MDR as well as drug-susceptible TB. The combination PA-824/moxifloxacin/ pyrazinamide is likely to pass phase 2b later this year but the high levels of pyrazinamide and probably moxifloxacin resistance among MDR-TB patients will leave a group of patients that will still need to be treated with second-line regimens.



Of course an effective and affordable vaccine would be the ultimate goal but despite the large number of candidates there is yet little evidence that any of these approaches would work in field trials due to the lack of an agreed biocorrelate of protection.

I would be reluctant to start large trials for vaccines without having such evidence.

This is an addition to my earlier contribution to the consultation, which is based on the discussions at the EDCTP stakeholder meeting on 28-29 October in Paris:

Future Directions

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There is a major need for a multisite initiative that would allow field validation of several candidate diagnostics against gold standard, importantly also in conjunction so that complementarity and optimized algorithms can be established, for adult as well as paediatric TB. There is in addition need for an initiative that allows testing the most promising assays and combinations of assays in diagnostic trials focusing on patient-important outcomes.

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The role of EDCTP

EDCTP should fund pragmatic trials of combined TB-HIV interventions. These will likely need to have community-randomized designs and alternative designs need to be considered to improve fidelity.

Diagnostic trials have thus far not been a primary area for EDCTP but should be considered. Other trials should allow for add-on studies in which e.g. biomarkers can be evaluated for their triage potential.

With regard treatment, EDCTP should focus on phase 4 trials of licensed drugs aiming at finding a shorter, safer and more effective regimens. Since for second-line regimens these trials may be difficult to conduct in SS Africa alone, combined multicenter trials with non-African sites (e.g. former Soviet Union, east Asia) need to be considered.

Key players in each of these areas are the WHO and the Stop TB Partnership, and major funders such as the Bill and Melinda Gates Foundation. USAID may play a funding role in TB-HIV integration. For new drug regimens, additional funding agencies with which synergies may be found includes UNITAID; other players in this field include the TB Alliance and the Critical Path Initiative.

The role of EDCTP

This is an addition to my earlier contribution to the consultation, which is based on the discussions at the EDCTP stakeholder meeting on 28-29 October in Paris:

EDCTP should strongly consider a call for a multisite diagnostic trial consortium that could validate candidate diagnostics for adult and paediatric TB as they come out of the pipeline, i.e. an on-going multicentre study in which new assays can be included sequentially or simultaneously. This would greatly accelerate the evaluation of such



new assays and assay combinations, such as add-on and triage strategies.

Such a consortium should ideally be built around existing EDCTP-supported TB vaccine trial sites. This will bring major efficiencies because these sites have quality-assured gold-standard culture available, optimized capacity for TB diagnosis in infants and children and established sample repositories. The sites in such a diagnostic consortium should furthermore use the existing capacity, or build additional capacity, for diagnostic trials of the most promising assays and combinations of assays for patient-important outcomes. This generally means involving several smaller health facilities in order to reflect routine practice and allow evaluation of heterogeneity in outcomes due to variation in patient populations and operator proficiency. The designs for such trials should be innovative with a view to limiting their sample size and duration, and allow adding study arms (cf the MAMS design). It is of primary importance that such studies are aligned with TB control priorities, and be able to do gold-standard drug resistance testing. Therefore consortium sites should have close links with the national TB control programs and national TB reference laboratories, and the consortium should include a partner with programmatic expertise to establish and maintain these links.

EDCTP should finally consider making this a brokered rather than a competitive call. This approach has proven very successful for TB drug trials (PANACEA consortium), and the lessons learned from this initiative should be used to guide future directions for a diagnostic trial consortium.

Prof Stewart Cole

EPFL

Current status of the field

Occasional lack of political will and secure, sustainable funding

Future Directions

There are a few new drugs nearing clinical trials, some arising from European initiatives, and these should be fed into EDCTP

The role of EDCTP

EDCTP should maintain and expand its advocacy profile and ensure continuity with other EC funded initiatives as part of FP7 and a joined-up strategy.

Dr Luis Cuevas

LSTM

Current status of the field

Access to diagnostics at the point of consultation

Access to treatment at the place of residency

Access to both HIV and TB monitoring at locations where it is easily accessed and affordable

Future Directions

Very good. It requires a combination of tools/approaches and a health system that supports these packages.

The role of EDCTP

National health systems



National control programmes
International funders
Academic Institutions
WHO

Dr Gerry Davies
University of Liverpool

Current status of the field

Shorter or more effective treatment for active and latent tuberculosis will be a critical component of future TB control strategies. The key challenges currently are:

1. How to select the best doses and combinations of existing and novel drugs for Phase III trials, given the relatively limited capacity available and high cost of trials
2. How to coherently develop new HIV-TB co-treatment strategies in light of new ART guidelines

Future Directions

Among the key areas where advances may be made are the following:

1. Improved bacteriological or host biomarkers of "sterilizing activity" and ability of regimens to prevent relapse after treatment
2. More efficient innovative Phase II or II/III selection designs based on time-independent endpoints and incorporating sequential elements
3. Better use of preclinical information in planning early phase trials using novel technologies and pharmacokinetic-pharmacodynamic modelling approaches
4. Better support for pharmacokinetic, pharmacogenetic and drug-drug interaction studies conducted within Africa which may facilitate deployment of TB-HIV co-infection strategies.

The role of EDCTP

EDCTP is uniquely placed to support collaborative activities that may contribute to these goals. In particular the following may offer useful opportunities to build on what has already been achieved by EDCTP and other EU programmes:

1. Support regional or continent-wide clinical trial networks capable of supporting Phase II and III trials. Phase II trials are a particular bottleneck at present and the laboratory capabilities required can only be created by sustained and intensive investment in quality and personnel. A good example of such a model is the PanACEA consortium and its recent expansion to sites in Blantyre and Maputo. Europe and Africa need a counterpart to the US TB Trials Consortium model that does not focus too excessively on South Africa. EDCTP2 could be a unique opportunity to achieve this.
2. Expand support for PK-PD studies and analysis. The PKPDia consortium and TESA-sponsored efforts involving the main Sub-Saharan centres are good examples of what can be achieved with little funding. Investment in training for clinicians and post-doctoral scientists is the key to carrying out these studies well with bioanalysis centred in a few quality-assured sites. Such studies would greatly enhance our understanding of the outcomes of clinical trials conducted in the region.
3. Improve linkages with preclinical science and industry. Co-funding of PanACEA activities by Sequella and donations from Sanofi are good examples of a new possible co-development model for TB drugs. Other European initiatives such as PreDiCT-TB (www.predict-tb.eu) and MM4TB (www.mm4tb.org) also have obvious potential linkages with a regional clinical trials network with significant capacity for high-quality phase II trials and engagement in a public-private development model.



Dr Bouke de Jong

ITM

Current status of the field

Case detection, quality assured laboratory services at sufficiently decentralized level with appropriate biosafety in place, implementation of novel diagnostics and treatment regimens for MDR-TB to reach the high risk groups, measuring the impact of interventions on transmission of TB.

Future Directions

New tools are available, although their implementation poses challenges and leads to confusion on the gold standard. We need better ways of following treatment response, also in clinical trials of new TB medicines. The gap in diagnosing and treating MDR-TB can now be closed with improved diagnostics and treatment.

The role of EDCTP

EDCTP can play a major role in recognizing African leaders and helping them to stay involved in African led science, at multiple levels, through e.g. pre-doctoral and post-doctoral fellowships. EDCTP can also engage the next generation of European scientists to engage in tropical infectious diseases research by funding pre-docs. Moreover, EDCTP can fund projects/studies that address the above challenges and opportunities, including yet also beyond clinical trials. Lastly, the newly established supranational TB reference laboratories in the African region will play an important role in supporting such studies, as well as the national reference laboratories in the region. In the absence of sustained funding for such reference tasks, this would be an excellent niche for EDCTP.

Prof Keertan Dheda

UCT

Future Directions

Important priorities I feel for TB research are as follows:

1. I strongly feel that we need to encourage innovation and product development that will benefit diagnostics, drugs and vaccines. We need to translate our basic science research into tangible products that will benefit society in Africa. Therefore, I strongly suggest innovation-related calls, focussing on product development, where there can be linkage with commercial partners, both in Europe and in Africa. This will encourage technology transfer between continents as well as capacity building. I think this should be encouraged in all calls.
2. Drug-resistant TB is now a burgeoning concern in Africa. In South Africa, there is a widespread systematic release of incurable and therapeutically destitute cases back into the community. We are back at the stage where there are no more effective drugs for TB and sanatoria are being reopened. This issue urgently needs to be addressed and various aspects of drug-resistant TB, including epidemiology, transmission, diagnosis and new regimens for XDR-TB need to be addressed. In the South African TB programme, despite drug-resistant TB forming less than 3% of the total case load, it is already consuming 65% of the entire NTP budget, a scenario that is clearly not sustainable, and threatens to destabilise many TB programmes in Africa. Thus, the issue of drug-resistant TB is a major priority. Transmission should be an important area of focus. We need to prioritise things other than a drug pipeline. On this vein we now need testing of regimens not just individual drugs
3. In terms of vaccines, we need to start afresh with understanding correlates of protection. There have been recent vaccine failures and what we have realised so far is that everything that we understood about TB immunology has been fundamentally incorrect! We need novel and fresh approaches to look at correlates of protection. It is only by doing this that we can select appropriate vaccines.
4. With regard to diagnosis of TB, we need more research on how to cobble together different types of diagnostics at point-of-care and in the lab, to maximally benefit tuberculosis. Thus,



integration and algorithms are as important as single diagnostics themselves. There is no “one-size-fits-all” and therefore how we combine different approaches (Xpert, smear, LAM, culture, NAATS etc) is critical.

