EDCTP

European & Developing Countries Clinical Trials Partnership

STAKEHOLDER MEETING

REPORT ON TUBERCULOSIS AND OTHER MYCOBACTERIAL INFECTIONS

PARIS, FRANCE

28-29 OCTOBER 2013

Towards the second EDCTP programme

The EDCTP Stakeholder Meeting on tuberculosis and other mycobacterial infections is part of a series of thematic stakeholder meetings planned to contribute to the shaping of strategy and funding approach of the second EDCTP programme. EDCTP organised meetings on neglected infectious diseases, HIV/AIDS, malaria, tuberculosis, as well as on Research Ethics Review and Regulatory Affairs. A stakeholder meeting on Capacity Development will take place in Berlin on 3 July 2014.

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EDCTP was created in 2003 as a European response to the global health crisis caused by the three main poverty-related diseases (PRDs) of HIV/AIDS, tuberculosis and malaria. Currently EDCTP is a partnership between 16 European countries, the European Union and sub-Saharan African countries. The aim of the programme is to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics for HIV/AIDS, tuberculosis and malaria through a balanced partnership of European national research programmes on PRDs with their African counterparts in collaboration with the pharmaceutical industry and like-minded organisations.

The second EDCTP programme will start in 2014 as part of the European research framework programme Horizon 2020. Its scope is based on the current objectives and achievements and will be expanded to include: all clinical trial phases I-IV including health services optimisation research; other neglected infectious diseases; closer collaboration with industry, like-minded product development partners and development agencies; and collaborative research with other developing countries outside sub-Saharan Africa when possible and desirable.

Contents

Acronyms and abbreviations

ANRS	Agence nationale de recherche sur le SIDA et les hépatites virales (National Agency for AIDS and Viral Hepatitis Research, France)
ART	Antiretroviral therapy
Aviesan	Alliance nationale pour les sciences de la vie et de la santé (National Alliance for Life and Health Sciences, France)
EDCTP	European & Developing Countries Clinical Trials Partnership
EDCTP2	Second EDCTP programme, which will start in 2014
ENL	Erythema nodosum leprosum
Gates Foundation	Bill & Melinda Gates Foundation
HIV	Human immunodeficiency virus
JA3	Joint Activities involving Member states and third parties
MDR	Multidrug resistant
PDP	Production development partnership
PSIA	Participating states-initiated activities
SAC	Strategic Advisory Committee
TAG	Treatment Action Group
TB	Tuberculosis
WHO	World Health Organization

1. Executive summary

This meeting was part of the preparations for the second programme of the European & Developing Countries Clinical Trials Partnership (EDCTP2). The two-day event was attended by 107 participants, including researchers, representatives of product development partnerships and the pharmaceutical industry, policy makers, funding agencies and other like-minded organisations.

Discussions were structured around the following presentations:

- Introductions by the Chairs
- Plans and Progress towards EDCTP2
- Keynote address
- Diagnostics
- Global vaccines portfolio
- Treatment I: Global treatment portfolio
- Treatment II: Clinical management of tuberculosis and mycobacterial infections
- Partnerships in treatment development
- Control and implementation research
- Partnerships for control and implementation research.

Presentations were followed by comments and recommendations from the meeting participants.

Diagnostics

- There are many candidates in the pipeline for *Mycobacterium tuberculosis*, but there are gaps for point-of-care tools, and for some groups such as children (fewer than 20% detected). Non-sputum tests are needed for all populations
- Innovative test approaches: there are some gene-based tests coming through but they are early stage and need time to be developed. Prioritisation is needed
- EDCTP has done important work so far for diagnostics. However, it should consider co-funding a trial platform against an established set of tests, so that trials can be done quickly and the less promising candidate tools can be eliminated
- Digital X-ray and smear test repurposing should be considered
- Improve infrastructure and laboratory capacity, e.g. supranational laboratories that can also perform external quality assurance. Sustained funding is needed
- Encourage more linking with clinical (vaccine and drug) trials to optimise the use of samples for identification of biomarkers and integration of diagnostic tool development
- EDCTP could establish a committee to see what we would like to have in five years and see what is available to make that happen
- EDCTP could look at infrastructure needs in order to encourage clinical trial centres to share their samples
- EDCTP needs to adopt flexible decision making on funding, i.e. not just at one point but over a period of time so that funding can be available as new tests become available (revolving call for projects).

Vaccines

- The overall market potential of a successful adult/adolescent vaccine seems sufficient to support meaningful financial returns to industry and potential niche public/private investors in the development of the vaccine portfolio
- If only an infant vaccine is developed, the overall market potential is more limited; however, it is feasible that a vaccine commercialised initially for use in infants, could bridge to an adolescent/adult prime boost approach and thereby increase market share and income
- Having a robust and diverse pipeline of vaccine candidates in early development stages will be critical to attract investment capital as the portfolio approach increases the likelihood of successful commercialisation and thus financial returns.

Treatment

- Development of therapies for reducing inflammation and immune-modulation (host-directed therapies) offers new possibilities for treating the mycobacterial diseases
- More research is needed on inhaled formulations; these formulations would offer advantages over injectable formulations, including administration and adherence; they could be assessed using positron emission tomography (PET) scans
- Biomarkers are also needed for treatment evaluation, since pertinent biomarkers could have considerable potential to shorten trials; better collaboration between researchers developing biomarkers and those developing therapies should be encouraged
- Molecular assays and viability count techniques are also needed for therapy assessment in trials to be used as surrogate outcomes with the potential of also shortening trials
- Innovative trial designs are needed, e.g. adaptive trials (play-the-winner) and seamless phase transitions in order to shorten development time and to identify, as early as possible, therapies that should not be developed further (reduction of development costs)
- Specific populations should be considered when targeting new therapies (e.g. patients with multidrug resistant tuberculosis (MDR-TB), children, patients with HIV co-infection
- Leprosy and Buruli ulcer treatment should not be forgotten; better partnerships and collaboration between these research communities are needed
- Although there is effective treatment for leprosy, there is room for improvement, particularly for treatment of nerve damage
- There also gaps in treatment options for paucibacillary leprosy
- Buruli ulcer could benefit from the development of host directed therapies (HDT)
- Capacity building for clinical trials should continue, particularly sustainable capacity, without stifling innovation (sharing of facilities between drug, vaccine and diagnostic trials); EDCTP2 will have an important role to play
- Stronger South-South partnerships for drug development are needed; in North-South partnerships there is a need to remember the equality of partners.

Control and implementation strategies

- Operational research could help improve programme performance and outcomes, with a focus on service delivery
- There is a need for a move from tools to strategies
- Leprosy cannot be eliminated but it is a rare disease that is not evenly distributed geographically; two out of three new cases are in Asia and South America. There is a need to develop collaborations outside Africa
- Diagnosis of rarer diseases, and even tuberculosis, is a challenge in terms of training healthcare professionals to recognise them; development of triage algorithms (new or existing tools) is needed
- Implementation of diagnostics: although the Xpert MTB/RIF assay was endorsed by WHO it is important to see how countries are going to implement it; local implementation strategies, as well as the integration of new therapies and therapeutic strategies need to be assessed
- Policy makers need evidence that an intervention works before they accept to pay for it; we need to ensure that it is available.

Partnerships

- There is a need to ensure that the research funded by EDCTP does not just add to our knowledge but that it makes a difference to

the morbidity and mortality from tuberculosis and other mycobacterial diseases, i.e. EDCTP should aim to be transformational
- Capacity building and partnerships are needed to ensure that robust outcomes research is done and that the efforts can be transformational
- Most African countries have combined tuberculosis and leprosy programmes (and some include Buruli ulcer); they develop effective sharing and synergies between these communities and partnerships to ensure integration of effective diagnostic tools, vaccines and therapies in real-life, but it is important to remember that these diseases have their specific problems as well as having common problems
- Synergies between funding agencies should be developed; potentially an important role for EDCTP.

The wide range of comments and suggestions made by participants over the two days show how much remains to be done in the fields of tuberculosis and other mycobacterial diseases such as leprosy and Buruli ulcer. No consensual recommendations were made or priorities identified but the input from this meeting will certainly contribute to the planning of the second programme.

2. First day

The meeting was the third of the five thematic stakeholder meetings held in 2013 as part of the European & Developing Countries Clinical Trials Partnership's preparations for its second phase of development (EDCTP2). The two-day event took place at the Fondation Del Duca in Paris, France and was hosted by the Institute of Microbiology and Infectious Diseases/ Aviesan and the French Ministry of Higher Education and Research. It was attended by 107 participants, including researchers from academia, representatives of product development partnerships and the pharmaceutical industry, policy makers, funding agencies and other like-minded organisations (see Annex I for the list of participants).

Introduction by Professor Jean-François Delfraissy

Prof. Jean François Delfraissy, Director of the French National Agency for Research on AIDS and Viral Hepatitis (ANRS), welcomed the participants and gave a brief summary of the organisation of infectious diseases research in France. The national life and health sciences alliance Aviesan was created in April 2009, as an umbrella organisation grouping 10 French agencies (including ANRS). Its objectives are to coordinate the strategic analysis, the scientific programming and the operational implementation of research. It has a budget of € 1.5 billion for infectious diseases and an important network for international collaboration.

As tuberculosis (TB) remains a problem (WHO *Global Tuberculosis report 2013*) especially with the increase of drug resistance, he emphasised the importance of investment, by funders and scientists, in the TB diagnostics pipeline to develop a rapid, accurate point-of-care diagnostic test that is affordable and can be readily implemented.

Plans and progress towards EDCTP2: Dr Gabrielle Breugelmans

Dr Gabrielle Breugelmans, North-North Networking Manager EDCTP recalled the mission, objectives and scope of EDCTP. She reported that, to date, EDCTP has provided € 73.8 million or 35% of total grant expenditure for TB projects.

Under EDCTP2 (2014-2023) the scope of the programme will be expanded to include:

- All phases of clinical trials, including phase I and IV
- Neglected infectious diseases, such as sleeping sickness, elephantiasis, Buruli ulcer, leprosy, river blindness, etc. based on the WHO list
- Other geographical areas, when relevant and through partnerships.

Grants schemes under EDCTP2 will include:

- Integrated activities (as under the first EDCTP programme)
- Participating States Initiated Activities (PSIA)
- Joint Activities involving Member states and third parties (JA3).

Criteria for establishing funding priorities will include disease prevalence, product opportunities, balancing immediate and long-term priorities, and maintaining a balance among clinical trial phases.

The expected outcomes from the stakeholder meeting are:

- Review of the current status in the field of tuberculosis and mycobacterial infections
- Identification of key research areas, current opportunities and barriers to progress

- Recommendations that will contribute to the EDCTP strategy for supporting TB and mycobacterial infections research. Suggestions are welcomed for:
  - Priority research topics for Calls for Proposals
  - Proposals for cooperative projects
  - Products in the pipeline for evaluation by EDCTP
  - Focused capacity building initiatives
  - Proposals for funding partnerships.

Comments from participants prompted Dr Breugelmans to provide the following clarifications:

- EDCTP will include implementation of epidemiology studies to establish baseline TB levels if recommended by stakeholders
- Diagnostics for case detection and point-of-care will be included if identified as a still existing gap
- TB/HIV co-infection will be included in both the TB and HIV research priorities
- Involvement of pharmaceutical companies and SMEs (e.g. manufacturing needs) will be examined
- Other poverty-related infectious diseases may progressively be added based on stakeholders' recommendations; the WHO list is a working document.

Keynote address: Professor Gavin Churchyard

Prof. Gavin Churchyard, Chief Executive Officer of the Aurum Institute, reminded everyone that mycobacterial diseases are preventable and treatable diseases of poverty and presented an overview of main points for tuberculosis, leprosy and Buruli ulcer.

Tuberculosis

The highest TB burden is found in India, China and South Africa, but it is also high in Eastern Europe. In India, MDR-TB is a growing problem but it is highest in Eastern Europe. The millennium development goals and Stop TB targets are:

- 2015: reduce prevalence of TB and TB-deaths by 50% compared with the 1990 baseline
- 2050: eliminate TB as a public health problem (defined as <1 case per 1 million population per year)

All areas have achieved the goals for incidence but many areas are not on track to achieve goals for prevalence and mortality.

The TB drugs pipeline contains both new molecules and new regimens. The needs and priorities differ in different settings (e.g. drug susceptible or resistant TB). Preventive treatments are also in the pipeline. HDT are a promising approach inducing enhanced protective immunity. The aims are to shorten treatment times, to have fewer complications and to reduce the rate of recurrent TB. Access to treatment needs to be facilitated. TB and HIV/AIDS co-infection is a challenge, with more understanding of possible drug-drug interactions with ART needed.