Prof Andreas Diacon

Task Applied Science & Stellenbosch University

Current status of the field

Need better drugs for treating tuberculosis. Those must be free of resistance, compatible with ARVs, safe, allow short treatment regimens and be affordable. We need biomarkers for the evaluation of treatment effects and better understanding how resistance is created and how it can be prevented.

Future Directions

The prospects are good but a lot of hard work is needed.

The role of EDCTP

Keep doing what you were doing and try to keep the admin simple. Promote African leadership.

Mrs Shiva Dustdar

RDI Advisory

The role of EDCTP

In my view, EDCTP should fund PDPs in its targeted disease area in collaboration with pharma companies. It should strive to be more industry oriented in its decision making approach while meeting its policy objectives. Lessons should be learned from EDCTP1 in particular its absence from the malaria vaccines trials.

Dr Kathleen Eisenach

University of Arkansas for Medical Sciences

Current status of the field

- Lack of point-of-care TB diagnostics
- Lack of understanding dynamics of TB transmission
- Lack of reliable health care systems in both rural, urban and city settings - to access active TB cases earlier and ensure TB drug delivery during course of treatment

Future Directions

New technologies will aid advancement of TB diagnostics; however studying TB transmission is more challenging and there is not much research in this area thus advancement in this area is not promising

The role of EDCTP

Continue to support clinical research which focuses on evaluation and implementation of TB diagnostics regarding TB transmission, collaborating with CDC which is strong in TB epidemiology would benefit investigations in this area

**Prof Sebastien Gagneux**

Swiss Tropical & Public Health Institute

Current status of the field

- Delays in diagnosis and treatment, leading to continued disease transmission
- Increases in drug resistance
- Co-morbidities

Future Directions

- Rapid diagnostic tools
- Better drugs and vaccines

The role of EDCTP

By funding translational research and the creation of research capacity in developing countries where TB is endemic.

Dr Alberto Garcia-Basteiro

Manhiça Health Research Center

Current status of the field

Great challenges ahead of us. New opportunities to make progress in TB Research in many fields.

Challenges:

Prevention:

- To come up with effective vaccine. Improved IPT algorithms are also needed for high burden HIV areas, and they have to be defined through clinical trials.

DIAGNOSIS: Further refinement of current molecular tests is a need. POC tests are a real need for those settings without good laboratory infrastructure. Second line DST tests have to be a priority to monitor DR patterns and improve DR treatment

CONTROL: New improved strategies for TB control have to be tested. Modified DOTs strategies have to be further studied, since the current DOTs does not work in certain settings.

TREATMENT:

Development of new drugs that we could use for both sensible and DR TB. We have to elucidate the role of non-steroidal anti inflammatories and repurposed existing antibiotics for TB treatment.

Future Directions

a) The support of a diagnostic platform / consortia seems a need in order to ensure there are sites ready to test new diagnostic devices/tests, They could set up a standardized data collection system for TB diagnostics evaluation, with current available tests for different samples from different age groups (including paediatric), and risk groups (HIV). They would partner with product development companies to accelerate quality validation studies in African settings.

b) To support the conduction of innovative trials, including repurposed antibiotics already available in those countries enduring the highest burden of disease that haven't been tested yet. In this line, testing non-steroidal anti-inflammatories (ibuprofen, aspirine) as coadyuvant therapies, seems an innovative bet, since



preclinical studies have shown very interesting results in both decreasing bacillary loads and increasing survival. These studies with anti inflammatory, or profibrotic agents, if they prove efficacious, would be very cheap drugs, already existing in high burden countries, which would ease regulatory approval processes. Moreover it will be hard to find pharma companies to fund these studies, since profit would be scant.

c) To ensure we keep upgrading existing African sites with the infrastructure needed for more demanding studies, in terms of lab capacity and quality control measures.

d) Phase I vaccine trials should definitely be supported by EDCTP. These trials are not easily funded by many agencies, and since safety (and preliminary efficacy) in African children/adolescents/patients is a must, I think EDCTP would always play an important role in this phase of vaccine development.

e) I would also support the idea of including operational research studies, as well as other epidemiological research relevant for designing or optimization of clinical trials. We also need to know whether the product or results of clinical trials are applicable and what are the system limitations or problems that might be encountered in the implementation of new tools for TB control. These studies will provide important information to better put in practice or evaluate apparently successful interventions.

The role of EDCTP

EDCTP has to continue supporting clinical trials in Africa, without neglecting capacity building activities.

a) Continuous support the existing successful platforms are key to accelerate drug, vaccine and diagnostic clinical trials.

Key partners: Established Research institutions, Areas, TBVI, TB Alliance, WHO, NTPs, World Bank, Global Fund, EIB, among others.

Dr Jan Gheuens

BMGF

Current status of the field

Poor health systems, underperforming products for HIV-TB setting

Future Directions

New performant and affordable diagnostics. New short TB drug regimens that are equally effective in drug sensitive and drug resistant TB. Paediatric drug formulations

The role of EDCTP

Fund R&D, in particular late stage clinical development of drugs and vaccines, in coordination with DAIDS (NIH), the TB Alliance and AERAS, UNITAID, the Gates Foundation and bilateral donors like USAID.



Prof Steven Gillespie
University of St Andrews

Current status of the field

There is a pressing need for new drugs and better diagnostics to control the continent wide pandemic. Developing the capacity of African researchers and institutions is urgently required to allow a local and appropriate solution to emerge. A true partnership with Europe is required to harness complementary skills and resources into a comprehensive programme.

Future Directions

The challenge of new diagnostics and therapeutics for TB is so large that only a Europe wide consortium like PanACEA can bring together the necessary skill set and resource to deliver real progress in this field

The role of EDCTP

The EDCTP can act not only as a funder but also as a catalyst of collaboration to unite key players on the two continent into a unified development programme

Prof Peter Godfrey-Faussett
UNAIDS

Current status of the field

Community involvement; earlier case detection; better diagnostics; HIV control.
Management of drug-resistant disease; new drugs.
Structural and health system weaknesses.

Future Directions

Community involvement and household interventions integrating Tb with HIV, MCH, malaria and other conditions according to local situation.
New diagnostics - gneXpert and beyond

The role of EDCTP

Linking closely to National Programmers and Planners and listening to their priorities.
Building capacity at local level for rigorous research, both randomised and observational.
Linking to long-established, field based research projects that have built community confidence with local clinics and their communities.
Strong European Universities in several EU member states

Prof Martin Grobusch
AMC

Current status of the field

- Failing public health system/basic tuberculosis care facilities and outpatient/follow-up facilities
- Lack of access to inpatient/outpatient services
Inadequate/failing supply chains for diagnostics/drugs
- Lack of a full set of DR-TB drugs which allow for comprehensive 6-9 months tb regimens of (M)DR-TB
- Lack of a sterilizing immunity-conferring vaccine

Future Directions

Health systems research alongside the development of novel diagnostics/drugs/vaccines to safeguard the efficacy of newly introduced tools (new)
Optimized drug regimens to shorten DS-TB treatment (existing/new) -



Optimized drug regimens to facilitate DR-TB treatment (existing/new)
Improved vaccines (new)

The role of EDCTP

EDCTP can best contribute by means of teaming up with other major funding bodies including the BMGF in order to finance larger-scale trials. Keeping clinical trials in the focus will allow for most efficient concerted efforts in the areas outlined above.

Dr Leander Grode

Vakzine Projekt Management GmbH

Current status of the field

Although BCG consistently protects against disseminated TB (TB meningitis and military disease) in young children in observational studies, it has limited protective effect against either pulmonary TB in children (>75% of the paediatric disease burden) or adult TB. It is not effective in either reducing the brunt of the childhood TB burden or having a significant impact on TB control. There is therefore an urgent need to develop more effective TB vaccine. Moreover, HIV-infected and immunodeficient infants are at risk of BCG-related complications with a risk of disseminated BCG disease ("BCGosis") in HIV-infected infants. BCG is associated with T cell activation, which may lead to increased HIV transmission risk and more rapid HIV disease progression in Sub-Saharan African infants.

Future Directions

A new vaccine for prevention is needed to control TB in cost efficient manner. VPM1002 is one of the promising low cost prime vaccine in the development pipeline. Based on available data for pre-clinical and clinical development of VPM1002 so far, it should be at least as immunogenic as the current strain and should have better safety profile than current BCG. A TB vaccine that can be used in settings with high burden of HIV is of critical importance given the unabated TB epidemic in settings with high burden of TB and HIV. Financial support from this call for the planned further clinical development of VPM1002 will contribute substantially in obtaining safety and immunogenicity data on VPM1002.

The role of EDCTP

In order to ensure a cost efficient vaccine as a final product, the development cost needs to be covered by organizations such as EDCTP otherwise the high risk investments from industries would then lead to higher prices of the final marketed product. Also, The rights of both HIV-exposed and unexposed infants in Sub-Saharan Africa to a safe and effective vaccine need to be considered. A safe recombinant BCG vaccine at birth would offer such a benefit. Key players is Serum Institute of India Ltd and can be interacted with through their collaborating partners Vakzine Projekt Management GmbH.



Dr Richard Hafner
NIAID/NIH

Current status of the field

- POC Diagnostics and rapid DST
- Development of new regimens that will significantly shorten treatment duration for both DS and DR TB
- Develop new therapies with better tolerance and fewer drug interactions

Future Directions

Promising areas are -

- Optimizing use of high dose rifamycins in combinations
- Determining safety best use of bedaquiline for MDR TB and possibly later for DS TB
- Determining roles of new nitroimidazoles, oxazolidinones in improved combination for DS and DR
- Assess BTZ compounds in early phase trials
- Assess potential roles of host-directed therapies to improve treatment outcome
- Surveillance of resistance and assisting with development of new DST for new drugs

The role of EDCTP

Maintain a robust and independent research agenda with an emphasis on performing Phase II trials of new combinations with old and new TB drugs and possible HDT drugs

Prof Mark Hatherill

University of Cape Town

Current status of the field

Key challenges (TB vaccine field): (1) Lack of a correlate of vaccine-induced protection against TB disease. (2) Lack of a validated correlate of risk for TB disease in infants and adults. (3) Lack of understanding of the immune mechanisms underlying the peak incidence of TB disease in infancy and adolescence-adulthood, and correspondingly the nadir of TB disease incidence in young children. (4) Lack of understanding of the potential role of immunotherapeutic interventions, including both drugs and new vaccines, to shorten/improve efficacy of TB drug therapy. (5) Slow pace of the TB vaccine development pipeline from Phase 1 through Phase 2b.

Future Directions

(1) and (2): Need studies of immune correlates of risk and protection in all new TB vaccine efficacy trials. (2) and (3): Need new "immuno-epidemiologic" cohort studies that bridge the age-TB incidence inflection points at 3-6 years and 10-13 years. (4) Need small safety and immunogenicity studies of new/existing immunotherapeutic drugs or vaccines in TB patients on treatment, to pave the way for future proof-of-concept efficacy trials. (5) Need to accelerate progression of new TB vaccines from Phase I trials in developed countries to Phase 2/2b trials in high TB burden countries.

The role of EDCTP

(1) Foster early involvement in trial planning between vaccine developers in developed countries and scientists and clinical triallists in high TB burden countries where TB vaccine efficacy trials will be performed. (2) Fund new immuno-epidemiologic cohort studies in infants, children, and adolescents. (3) Fund immuno-therapeutic Phase 1-2 drug/vaccine studies. (4) Fund Phase 2 TB vaccine trials in high TB burden countries.

**Prof Michael Hoelscher**

Ludwig-Maximilians- University Munich, Germany

Current status of the field

The two main issues that can have the most immediate impact on the health care system are the development of novel therapeutics and diagnostics.

Drug development:

If pharma is interested at all, they focus on drug resistant TB and the development of their individual drug candidate. There are 3 major and several smaller non-commercial groups established (NIH funded TBTC/ACTG, Gates funded GTBA and EDCTP funded PanACEA). All groups communicate well and have complementary drug portfolios but also research strategies.

Diagnostic assay development:

The development of Xpert MTB/Rif was a major achievement and has closed the gap in TB diagnostics for smaller district hospitals. However a useful point of care assay /bedside assay is still missing.

As TB treatment becomes more complex an assay that can monitor treatment success is urgently needed as well as a rapid method to identify resistance against the major drugs

Future Directions

Drug development: The pipeline of drugs that are ready to enter phase II is becoming critically small. There are a number of new promising drug candidates but they are still in the preclinical phase. Trials that advance drugs faster from phase I into phase II and III are needed. It is also essential to think early about combining drugs in novel regimens.

Assay development: A number of novel diagnostic approaches will reach clinical evaluation in the next 12-24 months.

The role of EDCTP

Drug development: In this area of research, large enough networks with comprehensive expertise are required. As they have to establish complex expertise and drug development is a long-term, multiple studies requiring exercise, the networks need to be funded for an extended period of time (with interims review). It is however important that pluralism in drug development is maintained.

Assay development: Continuous funding (once a year) of smaller, proof of concept studies is required as new technologies/assays emerge. If funding is given out in a single call, there is a risk that projects will be applied for prematurely.

Dr Amina Jindani

St Georges, University of London

Current status of the field

The standard 6-month treatment regimen is too long. In order to meet the UN Millennium Development Goals treatment duration must be significantly reduced.

Future Directions

The prospects of being able to safely increase the daily dose of rifampicin offers the best hope for treatment reduction in the next few years.

The role of EDCTP

EDCTP can support such Phase III trials that are carried out by the INTERTB Group here at St. George's, University of London. This group has a track record of delivering low cost pivotal trials which can be introduced into national treatment control programmes.

**Prof Beate Kampmann**

MRC Unit, The Gambia & Imperial College London

Current status of the field

POC diagnostics for children

Correlates of protective immunity for vaccines and prediction of disease

Growth inhibition assays for the assessment of mycobacterial survival are poorly standardised and implemented

Future Directions

Immunological studies of childhood TB, household cohorts as a possibility to assess transmission and immunity in a more controlled environment

The role of EDCTP

Facilitate set up of prospective cohorts which also include banking of well characterised samples expansion of clinician-scientist training opportunities

expansion of capacity in host defence studies in the African setting, led by established institutions who can network in this area and provide training +/- European partners

Dr Lynn Katsoulis

Triclinium

Current status of the field

TB Vaccines: The ability to do several concurrent Phase 2 type clinical trials to determine the optimal dosage regimens for single vaccines and optimal combination regimens to induce effective immune responses to vaccination.

TB treatment: The PanACEA model for selecting optimal treatment regimens seems as if it will be cost effective strategy. It is the logistical aspects of collecting high quality data in an efficient and affordable manner that will determine the speed at which the future trials can be conducted.

Future Directions

TB Vaccines: Apart from the vaccines being developed by Aeras, the VPM 1002 and RUTI vaccines are both in late stage clinical development. The RUTI vaccine requires funding for the Phase 3 clinical trials.

The role of EDCTP

The consortium mentioned above requires funding to conduct a Phase 3 clinical trial in Sub-Saharan Africa to determine the efficacy of the RUTI vaccine as a therapeutic vaccine.

Archivel will be forming similar collaborations with consortia in Asia and South America to determine the efficacy in the various regions. The safety data from the three relatively small Phase 3 clinical trials will be combined to support registration in all regions.

TIA would provide the co-funding, BioVac will be involved in the packaging and distribution of the vaccines throughout Sub-Saharan Africa and Triclinium will lead the implementation of the clinical trials in EDCTP sites throughout Africa with input from leading TB vaccine clinicians and experts from around the world.

Prof Stefan Kaufmann

Max Planck Institute

Current status of the field

Key issues include:



- Coinfection with HIV and *M. tuberculosis*
- Frequently TB and AIDS are treated independently and not as two diseases in one patient
- Increasing incidences of multi, extensive and even total drug resistance
- High risk environment such as mining in South Africa
- Lack of adequate diagnosis notably of multi-resistant TB
- Long duration of treatment resulting in compliance failure
- Few appropriate high risk groups
- Relatively low proportion of TB patients even in highly endemic areas requiring large study populations for IIb/III clinical trials
- Few appropriate study sites outside of South Africa.

Future Directions

- Availability of promising drug candidates and drug combinations
- New diagnostic tests (GeneXpert)
- Profound number of vaccine candidates.

The role of EDCTP

- Establishment of coordinated multi-national clinical trial centers
- Harmonization of clinical trials
- Development of appropriate monitoring systems for clinical trials (predictive biomarkers)
- Comparative clinical trials with more than one candidate
- Clinical trials with drug combinations
- Clinical trials with vaccine combinations
- Improved interactions between clinical trial sites, analytical monitoring labs and sponsors.

Key players:

- Clinical trial sponsors
- Clinical trial sites: clinical part
- Clinical trial sites: wet lab part
- Governmental health and research departments
- Non-governmental organisations.

**Dr Herman – Joseph Kawuma**

German Leprosy and TB Relief Association

Current status of the field

The effect of the HIV-AIDS epidemic, lack of awareness of the symptoms and curability of TB, limited access to health services (including those for diagnosis and treatment of TB), inadequate commitment (including financial) by national governments to the control of TB. The apparently increasing emergence of drug resistant TB and access to second line medicines as well as the other resources for the programmatic management of drug resistant TB.

Future Directions

The advances in new diagnostics including the more extensive use of fluorescent microscopy and GeneXpert technology. Greater use of newer communication technologies for improving community awareness but also for collecting programme monitoring information.

The role of EDCTP

I am not sure as this will be my first encounter with EDCTP but I believe in strengthening the roles of partnerships in order to optimize the contribution of non-government players in controlling TB. Research initiatives e.g. in diagnostics, new drugs and vaccine development could be done alongside similar initiatives for other Mycobacterial infections e.g. leprosy and Buruli ulcer.

Dr Hannu Laang

European Commission

Current status of the field

Mechanism of the disease is not understood well enough. This lack of knowledge about the host-pathogen interaction prevents us from developing better drugs, vaccines and diagnostics against tuberculosis.

Future Directions

Significant advances will be made, but it is more a matter of good luck than based on sound knowledge about the disease. Many products need to be tested in the field, but more attention should be given to the selection criteria of new drugs and vaccines.

The role of EDCTP

Good selection criteria for the best available treatment and prevention methods. The whole scientific community should work together.

Prof Christoph Lange

Research Center Borstel

Current status of the field

Key issues:

- Emerging M tuberculosis drug resistance
- TB/HIV coinfection
- Early case finding
- Improving prevention by better identification of those who will develop TB in the future (improving TST/IGRAs)
- Individualize the duration of therapy
- Comorbidities



Challenges:

- Health capacity building, especially personnel
- Emerging *M. tuberculosis* drug resistance
- Complications of treatment in HIV/TB coinfection
- long turnaround time of drug research and development due to the long treatment duration in TB.

Key limitations:

- Limited insight in the mechanisms of susceptibility for TB in individuals with HIV-coinfection
- Lack of an effective vaccine
- Lack of education
- Lacking health care capacities

Future Directions

- Evaluation of biomarkers to individualize the duration of therapy
- R&D in TB vaccines
- R&D in new anti-TB drugs
- R&D of POC tests for TB diagnostics
- R&D in novel methods for preventive therapies

The role of EDCTP

Supporting collaboration of translational oriented European research groups with established sub-Saharan research groups PLUS supporting South-South capacity building

Including European Research Networks, e.g. TBNET (www.tb-net.org) to formulate research priorities and to support research collaborations education and teaching.