Many new diagnostics are in the pipeline. The WHO has endorsed the Xpert MTB/RIF assay after an online WHO expert meeting considered the results from a meta-analysis. It has been shown to have good specificity but variable sensitivity. The WHO recommendations are:

- Xpert MTB/RIF assay should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults presumed to have MDR-TB

or HIV-associated TB (strong recommendation, high-quality evidence)
- Xpert MTB/RIF assay may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults presumed to have TB. (Conditional recommendation acknowledging resource implications, high-quality evidence).

Early detection of TB could contribute to prevention, since infected subjects are infectious while initially asymptomatic. There is a need for point-of-care diagnostic tools for home or primary care testing. Same-day microscopy prevented about 11.0% of TB incidence over 10 years and prevented 11.8% TB mortality. Scaling up the Xpert MTB/RIF assay to all centralised laboratories to achieve 75% population coverage had similar impact on incidence (9.3% reduction) and a greater effect on mortality (23.8% reduction). Combining the two strategies (i.e. same-day microscopy plus Xpert MTB/RIF assay) generated synergistic effects: an 18.7% reduction in incidence and 33.1% reduction in TB mortality. By the end of year 10, combining same-day microscopy and Xpert MTB/RIF assay could reduce annual TB mortality by 44% relative to the current standard of care (Therone et al., *Lancet* 2013; Dowdy et al., *PLOS One*, 2013).

Vaccines for TB

There is an encouraging pipeline, one vaccine in phase III, eight in phase II/IIb. These include pre-exposure priming, sub-units for boosting and some therapeutic vaccines. The blueprint for TB vaccine development proposes five keys to progress (Brennan, Tuberculosis, 2012):

- Creativity in research and discovery
- Correlates of immunity and biomarkers for TB vaccines
- Clinical trials: harmonisation and cooperation
- Rational selection of TB vaccine candidates
- Critical need for advocacy, community acceptance, and funding.

Buruli ulcer

Buruli ulcer is a neglected disease which needs to be detected and treated early in order to prevent disability. In 2004-2008, there were 26,000 cases worldwide with most of the burden in Africa. The prevalence in Ghana and Benin ranges from 50-3,500 cases per 100,000. The *Mycobacterium ulcerans* needs an animal host. Infection is associated with swamps and slow-moving water but transmission to humans is not understood. In Australia it is thought transmission to humans involves mosquitos.

- Diagnosis: several methods available but currently no rapid point-of-care test
- Treatment: antibiotics (3 months) and surgery to remove necrotic tissue
- Vaccine: currently none, the BCG vaccine seems to provide only short-term protection.

Leprosy

Leprosy still carries social stigma. There are about 250,000 cases per year; although the prevalence has decreased transmission continues (Rodrigues, *Lancet ID*, 2011). The clinical symptoms are caused by chronic granulomatous inflammation in skin and peripheral nerves (WHO classification: <6; 6+ skin lesions).

- Treatment: combination treatment, infectiousness reduced; relapse rate 2-3%; immune-mediated reactions (30% of patients with multi-bacillary disease); main treatment is steroids
- Prevention: chemoprophylaxis reduces risk for household contacts

- Vaccine: vaccination with BCG provides protection; no suitable animal model to assist search for specific vaccine.

TB research priorities

The WHO-TDR publication of 2013[1] and the WHO-Stop TB roadmap of 2011[2] list 10 priorities which are the same for TB, leprosy and Buruli ulcer

1. Improve diagnostics for infection, disease and drug resistance, especially point-of-care tests
2. Develop improved treatment and prevention regimens (based on current and new drugs)
3. Identify and validate biomarkers that facilitate the development of vaccines, diagnostics and drugs
4. Increase understanding of the disease pathogenesis to fuel discovery of drugs, vaccines and diagnostics
5 Increase understanding of the burden of disease, the modes of transmission and the impact of public health interventions
6. Develop novel vaccines and optimise current vaccines
7. Evaluate and optimise strategies to improve case finding and reduce barriers to treatment access
8. Optimise implementation of preventive therapy (for TB and leprosy), TB infection control and patient-centred TB management, especially drug-resistant TB
9. Evaluate and optimise new and current strategies to quantify, prevent and minimise disability and stigma resulting from these diseases
10. Evaluate strategies to strengthen health care systems to support control of these diseases.

We need to change the image of TB research and develop integrated, multidisciplinary approaches for mycobacterial diseases.

Conclusions

- TB, leprosy and Buruli ulcer remain important public health problems
- New diagnostics, drugs and vaccine(s) are needed to reduce the burden of disease, morbidity and mortality.

Comments

In the discussion that followed Prof. Churchyard's presentation, the following points were raised:

- Point-of-care testing: quality assurance is needed; bear in mind for EDCTP2 funded trials
- Alternative markers are needed
- Combining drugs with immune response to move forward. Although in trials the drugs were not inferior, there was a higher relapse rate. Therefore, immunotherapy should be included (some disagreement about this)
- For leprosy, there are drugs to stop the disease but not the inflammatory processes. Therefore, immune therapy will be important
- Although similarities between these diseases exist, differences and different priorities need to be recognised Pyramid of diagnostics with home test at the bottom: EDCTP should evaluate what exists and what is needed; there are many tests in the pipeline, but not all are really needed.

Diagnostics: Dr Catherine Boehme

Dr Catherine Boehme, Foundation for Innovative New Diagnostics (FIND) commenced by stating that interest and use of

1 www.who.int/tdr/publications/tuberculosis_research/en/index.html

2 www.stoptb.org/assets/documents/resources/publications/technical/tbresearchroadmap.pdf

TB diagnostics has increased over the last 10 years, particularly for MDR-TB detection. New WHO-endorsed diagnostic tools can enhance rapid detection and treatment, however, their potential impact is higher than that currently observed.

This is due to patient drop-out rates, delays to treatment and poor patient access (technical limitations, coverage and linkage to care). Partnerships should be developed to help understand healthcare systems, to identify how infrastructure and linkage to care can be improved. Since up to 60% of cases are diagnosed in the private sector, they should be involved in these partnerships.

The development pipeline contains many low, median and high complexity tools, especially in early development; on each level of complexity, one tool is on the clinical trial pathway to WHO endorsement.

The main unmet needs for diagnostic tool include: a triage test (to detect those with high risk of disease progression); more sensitive tools for work-up and treatment choice; and tools for treatment monitoring. We need to extend the utility of molecular tools, improve extra-pulmonary diagnosis and paediatric diagnosis. There is only one validated marker that is used in a urine test: lipoarabinomannan (LAM). More are needed; there are some in the pipeline which will be critical for filling the point-of-care gap. Collaboration is needed to share resources and set up biobanks to develop and test new tools. Also, the role of radiography in TB diagnosis should be re-evaluated.

Currently there are more than 90,000 people in on-going diagnostic trials. These are mainly impact trials after WHO endorsement but there are some pre-WHO endorsement trials. WHO endorsement of TB diagnostic tools is essential for public uptake and requires clinical trials with patient-reported outcomes. It is important to identify low-performance tests early to avoid further development (reduction of costs).

Research infrastructure should be strengthened, including:

- Access to bio-samples, e.g. MDR-TB and children
- Funding for clinical trials
- Maximising the impact of new tools (tracking and measurement)
- Partnership between researchers and national reference laboratories
- Providing expert guidance and training
- Post-marketing quality assurance.

Panel discussion on diagnostics

The presentation was followed by a panel discussion on diagnostics with contributions from Dr Catherine Boehme (FIND) and Dr Jim Gallarda (Bill & Melinda Gates Foundation) as well as the participants. The importance of biomarkers was highlighted again. Biomarkers help identify those who need treatment (and thus also to avoid over-treatment), identify likely responders, and enable phenotypic resistance testing. There is a continuum here between research and early development. Biomarkers can also be useful to assess treatment success or failure early on.

Requirements of an effective point-of-care test are:

- Good infrastructure
- Biomarkers for developers
- External quality assurance (sentinel markers)
- Harmonisation of regulatory procedures. At present country-specific results must be provided which is expensive and labour-intensive for small diagnostics companies and increases time-to-market.

Summary from Chairs

There are many candidates in the pipeline, but there are gaps for point-of-care tools, and for specific groups such as children (fewer than 20% detected) and paucibacillary leprosy. Non-sputum tests are needed for all populations. Innovative test approaches such as gene-based tests are in early stage development. Digital X-ray and smear test repurposing should be evaluated.

EDCTP has done important work so far for diagnostics, but it should cofund a trial platform with an established set of tests, so that trials can be done quickly and development of less promising candidates can be halted.

Sustained funding is needed for supranational laboratories that can perform external quality assurance and improve infrastructure and laboratory capacity.

More linkage with vaccine and drug clinical trials could be encouraged to optimise the use of samples for identification of biomarkers for diagnostic tool development.

To further optimise development EDCTP could:

- Set-up a committee to see what would be needed in five years and what is required to make this happen
- Look at infrastructure needs
- Open a continuous call for proposals so funding can be available as new tests become available.

Comments from the participants

- Pragmatic trials to assess implemented diagnostics to identify weaknesses early in order to find solutions and avoid under-performance (as with the Xpert MTB/RIF assay)
- Invigorate research by task shifting and moving into communities in HIV. Maybe more effort should be put in people in the community who are infected but asymptomatic. Serial testing (occupational/school) could detect recently infected persons and help understand the disease process
- Case studies demonstrating successful partnerships (funded by EDCTP), e.g. the 15 sites involved in the Xpert MTB/RIF assay trials that lead to WHO endorsement
- Draw parallels between TB and leprosy
- Important to consider healthcare settings and what happens to patients when diagnosed
- Joint calls from EDCTP2 to set-up collaborations between centres that can do clinical trials and those that can do diagnostics trials
- Better data sharing (too much duplication); there is a need for a mechanism to share data (comparable to biobanks)
- Systematic biomarker discovery; identification of antigens present in early infection that correlate with active rather than latent TB; biomarkers to know when to stop treatment
- Global partnerships needed for diagnostics as WHO endorsement will not be given based on African data alone; role for EDCTP in setting-up partnerships?

Global vaccine portfolio: Professor Stefan Kaufmann

Prof. Stefan Kaufmann, Max Planck Institute for Infection Biology, Germany discussed the global vaccine portfolio. Vaccines can be used pre-exposure (primary prevention), post-exposure in latent TB infection (secondary prevention) and in active TB (therapeutic/curative use). Current TB vaccines only provide partial protection (including for leprosy and Buruli ulcer). They can prevent disease outbreak,

but there is an urgent need for vaccines that prevent disease and that have a sterilising immunity.

There is a development pipeline of TB vaccines with different target populations: uninfected infants, infected adolescents/adults and adults with active disease. Other mycobacterial diseases could follow the lead of the TB vaccine pipeline.

Vaccine efficacy assessment requires biomarkers or biosignatures that are indicators of a biologic, physiologic or pathologic state; they could also identify high-risk subjects for vaccination and other preventive measures.

Future priorities

- Global portfolio management involving all stakeholders
- Rational selection of vaccine candidates
- Harmonisation between clinical sites
- Head-to-head trials for booster or combination, early safety, and immunogenicity trials:
  - This is a challenge because there is yet no immunogenicity outcome and therefore it is too early to go to head-to-head; there is a need for 'experimental medicines trials' for vaccines in order to develop preventive markers
  - Possible model: phase IIB HIV-vaccine trials with clinical protection led to the identification of unknown antigens. Encourage EDCTP to fund phase IIB TB-vaccine trials.
- Harmonisation with clinical trials in other disease areas (e.g. HIV and HIV-TB co-infection).

Comments

In the discussion that followed Prof. Kaufmann's presentation, the following points were raised:

- Co-infections (helminthic worms) and comorbidities (e.g. diabetes) can modify the effects of vaccines
- Head to head for safety and immunogenicity could be funded by EDCTP
- Need to test outside Africa to prove efficacy against different strains; EDCTP could set up partnerships
- Therapeutic vaccines follow the drug development process unlike preventive vaccines; enrol fewer participants.

Panel discussion: Global vaccine portfolio

Dr Hannu Lång, European Commission and **Ms Shiva Dustdar**, European Investment Bank (EIB), gave short presentations as introduction to the discussion on partnerships for developing the global vaccine portfolio.

Dr Lång reminded the participants that the European Union funds through the European Commission pre-clinical and phase I vaccine trials and that EDCTP is the relay for the subsequent phases. EDCTP is an excellent example of cooperation, not only within Europe but also with African countries. He mentioned the TB Vac project funded by the European Union for developing candidate vaccines which has an impact on the TB vaccine field.