Dr Odile Leroy

European Vaccine Initiative

Current status of the field

A lot of progress has been accomplished during the last 5 years in the field of tuberculosis vaccines

The key remaining issues are:

- 1) Discovery: there are still too much unknowns for implementing a rationale screening approaches for new antigens
- 2) Vaccine process development: lack of harmonisation and validation, including lack of comparability of the preclinical results
- 3) Vaccine clinical development: more harmonisation is needed

Future Directions

- 1) Discovery:
 - a. the immune mechanisms regulating the host-pathogen relationship are not enough explored, this includes knowledge in microbiology, molecular biology, and immune-epidemiology
 - b. the immune mechanisms leading to protection
 - c. rational screening of new antigens, including comparative platforms of different antigens in pre-clinical animal models with validated screening functional assays
 - d. to stimulate the innovation by addressing the questions through inter-disease approaches (i.e. to benefit from the other diseases vaccine fields)
 - e. to stimulate the innovation by investigating other mechanisms which could bring breakthrough in understanding the immune mechanisms (role of microbiome, genetics, hormonal regulations, gender)
 - f. to train the scientists on immune/omics/system biology)



- 2) Vaccine development
 - a. invest in comparative platforms of new available technologies for selecting the more cost/time efficient ways
 - i. to improve antigenicity
 - ii. to produce the vaccine (robust, high yield, easy to transfer, cheap process)
 - iii. to improve the immunogenicity (delivery systems, adjuvants, vector based...)
 - b. invest in training scientists on how develop a vaccine (pre-clinical assays, formulation, new technologies deployment and transfer, formulations....)
- 3) clinical development
 - a. rethink the clinical strategy in the perspective of experimental medicine, optimising the early clinical phases (phase I)
 - b. cross analysis of animal pre-clinical and human clinical data to validate models and build new hypothesis, including systematic analysis of potential immune markers for both safety and efficacy
 - c. ensure the comparability of the results by harmonising the safety and immunological criteria
 - d. baselines studies to better understand the burden of disease and to better define target populations
 - e. design clinical development plans to investigate multi-variable criteria which are interfering with the immune response/efficacy/safety such as age, gender, concomitant infections/diseases. Other vaccinations etc...
 - f. training of scientists

The role of EDCTP

- 1) EDCTP role in Europe and developing countries:
 - a. Partners: TBVI, EVI, Research Institutions in EU, and DCs (Pasteur Institute networks, Stop TB network), biotechs, vaccine pharma (EFPMIA and DCVMN)
 - b. EDCTP should take a leading role for the clinical development strategy ensuring the consistency, best practices, best standards, comparability of the different approaches
- 2) EDCTP should invest in the item 3 above as well as the capacity building not only in clinical trials but also in technology transfer (from process development to biomarkers)
- 3) EDCTP should privilege the most promising candidates (not only on scientific excellence but also on feasibility and deployment)
- 4) Because of the EU huge investment, EDCTP needs to think the strategy also to ensure that the knowledge management, IP, business assets of Europeans and their DCs partners are well protected, to ensure that the infrastructures in both EU and DCs will equally benefit.
- 5) EDCTP should continue to promote DCs scientists empowerment and leadership



Dr Christopher Locher

Vertex Pharmaceuticals Incorporated

Current status of the field

The key issues are building infrastructure, laboratory capacity, new TB drug regimens, and funding.

Future Directions

The prospects include an increased commitment by non-government and some private organizations to address the problems and disparity of health care and pharmaceutical development.

The role of EDCTP

By influencing governments and non-government funding agencies, as including those in the United States (USAID, CDC, Clinton and Gates Foundations, etc.) and in the Developing World (South Africa, UN) as well as private companies (oil and mining companies) in Africa to harmonize efforts and provide additional funding and support.

Dr Camille Locht

Institut Pasteur de Lille

Current status of the field

The lack of sufficient basic knowledge on the mechanism of protection against tuberculosis

Future Directions

As we learn more about the immune mechanisms and markers of protection, we will be able to produce novel effective vaccines

The role of EDCTP

EDCTP can help by fostering close interactions between endemic countries and other countries. Only by doing so we will be able to make significant contributions to the understanding of immune mechanisms related to protection against tuberculosis

Professor Diana Lockwood

London School of Hygiene & tropical Medicine

Current status of the field

Leprosy:

Promoting early case detection, Switching off inflammation post treatment, Compliance.

Regarding leprosy the key challenges are the development of alternative chemotherapy regimens such as single monthly regimens.

The other need is to develop ways of switching off leprosy associated inflammation

Future Directions

Promotion of case detection, Better immunosuppressants, Less toxic drug regimens.

Funding trials in leprosy endemic regions in Africa testing out single monthly dose regimens.

The role of EDCTP

Promoting work on management of nerve damage in leprosy, Promoting work on better drug regimens.



Leprosy programmes at ALERT Ethiopia, GLRA supported national programmes in Uganda and leprosy programme in Mali.

Prof Lut Lynen

Department of Clinical Sciences ITM, Belgium

Current status of the field

- The continued problem of late presenters in HIV, fuelling further the TB epidemic
- The emergence of MDR-TB
- The lack of evidence on how to best use new drugs and diagnostics
- Lack of knowledge on best practices to perform infection control in high burden TB health care setting.

Future Directions

- The new diagnostic tools
- The new TB drug pipeline and the possibility to combine them with second-line ART
- Search for biomarkers to facilitate evaluation of treatment

The role of EDCTP

Support to National TB programs to establish reference laboratories, collaborate with TB alliance, the IUTLD, support academic institutions to develop clinical trial capacity for innovative approaches and/or alternatives to clinical trials

Dr Leonard Maboko

NIMR - Mbeya Medical Research Centre

Current status of the field

Key issues include development sensitive TB diagnostics to be used at the point of care and shortening of TB treatment. The developed Xpert MTB/Rif cannot be used at the primary level of health care. Long TB treatment is still a challenge.

Future Directions

Future direction should include development of both a sensitive diagnostic to be used at the point of care and TB drugs that can shorten the TB diagnosis

The role of EDCTP

EDCTP should contribute by supporting drug trials that aim to shorten TB treatment and development of TB diagnostic assays that are sensitive and can be used at the point of care level.

Dr Dermot Maher

Wellcome Trust

Current status of the field

Lack of human capacity to undertake high quality diagnosis, treatment and follow-up of people with TB, to manage effective TB programmes (at district, provincial/regional, national and international level), and to undertake high quality research.

Future Directions

The prospects depend on a massive effort to improve the quality of a) the individual clinical management and follow-up of people with TB, b) the management of TB programmes (at district, provincial/regional, national and international level), and c) research (laboratory, clinical and population-based). This in turn depends on improving the quality of medical education in medical schools, the quality of training of other key health staff such as nurses



and clinical officers, the quality of research training of researchers, and improving the retention of good quality staff in Ministry of Health positions. This spotlight on quality is crucial to be able to make the most of technological developments in TB control (new diagnostics, drugs and vaccines).

The role of EDCTP

EDCTP could play a stronger role in investing in increasing the cadre of well trained researchers in Africa, and in expanding the scope of research to cover key areas of research beyond clinical trials (e.g. programmatic and health systems research).

Prof Carlos Martin

University of Zaragoza

Current status of the field

BCG, the present vaccine against TB in use today, is not protecting against pulmonary form of TB.

Future Directions

A new TB vaccine with a better protection against pulmonary TB will have a tremendous impact in TB transmission.

The role of EDCTP

Sponsor of clinical trial for new TB vaccines.

Other key players: European Union and Bill Gates Foundation, biopharmaceutical companies interested in TB vaccines

Dr Alberto Matteelli

Department of Infectious and Tropical Diseases at the University Hospital in Brescia

Current status of the field

Financing, managerial capacity, health structure strengthening

Future Directions

TB vaccine, Short (2-months) treatment regimens, molecular diagnostic tests for TB and MDR-TB

The role of EDCTP

Funding of fundamental clinical trials and research, connecting northern Institutions with southern institutions and control programs

**Prof Markus Maurer**

Karolinska Institute

Current status of the field

Diagnosing XDR TB and improvement of treatment of MDR/XDR TB including adjunct therapies to shorten treatments and to reduce unproductive inflammation (in the lungs)

Better understanding and insight in TB vaccine(s) / role of repetitive exposures to MOTT and M.tb.

Treatment: Role of co-infections, limiting damaging inflammation that goes along with active TB.

MDR / XDR TB strains have shown in different studies aberrant immune responses. This is clinically very relevant, i.e. whether mutations in M.tb do not only affect response to antibiotics, yet also anti-M.tb immune responses, as well as the quality and quantify of the host response.

Future Directions

A number of new studies showed that anti-inflammatory drugs can help to reduce lung damage, they appear also to accelerate M.tb culture conversion.

We have recently successfully finished a phase I study using MSC to treat patients with MDR/XDR. It was safe and the individuals (n=30) showed promising clinical results.

Phase II clinical trials are now needed to test whether the combination of anti-inflammatory drugs/therapies can aid to achieve better clinical results. This has to be clinically sound and guided by relevant marker analysis. Not only the quantity and quality of the immune responses is important, yet the timing of these anti-inflammatory treatments in the course of TB.

I predict that multimodal therapies, like in cancer, will change the face of future anti-TB therapies: not only the bug, yet also the patient needs to be treated. Non-productive immune responses can be changed into focused, non-damaging immune responses that aid to control M.tb infection, even if the patient is infected with an XDR TB strain.

The role of EDCTP

Funding of clinically relevant and promising phase II studies addressing new treatment modalities in TB.

This is most cost-saving using local structures and resources in sub-Saharan Africa aligned with experienced academic institutions with an excellent track record concerning clinical trial development.

Dr Harriet Mayanja-Kizza

Makerere University

Current status of the field

1. Diagnosis of active TB. Smear positive is a late stage diagnosis.
2. Treatment compliance - especially after the intensive phase of treatment
3. Management of MTB infection
4. Chronic malnutrition and crowding in sleeping places

Future Directions

1. Estimation of MTB load in body (rather than sputum exam mainly - here I see immune markers as better prospects of estimating MTB load in the body).
2. Shorter more efficacious therapy; especially with new drugs.
4. New single drug for LTBI - not part of the treatment regimen



3. Nutritional mechanism of disease progression - LTBI seems to progress "below certain weights"

4. Vaccine to halt progression of latent TB to active disease - given at adolescence eg 10-12 years together with HPV, mumps, tetanus and other vaccines for this age group.

5. Adjunct therapy eg nutritional supplements, NSAIDS (as shown in some recent studies) etc that would improve sputum clearance

The role of EDCTP

1. LTBI clinical trials persons with HIV may be the best study population - but not with drugs of the EHRZ regimen.

2. Molecular diagnosis of MTB load, disease - host or bacilli factors - population studies with promising current strategies eg nucleic acid, cytokine/chemokine markers. This is non invasive - may be time to start testing these in larger populations. So far they are not perfect but promising.

3. Collaborative work best strategy - sets of high endemic countries with Northern partners through EDCTP. These multi national studies appear costly but they offer better chances of getting enough data and without the need to repeat same studies in different countries.

4. Research question could be broad – e.g. Studies that would impact on TB outcomes in the medium term - towards control of TB in high endemic countries.

Prof Helen McShane

Company: University of Oxford

Current status of the field

My comments relate to vaccine development. It is essential we continue the momentum gained in the last 10 years, and continue with TB vaccine R&D, in parallel with the perhaps lower hanging fruit of drug and diagnostics development. The first new TB vaccine in infants did not work. We now know that the level of immunity it induced is not sufficient. We do not know if something different is needed or just more. We must be careful not to throw out the baby with the bathwater and be clear as to what we now know, and what we still do not know, as we move forward

Future Directions

Efficacy is the bottom line. We don't know what the animal models mean and we don't know what the immunology means. We will only know what they mean once we have an effective vaccine. So we need to do more efficacy trials and find innovative ways of doing and funding them. (Adaptive trial design?)

The role of EDCTP

Work with other funders to continue development, more head to head clinical trials (phase I/IIa) which allow down selection of best and different candidates to put into efficacy trials. Developers may not like head to head trials but funders are in a position to insist on it and is only ethical way to use limited resources.

Dr Corinne Merle

London School of Hygiene and Tropical Medicine

Current status of the field

Insufficient funding for TB research, TB drug development project are longer projects compared to other diseases, lack of surrogate markers to assess quickly treatment efficacy, lack of full understanding TB infectiousness and risk factors of TB disease, lack of involvement of National TB programmes in TB operational research (lack of expertise) to improve TB



control in their own setting.

Future Directions

- Shortening TB treatment with testing new TB regimen integrating new drugs which are in the development pipeline (TB sensitive and MDR-TB)
- Defining what could be the more cost efficient strategy for an earlier detection of TB in HIV patients
- Evaluating the role of certain potential TB risk factors such as vitamin D and the potential benefit of supplementation
- What are the best strategy to improve TB treatment adherence (cash transfer, health supporter)

The role of EDCTP

EDCTP is already doing a lot in terms of funding and such stakeholder meeting can be good platform for a better integration of TB projects and TB teams research. Closer collaboration with the National TB programmes can help to define the best and more useful TB research directions to take.

Dr Pascoal Mocumbi

Manhica Foundation

Current status of the field

Antibiotic resistance tuberculosis bacillus
Multidrug resistant

Future Directions

To combat the increasing emergence and dissemination of antimicrobial resistance pathogens from a multidisciplinary approach to fight poverty and disease.

The role of EDCTP

EDCTP is already considering private actors as stakeholders with whom to consolidate collaboration in the fight against disease and poverty research

Dr Perry Mohammed

Janssen

Current status of the field

Diagnosis, retention in care and MDR TB
Coinfections treated separately like HIV in various centres

Future Directions

Treatment of MDR TB
POC testing



Prof Maowia Mukhtar

Institute of Endemic Diseases

Current status of the field

Early case detection, diagnostics, treatment duration, and effective vaccination

Future Directions

New drugs and diagnostics

The role of EDCTP

Invest in product discovery and in clinical trials plus health system research. The key players are laboratory scientists, Pharma, field researchers and health providers in endemic countries. Interaction could be by developing collaborative activities funding of activities, scientific meetings and conferences.

Dr Carol Nacy

Sequella

Current status of the field

New tools to shorten diagnostic algorithm, shorten and improve treatment for all forms of TB, including TB with underlying AIDS. A better understanding of disease course and identification of biomarkers and surrogate endpoints would facilitate creation of new and better tools.

Future Directions

High probability of new and improved diagnostics and new and better drugs. New and more effective vaccines will require significantly more effort and time, as an understanding of protective immunity is lacking.

The role of EDCTP

Most important that there be more than one approach, and more than one voice, to ensure that innovation has the maximum probability of occurring. OK to interact with other funders, but an independent voice and approach to problem solving is essential. Do not lose the EDCTP independent voice!

Dr Alasford Ngwengwe

School of Natural Sciences, Zambia

Current status of the field

The major issues are the low uptake of early detection and completion of TB treatment. The poor treatment is due to low compliance by clients as well as the poor delivery health system

Future Directions

The prospects for making significant are high by improving the health delivery system and increasing the community support for the rural poor

The role of EDCTP

EDCTP can help by also looking at the health delivery system in addition to the clinical side of the disease

**Prof Mark Nicol**

University of Cape Town and National Health Laboratory Service

Current status of the field

1. Delayed diagnosis
2. Poor linkage to care
3. Weak control programmes
4. Outdated treatment retention strategies
5. Losing the battle against MDR-TB

Future Directions

Innovative and widespread use of new rapid diagnostics; technological solutions to improve linkage to care and adherence; treatment shortening regimens; treating drug-resistant TB as a public health emergency; develop better tools for to enable tailored treatment for highly resistant TB.

The role of EDCTP

Develop a programme of research to enhance the full package of delivery of care from diagnosis to treatment completion; focus on drug-resistant TB; look at innovative solutions.

Dr Evangelia Ntzani

School of Medicine Ioannina, Greece

Current status of the field

Key challenges: 1) health system strengthening (human resource and laboratory), 2) TB-HIV collaborative activities, 3) Multi-drug resistant (MDR-TB) and Extensively Drug Resistant (XDR-TB).

Future Directions

Provide normative guidance and generic tools to member states for intensifying TB prevention and control efforts towards attainment of global, regional and national goals and targets; provide technical support to countries for accelerating and scaling up implementation of all interventions in the Stop TB strategy; especially strengthening core DOTS services, TB/HIV collaborative interventions, management of drug-resistant TB, and engagement of all care providers in the prevention and control of TB; support countries in accessing and managing additional resources (including anti-TB medicines and other commodities) from global, regional and national partnerships for the fight against TB; provide technical support to member states for strengthening procurement & supply management systems and laboratory services and networks; support member states to strengthen surveillance, monitoring and evaluation systems, assess the burden of TB and establish trends through periodic conduct of TB disease prevalence and tuberculin surveys; strengthen capacity for the conduct of operational research for evidence-based decision making.

The role of EDCTP

Accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics, with focus on phase II and III clinical trials

Prof Andrew Nunn

MRC Clinical Trials Unit

Current status of the field

The continuing development of diagnostics which can rapidly identify patients with TB are critical to effective case finding and early commencement of anti-TB treatment. Early registration of promising drugs will enable trials to be done to assess the role of new and



hopefully shorter regimens in the treatment of all forms of TB. Concerns about the safety of bedaquiline may prove to be a limitation as is the delay in obtaining registration of delamanid.

Future Directions

I am not good at prediction but certainly hope that significant advances can be made in the treatment of both drug sensitive and drug resistant TB in the next 5-10 years. The prospects for dramatically shortening current treatment duration may be best for MDR-TB.

The role of EDCTP

EDCTP can assist with funding research groups with a proven track record who present proposals of a high standard. Key players would include the current PANACEA consortium and the MRC Clinical Trials Unit in London. Interaction in the form of discussion of new ideas before completion of LOIs or lengthy application forms would be beneficial to all concerned.

Mrs Mihaela Obrovac

Croatian National Institute of Public Health

Current status of the field

Key issues: implementation of rapid techniques for diagnostics; development of POC diagnostic tests, new vaccines and new drugs.

Challenges: access to TB care, administration of existing drugs, treatment outcome follow up (for preventing the development of resistance).

Limitations: inadequate TB and hospital network, insufficient funding of TB control, high rates of HIV coinfection.

Future Directions

- Investments in TB control diagnostics test such as Xpert MTB/RIF
- Detecting smear-positive TB cases
- Wider use of antiretroviral therapy

The role of EDCTP

EDCTP contribution: Funding the research to develop POC test(s) for TB and MDR-TB, new drugs and vaccines; supporting the implementation of national TB programmes and coordinating between different national programmes.

Key players: Ministries of Health in different countries; heads of national TB programmes.

Dr Shreemanta Parida

Karolinska Institutet

Current status of the field

Absolute need to map the landscape in terms of diversities of pathogens (Mtb) - phylogenicity, phenotype, genotype as well as disease manifestation, natural history of the disease in the specific geographic region with regards to the diversities of the human hosts and environment. This would enable us to make strategic planning based on evidences than on estimates or postulates!

Need to harmonise the harmonisers to draw up a standardised SOPs to be able to follow to gather data and collate those for various analyses and strategic planning.

Greater need of communication with increased sharing of data, knowledge and expertise across the TB scientific community in transparent and accountable manner

Urgent need to determine gaps and possibly follow the SWOT analysis at each level to address those gaps to make incremental progress.