Ms Shiva Dustdar stated that private-public partnerships, on a risk-sharing basis, are more effective for financing the development of TB vaccines. The EIB has established (2012), chairs and coordinates the activities of a Working Group with representatives from the EIB, the European Commission, the Gates Foundation, EDCTP, Aeras, and TBVI (Tuberculosis Vaccine Initiative). This group has developed a draft business case for TB vaccine investment: *Aeras TB vaccine research and development: a business*

case for investment[3]. In this analysis, they examined a global portfolio management approach for optimisation and transparency. They used a dynamic Monte-Carlo model to estimate the probabilities of success with a maximised public health impact of new TB vaccines. The key findings were that:

- A TB vaccine market exists (size 13-14 billion USD), mostly in developed countries, although only 25% of the market is due to differential pricing
- Benefit is long-term, suggesting that more investment and more candidate vaccines are needed to encourage public-private risk sharing
- Funders such as EDCTP have a role but they need to be flexible
- Revenues will come from high-income countries (many in Europe); these countries could pre-order so as to encourage vaccine industry to take the risk.

In summary, there is a significant market potential for TB vaccines, particularly an adult/adolescent vaccine. If only an infant vaccine were to be developed, the overall market potential is more limited. However, it is feasible that a vaccine commercialised initially for use in infants, could bridge to an adolescent/adult prime booster and thereby increase market share and revenue.

The overall market potential of a successful adult/adolescent vaccine seems sufficient to support meaningful financial returns to industry and potential niche public-private investors in the development of the vaccine portfolio. Having a robust and diverse pipeline of vaccine candidates in early development stages will be critical for attracting investment capital. A global portfolio approach will increase the likelihood of successful commercialisation and financial returns.

3 www.aeras.org/pages/the-case-for-investment-in-research-development

Comments and questions

- The model underpinning the business case is available for everyone – one can make one's own assumptions and investors to identify the inflection point
- Expectations for a succesful TB vaccine have a 'black swan' character. Who will take the risk? Set a strategy for the portfolio to allow flexibility
- Expectation that the GSK vaccine will be successful, leads to a higher likelihood of success between 2023 and 2024
- Portfolio management is perhaps possible for vaccines but for diagnostics and treatment it is more complicated to align all players and IP holders
- Industry point of view: once you have proof of concept industry will fund. As this analysis is based on modelling and assumes a (high) probability of success without a good animal model or biomarkers, we need to go to phase IIB to know if the chance of success is >20%. In the original model, the chance of success was low until phase IIB (~30%)
- As well as for more phase IIb trials, there is a need for funding of phase III trials so that development costs can be reduced
- Costs for treatment could be included in the overall model to offset investment costs
- Governance mechanisms are needed for the (growing) portfolio to identify any gaps.

Summary of the first day

Challenges for EDCTP2's future research agenda

- More attention should be paid to mycobacterial diseases other than TB
- EDCTP should be careful to integrate
  - Different communities

  - HIV and TB (both should be priorities in both programmes)
  - Pharmaceutical industry, in order to move forward for diagnostic tests.
- Point-of-care tests: more are needed as well as quality assurance procedures
- Fever occurs not only with malaria, but also with TB; portfolio for a range of diagnostic tests
  - Tools not for just one disease
  - New diagnostic tool for respiratory infections would need a wider partnership including other disease areas
  - TB diagnosis in those with fever and respiratory infections.
- Impact evaluations showed new tests were not as good as predicted; causes and remedies should be studied
- General agreement on the need for biomarkers and biosignatures; biomarkers are needed for clinical development (diagnostics, treatment and vaccines)
- Integrating diagnostics drugs and vaccine research by joining clinical sites into networks. Improved collaboration is needed; even within in the field of TB there are insufficient links between diagnostics, drug and vaccine research
- Biobanks from trials: there is a need for harmonisation, but samples are valuable and provide useful information
- Vaccines pipeline: good, robust but needs continued feeding; candidates need to move on; funding should be continued under Horizon 2020
  - EDCTP could play a role in supporting the development of gating strategies, portfolio management, and criteria for go/no go decisions (both for vaccines and diagnostics; the EIB has developed a model for vaccines)
  - More single vaccine trials are needed
  - For head-to-head vaccine trials immunological markers for comparison are needed.
- Strong endorsement for capacity building: policy makers and service providers should be brought in contact with researchers to improve implementation of innovations
- Capacity building for conducting operational or implementation research is important
- Service providers should link with those developing diagnostic tools
- The WHO will not give endorsement for products based on data only from Sub-Saharan Africa. Therefore, there is a need for partnerships to provide data from other regions
- National reference laboratories and supranational reference labs need sustainable funding
- Pharmacology is not studied enough, especially in paediatrics, drug-drug interactions; extrapolation from different populations and different parts of the continent is not possible.

3. Second day

Treatment I: Global drugs portfolio: Dr Richard Hafner

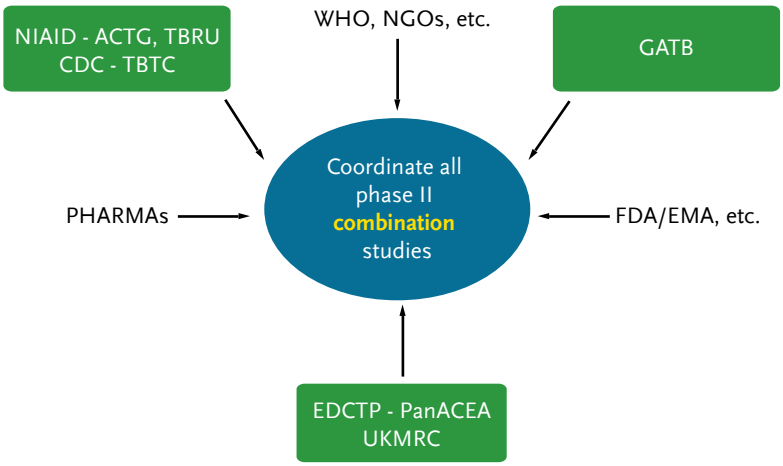
Dr Richard Hafner (National Institutes of Health/National Institute of Allergy and Infectious Diseases) warned that the drugs pipe line is not sufficient; there are a few molecules in phase II/III but none in phase I. Only 1 in 10 molecules in clinical development make it to market. If we aim to generate "five new or repurposed drugs and at least one 1-3 month regimen by 2020, this will require an estimated 21 additional new drugs to be in clinical development by 2015."[4]

There are safety and efficacy concerns with new drug classes. It is difficult to study the potential additive toxic effects with long half-lives and new metabolites for combination therapies. Therefore, it is important to optimise the use of existing treatments, e.g. different formulations/doses. The goals are to achieve sterilisation in the shortest time, to limit toxicity by using toxic drugs for short periods, to avoid simultaneous administration of three drugs or drugs with additive or similar toxicities and to prevent resistance.