Essentials to navigate for bigger picture:

1. Harmonising the harmonisers - bringing everyone onto the same page
2. To do a SWOT (Strength, Weakness, Opportunity and Threats) analysis across all sectors - individual, institutional, country, regional etc. to map the landscape and create a road map through consultative consensus building process
3. To embrace partnership, synergy & symbiosis on active "buy in" endeavours

Future Directions

Create eco-system in each setting to be able to do capacity building in terms of infrastructure as well as trained manpower and process-led systems to be able to do comparative assessment of existing/novel interventions (products) in terms of diagnostics, drugs and vaccines.

Also to do head to head comparative clinical trials than RCTs with individual intervention agent to reduce cost, biases, conflicts of interests to be meaningfully progress towards a viable effective product development.

High time to address our basic approaches for TB vaccine development, so also diagnostics. Support more clinical studies (not intervention or clinical trials, but understanding diversities of host-pathogen-environment interactions) in various settings to study natural history of disease to understand protective immunity better to design effective intervention(s).

Also to do more head to head comparative vaccine trials than individual investigator-driven vaccine trial.

The role of EDCTP

Need to be a honest broker and liaise with other funders to harmonise the funding to be more effective collating efforts than competing or dividing various initiatives towards our battle against resilient Mtb.

It should be a consultative consensus building process engaging various stakeholders across disciplines with a joint ownership and responsibilities.

Harmonisation across funding bodies is absolute key to make sure there is equity.

Increase its efforts in training activities across resource-constrained regions with due diligence and connecting all dots to create networks between the young generations of trainees and to do do more hands on training in those settings with experts from North on a regular basis.

Create e-learning tools to facilitate training of youngsters in resource-limited settings and empower the locals to address their global health issues with global standards (Think Globally and act locally - to be enabled and facilitated).

Dr Kim Pham

Thales Electron Devices SAS

Current status of the field

Early diagnosis of tuberculosis with low cost low dose mobile and portable X-ray imaging detectors is the best way to achieve efficiently the clinical trials, which are needed to progress in the prevention, control and treatment of tuberculosis in sub-Saharan Africa. Actually, instead of requesting the patient to go to the hospital, it will be the general practitioner who will go towards the patient, or at least the patient will be able to easily access a Point Of Care near his home.

Future Directions

Thales and Trixell in France have developed the world's lightest Wifi portable detectors for medical digital radiography : these ultra-light Wifi detectors can come in several different



formats, to fit all clinical use configurations. They are designed to facilitate examination conditions, thanks to their great versatility with several hours of autonomy, exchangeable battery, multi-share, auto-detection and image storage capacity.

The next challenge is to adapt these highly performant products towards the lowest cost by an optimisation of their technologies versus given targeted clinical needs, together with the best performances and the lowest dose.

The role of EDCTP

EDCTP will need to use the best high performance low cost low dose early diagnosis tools for tuberculosis during the clinical trials which will be the mandatory way to achieve new efficient treatments of tuberculosis.

Thales can propose to cooperate with EDCTP on this target, based on their worldwide leadership on this domain of portable digital radiography detectors, to enhance and deploy the best early diagnosis of tuberculosis in sub-Saharan Africa.

Dr Richard Phillips

Kwame Nkrumah University of Science and Technology

Current status of the field

Currently patients with the Buruli ulcer after strong clinical suspicion have either a Fine Needle Aspiration or swab for AFB's or PCR confirmation in one of the WHO reference laboratories in the respective countries. This is not always available. The sensitivity of microscopy is low. Diagnostic confirmation currently relies mainly on PCR. There is the need for new and improved diagnostic techniques and improved capacity in this area. Treatment is currently based on the 8-week daily treatment with combination oral Rifampicin and IM streptomycin which is often administered at the health centres. The outcome is best for those who present early highlighting the need for early detection activities in endemic communities. There is the need for a full oral regimen and the ongoing WHO trial with Clarithromycin and Rifampicin daily for 8 weeks aims at addressing this need. However, there is still the need to develop improved antibiotic regimen for limited and extensive disease. Several options may be considered. Buruli ulcer currently attracts limited funding for research and capacity building that needs to be addressed.

Future Directions

There are very high prospects of patients with limited disease receiving full oral treatment with Clarithromycin and Rifampicin Development and testing of biomarkers for monitoring disease and treatment Introduction of new wound care techniques to enhance wound healing Testing of combinations that include high dose rifampicin to shorten therapy Improved diagnostic testing e.g mycolactone detection assay.

The role of EDCTP

EDCTP could interact with Researchers of the newly formed African Research Network for NTD (ARNTD) - an African led research network consisting of African based post doctoral fellows with the mission to empower current and future generation of African researchers to support evidence-based control and elimination of NTDs WHO technical advisory group into treatment of Buruli ulcer.

Prof Gerd Pluschke

Swiss TPHI

Current status of the field

Buruli Ulcer:

- Mode of transmission has to be elucidated to identify preventable risks;



there is urgent need for a simple, specific and sensitive point-of-care laboratory diagnostic test

- Alternatives to the currently recommended streptomycin/rifampicin combination chemotherapy requiring daily injections have to be developed and tested; for the case of the emergence of rifampicin resistance an alternative drug has to be identified and tested
- Standardized BU wound management guidelines and procedures suitable for rural African settings have to be developed, evaluated and optimized
- A vaccine should be developed.

Future Directions

Buruli ulcer:

- Testing of rifampicin/clarithromycin combination chemotherapy
- Optimization and testing of decentralized chemotherapy
- Optimization and field testing of diagnostic antigen capture assays; testing of new scaffolds and compounds active against *M. tuberculosis* on *M. ulcerans*; separate optimization of highly active new scaffolds.

The role of EDCTP

Buruli ulcer:

Clinical trials of new combination chemotherapies and chemotherapy; optimization and evaluation of wound management procedures and devices; field testing of new point-of care diagnostic tests;

Key players:

Stop Buruli consortium

WHO

Dr M^a Eugenia Puentes

Biofabri

Current status of the field

Key issues: BCG is inconsistent in protecting against adults form of TB, new vaccines are needed to protect against all form of TB in all age groups. Challenges: No correlates of protection. Lack of knowledge of Mtb-host interaction. Validated animal models

Future Directions

Study different prime-boost combinations Portfolio diversity

The role of EDCTP

Maximise resources and finance clinical trials in all age groups

Dr Andrew Ramsay

TDR, World Health Organization

Current status of the field

In the absence of an adequate preventative tools, such as vaccines, successful TB control will remain dependent upon early detection and successful treatment of cases. Early case-finding is severely constrained by the lack of a sensitive, point-of-care diagnostic for tuberculosis. Furthermore, treatment success is threatened by drug resistance in several countries. New tools such as vaccines, diagnostics and drugs are needed. One of our most important knowledge gaps, however, is how to use the existing tools for maximum public health effect.

Future Directions

Clinical trials of promising new vaccines, drugs and diagnostics.



Implementation research in control programme settings to establish effective strategies for using combinations of case-finding and treatment tools.

The role of EDCTP

Supporting coordinated, multi-partner activities that are well-directed towards clear objectives and linked to adequate processes for translating research evidence into policy and practice.

Dr Voahangy Rasolofo

Institut Pasteur de Madagascar

Current status of the field

1. The burden of extrapulmonary tuberculosis?
2. Diagnostics of tuberculosis, specifically diagnostics of extra-pulmonary tuberculosis and tuberculosis in children
3. Tuberculosis and malnutrition: diagnosis of TB among population suffering from malnutrition, treatment outcome in these populations
4. Epidemiology: the burden of TB disease
5. Shortening TB treatment
6. New molecules to treat MDR-TB and XDR-TB

Future Directions

1. Development/Evaluation of rapid and simple new diagnostic tools for tuberculosis and specifically extrapulmonary tuberculosis and pediatric tuberculosis
2. How to diagnose TB in malnourished population? How to improve TB treatment in this population?
Clinical trials for short therapy regimen
3. Clinical trials to test new molecules against tuberculosis and especially to treat MDR and XDR TB.

The role of EDCTP

4. Finance projects that address these issues
5. Providing the means to upgrade the sites for clinical trials
6. Network of sites with complementary skills.

Prof Klaus Reither

Swiss TPHI

Current status of the field

Every year, more than 70,000 children die from tuberculosis, a preventable and curable disease. These figures and the unacceptable high TB incidence rate among children point toward the overall failure to deal adequately with the issue of paediatric TB. Hence, in the developing world, childhood tuberculosis is not under control, and, despite its importance as a child health problem, remains a neglected and often ignored disease. There is a need to integrate childhood tuberculosis into maternal and child health programs, and to intensify and most of all coordinate and streamline research efforts on new diagnostics, vaccines and adapted drug regimens.

Future Directions

We would need a kind of overarching and integrative, rather than competing approach in childhood TB research in which EDCTP could play a key role to address this important and still neglected field of TB research. These activities should be carried out in close collaboration with stakeholder from WHO and other leading institutions. Childhood TB should become one focus of EDCTP2. Main areas should be development and evaluation of adequate diagnostic tools and pathways for paediatric TB, which are adapted to the particular requirements for diagnosis of



childhood TB. Secondly PK and PD studies for children should be intensified for standard, second-line and new TB drugs.

The role of EDCTP

EDCTP can play a vital role in research on childhood TB in conjunction with FIND, TB Alliance, PanACEA, academia, and other institutions.

Prof Jerome Robert

Centre National de Référence des Mycobactéries et de la Résistance aux Antituberculeux

Current status of the field

Drug access and quality, infection control

Future Directions

Improvement of costless administrative infection control strategies;
quality of drug resistance surveys by rapid tools to base standard regimens on the up to date epidemiology of drug resistance.
Combination of HIV/TB testing and drug deliveries

The role of EDCTP

DOTS improvement and technology for patient follow up.
Efficient reference laboratories for drug susceptibility tests with good sampling strategy.
Help in the improvement of architecture of health centers and education on infection control strategies

Ms Danielle Roordink

TuBerculosis Vaccine Initiative

Current status of the field

The solution to the problem of TB is: We need a better, more effective vaccine to protect people from all forms of the disease. Prevention through vaccination has been the most cost-effective tool in eradicating and controlling every other major infectious disease in the history of mankind. TB is no exception.