Novel approaches are needed to assess efficacy of combinations, e.g. adaptive phase IIB trials with drop-the-loser/play-the-winner designs and seamless phase IIa-IIb-III transitions, with biomarkers for phase II assessment.

Host-directed therapies aim to reverse TB-induced immune defects and decrease tissue pathology/inflammation by autophagy[5]. However, this approach may not work and could cause harm; trials need to assess markers of lung function to monitor for worsening that indicates harmful effects.

Collaboration is needed in order to combine clinical trials capacity for the large phase III that are needed. No one group has enough resources for the necessary clinical trials. Phase II is critical, therefore there is a need for a planning and coordination forum (see diagram from presentation) which comprises members from the USA and EU, serves to exchange ideas and create synergy (3-monthly teleconferences), and fosters positive competition conducive to innovation (out-of-the-box approaches).



Comments

In the discussion that followed Dr Richard Hafner's presentation, the following points were raised:

- Drugs and immunomodulation (vaccine) could be combined so that drugs work better (autophagy). There is a lack of resources for TB compared with cancer or AIDS and this could help build bridges between disease research communities where inflammation is important
- EDCTP should fund combination drug trials for MDR-TB as this is where the future burden will be and treatment costs are high

4 www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011-2015.pdf

5 Choi et al., NEJM 2013;368(7):651-662

  - New drugs are needed not just for resistant strains; they can also be effective for non-resistant strains.
- Development of a formulation which could be inhaled instead of injected, would be great; however, it should be kept in mind that in the past it was shown that drugs go into healthy and not the damaged lung tissue
  - Different formulations can be tried and a PET (positron emission tomography) scan can be used to assess effects in the lungs.
- Promising drugs should be shared with the leprosy research community (immunomodulators have been used in leprosy for a longer period than in TB)
- Even when drugs are licenced, careful use is to be promoted (training); implementation studies should be important in EDCTP2
  - Specific studies in children and patients with HIV/AIDS should be conducted as there are not much data for news drugs on pharmacokinetics and –dynamics.
- EDCTP's aim to support African scientists should remain important:
  - Partners ask: "What will EDCTP do?" but the question should be "What can we do together?"
  - Capacity building and partnership: longer-term funding for capacity building consortia is needed.
- Outcome measurement should be improved with molecular assay (on-site) instead of culture
- Burden of Buruli ulcer is higher in children aged 5-15 years (treatment with high-dose rifampicin)
- There is clinical data on anti-inflammatories for active TB (and leprosy); EDCTP should prioritise these trials.

Treatment II: Clinical management of tuberculosis and mycobacterial infections: Professor Andreas Diacon, Professor Diana Lockwood, Dr Mark Wansbrough-Jones

Tuberculosis

Prof. Andreas Diacon, Task Applied Science, reminded the audience that before chemotherapy the 10-year fatality rate of TB was 70%[6]. Since the first drug in 1961, there has been a continuous development process with failures as well as successes. It is necessary to accelerate the time to approval. The time from first patient to FDA preliminary approval (not phase III) is more than seven years.

He stated that drug-resistance is not due to poor compliance but rather to some pharmacokinetic variability[7].

The goal for new regimens should be to have at least three drugs from new classes for all forms of TB, which are efficacious and safe, do not show resistance, have reduced costs for susceptibility testing, and can be combined with HIV treatments, while paediatric formulations are available.

Priorities to be discussed:

- Single drugs versus multiple drug regimens
- Funding: single studies (short-term) versus development programme (long-term)
- Adaptive trial designs versus head-to-head comparison
- Repurposing or optimising of old drugs versus development of novel drugs.

6 Tiemersma EW et al., PLoS One 2011 Apr 4;6(4):e17601. doi: 10.1371/journal.pone.0017601

7 Gumbo T et al., J Infect Dis. 2007;195(2):194-201; Dartois V, J Infect Dis. 2011;204(12):1827-9

Leprosy

Prof. Diane Lockwood, London School of Hygiene and Tropical Medicine, explained that in many settings TB and leprosy are treated together. Although the diagnosis of leprosy is more difficult, in contrast with TB there is an effective antibiotic treatment. Drug resistance has been limited by multidrug recommendations from WHO. Clinically, the inflammation that affects the skin and nerves can be treated with steroids. The associated stigma is strong.

There are 250,000 new cases per year. This is constant, so there is no break in transmission. More than 3 million persons are left with permanent disabilities.

Although combination therapy of rifampicin/dapsone/clofazimine (2 or 3 drugs for 6 or 12 months) has been successful, there is some evidence of resistance, adverse effects and poor compliance. Alternative regimens need to be developed.

Erythema nodosum leprosum (ENL) is a recurrent, long-term disease that can be treated with prednisolone or thalidomide. However, the mortality is high due to adverse treatment effects[8]. The ENL international study group (ENLIST) is collecting data prospectively (seven centres, four continents) to improve understanding, assess effectiveness of treatment and improve access to treatment. Currently there are 300 patients; the cohort can be used for future studies.

Remaining challenges for leprosy:

- Ongoing transmission
- Early diagnosis difficult
- Low capacity for clinical trials
- Chronic inflammation
- No reliable test for nerve damage
- Lack of biomarkers for prognosis
- Long-term immunosuppressants needed
- Stigma
- Funding for ENLIST.

Buruli ulcer

Dr Mark Wansborough-Jones, St George's, University of London, held a presentation on the clinical management of Buruli ulcer. In this disease the mycobacterium produces a toxin that causes sub-cutaneous necrosis which results in skin lesions. Although the incidence is low, it is a problem in the communities where it occurs, among others in Australia, near Melbourne, where there are mainly older patients; and in Ghana, where Buruli ulcer occurs in the south in shanty regions and rural areas around cities.

The current gold standard diagnostic test is PCR (polymerase chain reaction) on a swab/fine needle aspiration sample. Treatment is with antibiotics (and possibly amputation). It is important to focus on early detection; detected nodules can be excised with high success rates.

The research priorities are:

- Development of a low-toxic oral antibiotic
- Improvement of point-of-care diagnosis
- Capacity building
- Prevention is low priority since its transmission mode is not known and there are no vaccine candidates.

Future research priorities:

- Choice and dose of antibiotic (many patients are young)
- Duration of treatment (even after an 8-weeks treatment some patients remain infected)
- Optimal time for skin grafting

8 Addis Ababa series, *International Journal of Leprosy and other Mycobacterial Diseases*, 1985

- Adjunctive treatment to improve wound healing such as dressings and absorption/ neutralisation of mycolactone.

Comments

The following points were raised by several participants:

- Buruli ulcer is a rural disease where the incidence of HIV is lower; optimal time to start ART treatment should be determined
- Diagnosis of leprosy is difficult and therefore often late; infected people are often infectious for several years before diagnosis. There is also wide-spread environmental contamination in endemic areas making it difficult to break transmission
  - No consensus on utility of chemoprophylaxis to break transmission
  - A single dose is unlikely to lead to resistance but treatment needs to be widespread; this should be evaluated.
- A sub-unit leprosy vaccine should be in phase I next year; combined chemo- and immunoprophylaxis might be useful to break transmission.

Panel discussion: Partnerships in treatment development

Dr Carl Mendel: Global Alliance for TB Drug Development

In 2000, the Global Alliance was 'invented' as a product development partnership (PDP) in response to the absence of new drugs for neglected infectious diseases because there was no pharmaceutical industry involvement. This PDP is like a non-profit pharmaceutical company which collaborates with academics as well as with pharmaceutical companies.

Dr Perry Mohammed: Janssen Pharmaceuticals

Dr Perry Mohammed stated that collaboration between industry and local communities is the only way forward to ensure success in increasing access to HIV treatment in resource-limited settings. Industry contributes products, scientific expertise and trial experience to this process. Collaboration with regulators is also needed, not just for product authorisation, but also for implementing clinical trials.

It is important to have paediatric investigation plans and real world data, not just regulatory data. Pharmacovigilance systems should unify all registries, e.g. vaccines and drugs. Industry also brings expertise in medical education, which is essential for the appropriate use of drugs, but this should be a collaborative initiative.

Dr Dorothy Yeboah-Manu: Noguchi Memorial Institute for Medical Research

The Noguchi Memorial Institute for Medical Research in Ghana has implemented successful partnerships for TB and Buruli ulcer. There are national surveys of TB that provide data on TB resistance patterns in Ghana. PhD students involved in clinical studies are trained in the North and return to set up laboratories for 'on-site' analysis, thus building local capacity. There are partnerships with other African countries for population-based studies to study Western African genomics. Similar partnerships have been set-up for Buruli ulcer.

Discussion

In the discussion that followed the panel members' presentations, the following points were raised:

- Another example of a partnership is the PDP Funders Group consisting of funders (including EDCTP) and development agencies in which information and experiences are regularly shared in order to, for example, align reporting procedures

- Capacity building is important but needs sustained funding. Otherwise contract staff will leave after the clinical trial is closed. More transparency about what is in the pipeline would help research centres to plan and ensure sufficient capacity, not just in clinical centres, but also at clinical research organisations and data management teams
- Competitive calls for proposals could lead to unnecessary duplication. How could information be shared to allow collaboration and avoid duplication? [EDCTP responded that calls are competitive but that EDCTP encourages the establishment of consortia to apply for funding collaboratively]
- Alliances and academic freedom: the North-South relationship situation has changed over the last 10 years. Organisations from the North are often true partners and there is also an increase in South-South partnerships. It is important to identify the commonality in the objectives of partnerships and alliances and at the same time be aware of the symbiotic qualities of the relationship. Everyone brings something different to the table
- Co-infections are not sufficiently covered by partnerships: issues such as drug-drug interactions (synergistic toxicity) should be addressed; EDCTP could have a specific role in supporting this.

Control and implementation research: Dr Christian Lienhardt

Dr Christian Lienhardt, WHO Global TB programme, gave an introduction to operational research which aims to improve programme performance and outcomes. For example, deficiencies in TB-HIV control could be improved using technical or managerial interventions. We need better functioning programmes as well as new interventions to improve TB control and policy recommendations should be informed also by evidence from operational research.

This involves a paradigm shift to focus on needs. We can use effectiveness studies embedded in TB programmes, using routinely collected data and the increasing availability and use of individual patient-based recording systems. Recent methodology developments can also be used, e.g. pragmatic randomised controlled trials and phased implementation.

There is also a need to move from tools to strategies (from evaluation to impact), as in the implementation study for the Xpert MTB/RIF assay in Brazil. This was a stepped-wedged cluster randomised clinical trial, enrolling approximately 8 million people in more than 200 clinics to assess replacing the standard two-smear test with the Xpert MTB/RIF assay and then treatment.

Diagram of SORT IT approach from Dr Lienhardts'presentation

Creation of an enabling environment for performing operational research is key: WHO-TDR supports SORT IT (Structured Operational Research and Training Initiative)[9] which aims to improve healthcare systems through research on knowledge management and planning of capacity building.

9 www.who.int/tdr/capacity/strengthening/sort/en. This is a collaboration between TDR, The Union, and Médecins sans frontières

This approach is based on a proven workshop- and mentorship-based training model to build operational research capacity. It was developed by The Union and Médecins Sans Frontières. The training aims to teach practical skills to conduct operational research and publish the results.

Comments

The following issues were then raised by several participants:

- There is a need to bridge the gap between governments and researchers, as research evidence should be integrated into strategy development and policies
- EDCTP needs to recognise that operational research can be conducted according to a rigorous methodology and should be funded. In order to promote operational research, partnerships with existing projects could be established.

Panel discussion: Partnerships in control and impleentation research

The discussion on the importance of implementation research was started with presentations on leprosy and TB control by Dr Joseph Kawuma, WHO Treatment Action Group and **Dr Zaza Tsereteli**, Coordinator of the Barents TB Programme at the Barents Euro-Arctic Council, respectively.

Leprosy cannot be eliminated, but the incidence is now low, with 2/3 of new cases occurring Asia and South America. Most African countries have combined TB and leprosy programmes (some include Buruli ulcer also). TB is not usually considered a 'neglected disease', particularly since its association with HIV, but this lowered the attention on leprosy.

Outcomes research can improve health systems because the systems are empowered by doing the clinical study. For example, a healthcare systems research programme implemented by several partners, including the Welcome Trust in the UK, will fund research in low-to-middle income countries with approximately 5 million euro per year for a period of three years.

In this field EDCTP could be innovative, even audacious. Its original objectives were capacity building for clinical trials on drugs and vaccines. However, trials on diagnostic tools needed for drugs and vaccines trials could be included as well as research related to universal health care coverage. TB, leprosy and Buruli ulcer are poverty-related diseases and one of the major problems is how patients can have access to healthcare. There could be a call for proposals without specifying the trial design. One criterion for judging the proposals could be the suitability of the design proposed since the 'best' design depends on the study questions.