Future Directions

In March 2012, the European Commission and European Investment Bank (EIB) asked Aeras and the TuBerculosis Vaccine Initiative (TBVI) to develop a viable business case for the advancement of TB vaccine research and development efforts. One of the primary goals was to present a scenario in which commercial and public-sector interests could be balanced and in sync. "TB Vaccine Research & Development: A Business Case for Investment". The business case shows how the public and private sectors can work together to develop a robust

portfolio of new TB vaccines in a cost-effective manner and also recommends the implementation of portfolio management as the most efficient and effective mechanism to advance the global vaccine pipeline.

The only available TB vaccine, Bacille Calmette-Guérin (BCG), has little to no efficacy in preventing pulmonary TB, the most common and infectious form of TB and its impact on the global TB epidemic is therefore limited. Through renewed efforts over the last ten years, a rich pipeline of new TB vaccines has been developed, with 14 evaluated in clinical trials and many more in discovery or preclinical development. More than half of the vaccine candidates in clinical trials right now induce similar immune responses elicited by that candidate.



Therefore, diversifying the tuberculosis vaccine portfolio is critical to improving our chances of success. Support towards portfolio management will ensure diversity of the global TB vaccine portfolio.

The role of EDCTP

For TB vaccine. EDCTP should work with the key stakeholders that support also TB vaccine R&D before EDCTP funding comes in the picture, like TBVI and Aeras. In this context it would be valuable if EDCTP also supports and contributes to the portfolio management approach to make sure the candidates which have the best success rate can move further down the pipeline.

Dr Luis Ruiz Avila

Archivel Farma, S.L.

Current status of the field

The challenge is to act quickly in order that new clinical studies allow to find new antibiotics and vaccines to control the disease progression, desirably reducing the duration of treatment. Also, the reduction of relapse cases would help to avoid retreatments.

Future Directions

Is possible to make significant progress in this field with the RUTI vaccine, an immunotherapeutic product derived from M. tuberculosis which has completed a phase II clinical trial and that is ready to

1. Demonstrate efficacy as an adjunctive immunotherapy to standard antibiotic treatment to prevent active tuberculosis in high risk individuals with latent tuberculosis infection (a trial thought primarily to address the issue of HIV+ / latent TB patients in South Africa)
2. Demonstrate efficacy as an adjunctive immunotherapy to standard antibiotic treatment to prevent recurrence of active tuberculosis in tuberculosis patients (a trial thought primarily to address the high relapse rates observed in certain high prevalence areas).

The role of EDCTP

The funding of EDCTP partnerships with the product developer or promoter and local CRO's who have good knowledge of the field is the key.

Dr Jerald Sadoff

Crucell Vaccine Institute

Current status of the field

There is a tremendous need for a more effective vaccine to prevent acquisition in Naive individuals and reactivation in both latent HIV + and HIV - individuals. A better test for dx of TB in the field is also needed.

Future Directions

New Multivalent vaccines that are entering the clinic offer the best opportunity to reduce the epidemic in Africa. A vaccine to prevent HIV will also do much to prevent TB. Likewise early expanded therapy of HIV will prevent reactivation and spread of TB.

The role of EDCTP

EDCTP can best contribute by continuing to actively support the development and utilization of field trial sites for new TB and HIV vaccines in Africa. Direct support to supplement other donor and industrial support will be the only way to make a new TB vaccine possible since the commercial return on such a vaccine in Africa will be limited and therefore industrial support will occur only if it is a joint public private effort.

**Dr Thomas Shinnick**

U.S. Centers for Disease Control and Prevention

Current status of the field

Sustainability and affordability of interventions.
Low rate of detection of TB and MDR TB cases
Few drugs to treat MDR and XDR TB

Future Directions

New molecular tests have promise for improving detection.

The role of EDCTP

Promote research to evaluate new diagnostic tests, drugs, and vaccines.

Prof. Mahavir Singh

Lionex GmbH

Current status of the field

Inadequate, cost effective diagnosis which finally leads to mistreatments which finally results in MDR and XDR TB.

Future Directions

Novel drugs and regimens have been developed at LIONEX which have shown promising results in pre-clinical testing in mice. These drugs are effective against MDR and XDR strains in-vitro.

The role of EDCTP

EDCTP could play a central role in increasing the number of safe trials including Phase I which is the major bottle-neck for small companies. EDCTP could be a driving force in helping small companies for bringing their products in clinical trials. We should not leave everything to large institutions and Big Pharma, at least during the early phase.

Dr Mel Spigelman

TB Alliance

Current status of the field

The key issues and challenges to progress in TB control in sub-Saharan Africa are a combination of weak healthcare systems and inadequate tools, such as the diagnostics, drugs and potentially vaccines.

Future Directions

Significant advances could be made in the area of introduction of new drugs and treatment regimens over the next 5 to 10 years. Treatment for drug sensitive TB can most likely be reduced to at least 4 months and potentially less over that time period. Treatment of drug resistant TB could see major advances with shortening of present therapy by at least 75% and reduction in price of treatment by over 90%.

The role of EDCTP

EDCTP has become a major factor in the TB field in sub-Saharan Africa. The emphasis on late stage clinical trials and capacity building are exactly what is needed to enable progress.



Dr Charles Ssonko

MSF

Current status of the field

Diagnosis: Lack of simple, cheap and rapid point of care tests to rapidly diagnose TB/MDR-TB and rapidly initiate treatment in order to reduce morbidity and mortality and interrupt transmissions.

Treatment: drug shortages leading to rampant drug ruptures and treatment interruptions. MDR-TB treatment is quite long and toxic, posing difficulties to maintain patients on it.

Overall retention of patients into care to ensure treatment completion, particularly in unstable/conflict settings is a major challenge.

HIV is still an untackled issue greatly impacting negatively on TB in terms of high TB numbers, complicating diagnosis and treatment and leading to poorer outcomes. Above all the emergency of Drug resistant TB.

Future Directions

Research and development that has resulted in a number of new drugs now in the pipeline. Several of them in phase II and phase III trials. Drugs such as Bedaquiline and Linezolid have shown promising results.

There promising results from the field of implementation of shorter regimes for MDR-TB (9-12 months) such as the Bangladesh regimen, which has also been tested in African countries such as Cameroon.

Multicentric Shorter Drugs regimen trials that are underway, such as the STREAM. Improvements and scale up of rapid diagnostics such as the Xpert MTB/Rif and Hain (first and second line) for the rapid diagnosis of DRTB.

In terms of models of care, a shift from hospital based to Ambulatory and home based care (decentralization) together with improvements in knowledge and infection control standards have led to reductions in infection risk.

The role of EDCTP

The key players include:

The pharmaceutical companies; with their patent regulations over new products; this requires immediate intervention in order to get the new products to the majority of patients cheaply.

More funds for research and development in the area of TB/MDR-TB still needed. We still need more potent new drug molecules for both drug sensitive and drug resistant TB.

Implementing agencies; there is need to support more agencies to get into the field of implementation. Currently fewer are directly hands on to support national programmes.

The World Health Organization; to speed up evidence based guideline revisions and increase its support to National tuberculosis programmes.

Prof Olle Stendahl

Faculty of Health Sciences

Current status of the field

There are four main challenges: improve and facilitate diagnosis, improve and develop new vaccines, new antibiotics, and new adjuvant treatment to improve host defence.

**Future Directions**

The most promising development is the improved diagnostic tools (GeneExpert), which had lead to rapid diagnosis of TB in many remote areas. Within five-ten years new adjuvant treatment related to nutrition will be used.

The role of EDCTP

The main goal of EDCTP will be to facilitate collaborations, both between European and African countries.

Dr Ymkje Stienstra

University Medical Center Groningen

Current status of the field

Same question for Buruli ulcer: Challenges: Healing rate is currently very slow. Antibiotic treatment is 8 weeks for all but healing takes on average a year. Focus has been on the antimicrobial treatment, whereas most of the healing takes place long after the antimicrobial treatment; treatment studies should include focus on wound care, surgical intervention and not exclusively at the antimicrobial treatment and healing rate after 1 year. Another challenge is to develop treatment strategies adapted to the stage of Buruli ulcer. In many countries patients still present in a late stage. The slow healing rate contributes to this late presentation.

Future Directions

Completely oral antimicrobial treatment instead of the streptomycin daily im. - knowledge on the role of surgery and the timing of it - Improved wound care would very much make a difference in the treatment. There have been initiatives to improve the wound care but with difficulties.

The role of EDCTP

Funding strategies should emphasize that Buruli ulcer is not 'Tuberculosis light', but a different disease. Calls should therefore be open not only for research on antimicrobial treatment but also be open for wound care interventions with appropriate endpoints in the studies, such as long term consequences of the disease instead of healing rates after 1 year. Only three RCTs are performed in Buruli ulcer, yet there are many clinical questions to be answered. EDCTP may also be helpful in facilitating the start of a system to exchange researchers between different RCTs that can be helpful with each other's external auditing. Key players can easily be identified on clinicaltrials.gov since only three studies have been registered.

Dr Grant Theron

University of Cape Town

Current status of the field

Key challenges in my opinion include: Difficulty in meaningfully evaluating the impact of recent progress in TB control in *programmatically-representative* settings. For example, are new interventions like Xpert fulfilling their full potential, or is their population-level effect undermined by misguided policy decisions (e.g., not being placed at the point-of-care, or poor empirical treatment practise)? - Targeting the high burden of TB that never enters the healthcare system. Some studies estimate this to be as high as 60% of the total TB case load. How can we find these patients, get them on care, and stop them transmitting? - Reduce the transmission of drug-resistant TB. Data from SA shows that 80% of MDR-TB is transmitted via the primary route. Although DR-TB is less than 5% of cases in SA it consumes approximately 60% of the TB drug budget. - Finding biomarkers for active TB that work well in HIV-infected patients and can be easily incorporated into simple point-of-care diagnostic devices.