EDCTP has contributed to capacity for clinical trials and it will expand to phase III/IV in the second programme. But it is important that the clinical trials also answer important questions about how best to implement a new treatment, vaccine or diagnostic tool, if the research is going to have an impact on patients. Developing diagnostics and treatments that do not make a difference could be considered a waste of money.

Implementation research includes addressing the challenge of training healthcare workers to recognise rare diseases (and even TB) and to diagnose children, who are usually sent elsewhere. The use of existing or new tools for triage should be assessed. For example, the Xpert MTB/RIF assay has been endorsed by the WHO, but countries need to assess how to implement it in the same manner as for new drugs. In addition, policy makers need evidence that an intervention works before they will accept to pay for it.

EDCTP recognises the need to add value and its Strategic Advisory Committee has suggested to expand the programme to post-registration trials, cost-effectiveness evaluations, and pharmacovigilance. Thus, EDCTP will continue to stimulate the implementation of new products which should not stay 'on the shelf'.

However, EDCTP cannot be involved in all healthcare services research. This is the role of other partners and alliances; therefore it is not a question of go/no go but of who to go with! EDCTP needs to decide to be transformational; to be transformational it needs to support operational research. Its aim should not just be to contribute to our knowledge base, but to make a difference for people.

Summary and recapitulation of comments

The Chairs pointed out that these are comments for further consideration, not recommendations since it was not possible to prioritise them with input from all the stakeholders present at the meeting

Challenges for EDCTP2 future research agenda:

- EDCTP has achieved a lot and one of its challenges now is how to continue investing in the most productive and strategically important research, while also expanding its remit
- For TB, things are going well but we need to move faster.

Diagnostics:

- We need to be more innovative, so as well as assessing new approaches we should assess renewal of old tests (X-ray, smear) using digital reading
- EDCTP needs to support the more difficult fields such as diagnosis of TB in children, and to develop tests suitable for patients with TB and HIV co-infection.

Vaccines:

- Despite the fact that MVA85A did not demonstrate protection in a trial in children, it may still have potential in other age groups
- We will learn from the analysis of the banked samples; the good news is that we have a very varied portfolio
- The capacity to do phase I vaccine trials in Africa should be expanded
- There is a need to do head-to-head vaccine trials but in order to do that we urgently need biomarkers and biobanks
- The idea of global TB vaccine portfolio management initiated by TBVI and Aeras with potential co-funding through the European Investment Bank is innovative and could help provide the funding for future trials
- This model could also be used in other areas if it proves successful.

Drugs:

- There are international alliances, a pipeline and some promising new drugs and drug combinations
- But the clinical trials take too long, and we really need to move faster to get better regimens and MDR-TB drugs (which could also be used for non-resistant TB)
- Research data on drugs should be shared between the TB, leprosy and Buruli ulcer research communities
- Pharmacokinetic variability needs to be better understood
- Treatments that are being explored: host-directed therapies and autophagy that modulate host immunity.

Research in general:

- Adaptive trial designs offer promising possibilities for clinical trials. Support for new approaches to clinical trial designs could accelerate development of new drugs. What is the role of EDCTP in developing these innovative trial designs?
- Operational research could be integrated into different areas. This field is developing and could help measure and improve impact at population level
- The leprosy research community has received less attention; the HIV-TB coinfection issue attracts more attention and funding. Even TB research is not considered as attractive as HIV
- More multi-disciplinary approaches (also for leprosy and Buruli ulcer) need to be developed
- Although there was broad support for EDCTP to start to invest in this area, the recommendation was to be cautious
- EDCTP wants to ensure that new tools or treatments developed through its projects will be implemented so that they have the impact expected. This could be achieved through partnerships
- Policy makers need evidence to convince them to adopt new tools, treatments and vaccines.

Cross-cutting issues:

- There is a need to look for synergies between TB, leprosy and Buruli ulcer research in diagnosis, vaccines and drugs
- The same clinical trial sites could be used for different studies in order to ensure that trained staff remain
- The importance of biomarkers and biosignatures for diagnostics and also assessing treatment efficacy was stressed
- Many participants called for support of establishing accessible biobanks
- There is a need for pharmacokinetics and pharmacodynamics research in paediatric populations
- Operational research should move from validation studies (assessing a tool) to implementation studies (assessing how the tool can be used effectively)

- Laboratory strengthening is much needed even though a lot has been achieved. The goal is to have in each country as much laboratory work done as possible
- Capacity strengthening also needs to be prioritised under EDCTP2.

Partnerships:

- Equality is needed in partnerships, without Northern domination
- EDCTP1 has supported a number of very productive consortia and networks; EDCTP2 will hopefully support many of these; the value of strengthening networks of excellence was recognised
- EDCTP should support the development of South-South partnerships as well as North-South partnerships
- One challenge for EDCTP2 will be to prioritise the requests for funding from the TB, leprosy and Buruli ulcer research communities
- Clinical trial capacity building should continue with a partnership approach such as that of the Wellcome Trust which encourages synergy between funding agencies
- EDCTP needs a long-term strategy for continuous support to clinical trial centres; it could strengthen its ties with the existing TB and NID partnerships
- Multi-country trials (including outside Africa) are needed for leprosy and Buruli ulcer; partnerships and networks (e.g. ENLIST) need to be created
- Important to remember that the three diseases have their commonalities but also their specificities; the joining of these research communities should bring added value.

Professor Patrice Debré, EDCTP General Assembly representative for France, extended at the end of the meeting words of thanks to the speakers, participants and the organising team.

Professor Charles Mgone, EDCTP Executive Director, closed the meeting after having summarised the next steps in using the results of this and other stakeholder meetings. The EDCTP Strategic Advisory Committee will advise the General Assembly in deciding what will be in the scope and what will not be in the scope of EDCTP2. Some of the points raised have already been implemented:

- Future calls will be broader as was mentioned in this meeting
- The Strategic Advisory Committee has already approved the continued support for the Networks of Excellence
- Global partnerships are already and will be established (also for leprosy); partnerships with countries outside Africa will be established through partnerships with organisations working with non-African countries. Some clinical trials already have network connections outside Africa
- Regarding biobanks, expert meetings will be organised to discuss the issues
- Indirect costs will be recognised: full costs will be reimbursed under EDCTP2 in line with Horizon 2020
- Action for ethics and regulatory issues has already been initiated.

Annex 1. List of participants

Name	Institution	Country
Aklillu, Eleni	Karolinska Institute	Sweden
Arthun, Erika	Bill & Melinda Gates Foundation	USA
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