Future Directions

Assessing the impact of new interventions: Prospects here are ultimately good but currently there is a lack of work assessing them in real-world settings, however, the roll-out of Xpert will give a unique opportunity to do so, with the first population level studies expected in mid-2014. - Active case finding: Difficult to gauge the long term prospects of this. We currently do not know how well active case finding performs in conjunction with new diagnostics, and especially when these new diagnostics are themselves mobile. Although affordability is a key issue, cost-effectiveness studies, which are needed to drive programmatic willingness are needed. - Transmission: New diagnostics should help reduce transmission, however, there are no POC diagnostics for drug resistance. Technologies such as Xpert XTEND may hold some promise. - Biomarkers: "Omics" and panel-based approaches have promise but are still at an early stage, and are tripped up by HIV infection. When available, field-evaluation studies of these new technologies will be required.

The role of EDCTP

It can have calls focused on the above areas. Funding targeted at future research leaders (who are presently junior) are desperately needed. There is a need for projects not led from South Africa, but capacity in other countries needs to be improved needs to be enhanced. The EDCTP should co-ordinate with leading institutions in Africa, such as the University of Cape Town or KEMRI, to do so. The expertise exists within Africa, however, it is still very uneven. The EDCTP should also focus more on Africa-grown basic science discovery research. Presently, a great deal of EDCTP TB projects are "technology testers", rather than producing original IP. To produce innovation and bring the EDCTP to same level as the NIH or Wellcome such focus is needed.

Dr Jelle Thole

TuBerculosis Vaccine Initiative (TBVI)

Current status of the field

The solution to the problem of TB is: We need a better, more effective vaccine to protect people from all forms of the disease. Prevention through vaccination has been the most cost-effective tool in eradicating and controlling every other major infectious disease in the history of mankind. TB is no exception.

Future Directions

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The role of EDCTP

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Dr John Thomson

Vertex Pharmaceuticals, Inc.

Current status of the field

Funding limitations & need a more effective "divide and conquer" mentality and action plan for the diverse challenges, and need better drugs

Future Directions

We should focus on control and diagnosis technologies and social programs for advances in the <5 year time frame. In terms of transformative drugs, prospects are low for dramatic advances in 5 years, but are improving in the > 5 year time frame. To sustain this, we need a robust commitment to ongoing new drug research and development, and it is very important that we have an effective dialogue of stakeholders and regulators to ensure that innovation in pivotal trial designs can enable efficient delivery of new innovations into availability of new therapies.

The role of EDCTP

Acting as liaisons between biotech and pharma and the global regulators to help streamline new TB drug approval processes.

Prof Philippe Van De Perre

Montpellier University

Current status of the field

- Specific Tools for diagnosing early active TB
- Diagnostic Tools to discriminate latent versus active TB
- TB diagnosis in children
- Entry points for TB care

Future Directions

- Immunologic diagnosis of (latent and active) TB
- Use of existing opportunities of contact with the health system to ensure TB diagnosis and care

The role of EDCTP

- Support of evaluation of original diagnostic strategies
- Set up panels of clinical samples for comparison of diagnostic performance
- Boost the exploration of original test and treat TB strategies

Dr Suzanne Verver

KNCV

Current status of the field

- Prevention: availability of ART for HIV infected people, poverty, housing, cure of existing cases
- Control: new diagnostics are expensive. Need low cost point of care test. Need



integrated TB and HIV care. TB among miners and migrants: need better TB care systems for linking between countries

- Treatment: long duration of treatment for drug sensitive cases; expensive drugs for second line treatment with lots of side effects. Need for new short course regimens. Countries need assistance in implementation of new short course regimens.

Future Directions

- New diagnostics are being tested and implemented but need implementation studies to support impact assessment. For example strategic and planned roll-out of Xpert with proper impact evaluation
- New 2nd line drugs and shorter regimens still need implementation trials and impact evaluation of introduction, especially in SSA; eg Bangladesh regimen, bedaquiline, delamanid, remox
- Innovative designs that have been used for drug trials for drug sensitive TB can also be used also for drug trials for MDR TB
- Inclusion of sample collection for biomarkers studies in trials
- Small studies have been done on combined integrated decentralised TB/HIV services; need larger studies to expand this
- Evaluation of introduction of innovative mobile services such as sms-services for improving treatment completion rates has been done on small scale but needs expansion to large scale and sustainability
- New WHP policies on integration of childhood TB services into MCH services need evaluation of their effect on detection of childhood TB
- Use of modelling where trials are difficult.

The role of EDCTP

- Funding strategy & activities: fund not only trials but also implementation and evaluation studies; cost-effectiveness studies and modelling work
- Selection of vaccine trials to be more strict
- Fund studies where many recommended interventions are combined to assess impact of combined interventions; eg for people with co-infection of TB and HIV
- Partners: EDCTP already knows FIND, TB Alliance and Aeras and many trial sites in Africa for trials in EDCTP1. In EDCTP2 expanded focus on groups with experience in implementation studies are KNCV Tuberculosis Foundation, Academic Medical Centre Amsterdam, Radboud University Nijmegen, Stellenbosch University South Africa, University of Cape Town, Aurum, LSHTM. Important is to link TB&HIV research groups, support research sites where research is done on several interventions and diseases, link basic science groups (eg on biomarkers) to larger trials.

Dr Stephen Walker

LSHTM

Current status of the field

Leprosy reactions are a significant cause of morbidity and mortality

Future Directions

Improving the management of leprosy reactions by increasing the evidence for effective treatments

The role of EDCTP

Funding directly or linking funding with Leprosy Research Initiative monies for leprosy reaction management



Dr Mark Wansborough-Jones

St Georges University of London

Current status of the field

Buruli ulcer is a NTD occurring predominantly in rural areas of W African countries. Delivery of newly developing antibiotic therapy to remote areas requires capacity building in conjunction with clinical trials and development of simplified diagnostic techniques.

Future Directions

The prospects are excellent following the completion of the recent BuruliVac FP7 project which has produced novel information about the mechanism of action of mycolactone toxin as well as new directions for the development of diagnostic techniques.

The role of EDCTP

Capacity building to support clinical trial work building on the BuruliVac work in this field, funding for further clinical trial research for antibiotic and other management as well as diagnosis research and development. WHO TAG is well placed to interact with EDCTP.

Prof Robert Wilkinson

UCT/Imperial College

Current status of the field

1. Lack of sensitive marker of bacillary load
2. Lack of a marker of immune protection or pathology
3. Lack of a short course regime to treat latent tuberculosis
4. Lack of a marker to evaluate novel treatments for latent tuberculosis
5. A shortage of new drugs to treat both drug resistant disease and to shorten treatment
6. Lack of adjunctive therapies that could hasten cure and decrease immunopathological tissue damage
7. Lack of markers that could be used to infer likely treatment efficacy
8. A relative shortage of clinical research facilities capable of advancing knowledge of the above and to test novel interventions

Future Directions

1. There are new drugs that will require testing in phase I/II and potentially III trials. Testing combinations will important, as will understanding the pharmacokinetic and pharmacodynamic properties. It will be very important to factor the use of drugs with concurrent antiretroviral therapy and also the possibility to repurpose some existing drugs.
2. There is the potential to reduce immunopathology (and more speculatively to shorten treatment) via the adjunctive use of immunomodulatory compounds such as COX inhibitors, Angiotensin converting enzyme inhibitors, Angiotensin receptor antagonists, 5-lipoxygenase inhibitors and vitamin D
3. There is the potential to reduce the risk of reactivation of tuberculosis by vitamin D and by vaccination
4. The preclinical efficacy of novel vaccines in the pipeline appears only moderate. There is therefore a necessity to derive new pre-clinical models to evaluate such intervention. Nevertheless a few products have reached studies in humans and these should continue on a case by case basis and matched carefully to clinical environments. The overall capacity to conduct vaccine trials remains poor.

The role of EDCTP

EDCTP can contribute by:

1. Career support
2. Direct support of clinical sites



3. RFPs in specific areas that nevertheless encompass investigator initiated approaches
4. Greater funding to understand pathogenesis and thus the basis for pathologic and protective immunity

Key organisations in the arena are the Bill and Melinda Gates Foundation, National Institutes for Health, Aeras, the Global Alliance and various independent or national funders such as the Wellcome Trust and HHMI. As projects and clinical site support may be large collaboration in certain areas is likely to be beneficial. However formal co-funding stipulations are cumbersome and disliked by both investigators and institutions.

Prof Dorothy Yeboah-Manu

Noguchi Memorial Institute for Medical Research, University of Ghana

Current status of the field

Buruli ulcer: Lack of point of care diagnostics, cases report late with large ulcer, no standardized wound care procedure, low funding

TB: at least six month treatment, diagnosis at facility level, lack of effective vaccine, no true point of care diagnostic for case diagnosis and DST,

Future Directions

Improve early case detection in the community, capacity building at both institutional and individual level in Africa, include West-Africa in TB trials taking into consideration the prevalence of *M. africanum*.

The role of EDCTP

Funding and bringing together partners to form consortium

Prof Ali Zumla

University College London

Current status of the field

This has been extensively covered in the March 2013 Lancet Infectious Diseases TB Theme series volume of 6 articles edited by Professor Zumla. The set of articles can be sent as pdfs to the organisers for circulation

Future Directions

This has been in the March 2013 Lancet Infectious Diseases TB Theme series volume

The role of EDCTP

The EDCTP will play a crucial role in:

1. Developing capacity and training young African scientists.
2. Linking pharma, funders and developers with research consortia to perform priority research (bench, bedside and translational clinical field site) on health policy relevant, implementable and practically important issues

Drugs, diagnostics vaccines and biomarkers are always on the frontline agenda