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Title: Taking forward the World TB Day 2016 theme “Unite to End Tuberculosis” for the WHO Africa Region

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Taking forward the World TB Day 2016 theme “Unite to End Tuberculosis” for the WHO Africa Region

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## HIGHLIGHTS

- Tuberculosis (TB) remains a 'global emergency' ever since it was declared as such by the WHO in 1993
- Of the 9.6 million people who developed TB in 2014, 28% were in WHO The Africa Region where the case rate was 281 per 100,000 population
- An estimated 1.2 million (12%) of TB cases were HIV-positive and the African Region accounted for 74% of these cases.
- The global spread of multi-drug-resistant TB (MDR-TB) is now a major public health challenge
- Scientific, Political and Funder communities seriously need to 'Unite to End TB', the theme for the 2016 World TB Day
- TB control programs in Africa can only succeed if mechanisms for close engagement of developing country scientists, healthcare workers, patient groups, governments and policy makers is ensured by funding and donor agencies.
- Several funder, political and community initiatives provide hope for achieving goals of the WHO post-2015 TB strategy.
- TB activities and funder investments in Africa need to be aligned in parallel with international efforts at improving social and living conditions, and with the 'one health' initiative

ABSTRACT

Tuberculosis (TB) remains a 'global emergency' with an estimated 9.6 million new TB cases worldwide reported in 2014. Of these 28% were in the WHO Africa Region where the annual case detection rate was 281 per 100,000 population -more than double the global average of 133 per 100,000. Of the 9.6 million people who developed TB, an estimated 1.2 million (12%) were HIV-positive and the African Region accounted for 74% of these cases. Three million people with TB remain undiagnosed and untreated. Globally, an estimated 480,000 had multi-drug-resistant TB (MDR-TB). Whilst from Africa, only South Africa has reported high prevalence of MDR-TB, it is likely that all of sub-Saharan Africa has unreported high load of drug resistant TB. Tragically, in 2014 only 48 percent of individuals diagnosed with MDR-TB had successful treatment and estimated 190,000 people died of MDR-TB. Of the global TB funding gap of US\$ 0.8 billion, the largest funding gap was in the African Region, amounting to US\$ 0.4 billion in 2015. The MDR-TB pandemic in particular now threatens to devastate entire regions and may fundamentally alter the life expectancy and demographic profile of many countries in sub-Saharan Africa. The Theme designated for this year's World Tuberculosis (TB) Day, March 24<sup>th</sup> 2016, is 'Unite to End TB. From the Africa Region, there is an urgent need to seriously address the political, economic and social factors, which influence host-Myco**ba**cterium tuberculosis interactions and result in disease. We discuss recent political and funder initiatives which provide renewed hope for alleviating Africa's TB and TB/HIV problems.

Tuberculosis (TB) remains a 'global emergency' ever since it was declared as such by the World Health Organization (WHO) in 1993 (1). The Theme designated for this year's World Tuberculosis (TB) Day, March 24<sup>th</sup> 2016, is 'Unite to End TB' (2). World TB Day is held to commemorate the day in 1882 when Professor Robert Koch announced his ground breaking discovery of the cause of TB, the bacillus *Mycobacterium tuberculosis* (3). At the time of Koch's announcement in Berlin, TB was widespread and rampaging through Europe and the Americas, causing the death of one out of every seven people (4). Over the ensuing 60 years, TB rates in Europe and USA started declining well before the advent of TB drugs and the *Bacillus Calmette–Guérin* (BCG) vaccine, highlighting that TB epidemics are driven by complex socio-economic factors and host- *M. tuberculosis* interactions (4-11).

It has been one hundred and thirty four years after Professor Koch's discovery of *Mycobacterium tuberculosis*, and yet, TB today remains the most common cause of death from an infectious disease worldwide (1). According to the 2015 World Health Organization (WHO) Annual TB report (12), in 2014, an estimated 1.5 million people died of TB from 9.6 million people who developed active TB worldwide. Of these 9.6 million TB cases, 28% were in the WHO 'Africa Region' where the incidence rate was 281 new TB cases per 100,000 population. This is more than double the global average rate of 133 per 100,000 (12). An estimated 1.2 million out of the 9.6 million TB cases (12%) were HIV-positive and the African Region accounted for 74% of them. It is important to note that in 2014, 3 million people with TB went undiagnosed and untreated or unreported. A significant proportion of these were in sub-Saharan African countries. Critical to reducing the global burden of TB and slowing down TB transmission rates, is to identify and treat all active cases of pulmonary TB and render them non-infectious (13). Furthermore, those individuals with high risk of re-activation of latent TB infection need to be identified and treated (12).

While the overall global incidence of TB has been declining slowly over the past decade, drug-resistant strains of *M. tuberculosis* have emerged worldwide. Tragically, in 2014, an estimated 190,000 people died of MDR-TB (12) and only 48 percent of the 480,000 people estimated by WHO to have multi-drug-resistant TB (MDR-TB) had received successful treatment. The number of MDR-TB cases in 2014 remains unchanged from the figure estimated in the previous year's 2013 WHO Annual TB report. This may represent an underestimate, or could be explained by inadequate laboratory infrastructures and resources to correctly diagnose and report MDR-TB at health facility and national levels. Whilst from Africa, only South Africa has reported high prevalence of MDR-TB, it is likely that all of sub-Saharan Africa has a significant burden of unreported drug-resistant TB.

Over the past three decades the world has experienced the most profound of public health challenges with the appearance of new infectious pathogens with epidemic potential such as Ebola virus (EBOV), Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV) and now Zika virus (ZIKV) and antibiotic resistant bacteria. We have also seen the resurgence of malaria, TB and other infectious diseases which were being brought under control (14). We have also seen the emergence of the devastating pandemic of the Human Immunodeficiency Virus (HIV), which was largely responsible for the breakdown of TB control programs. Together, TB and HIV have imparted a huge toll on health services and the economies of sub-Saharan African countries (15). The MDR-TB pandemic in particular now threatens to devastate entire regions and may fundamentally alter the life expectancy and demographic profile of many African countries (16). An urgent need exists to address priority needs for MDR-TB (16), especially in Africa where resources and capacity are limited. MDR-TB has relevance beyond the worst affected countries, since TB does not respect national or international borders. The number of people forced to flee their homeland due to conflicts or natural disasters in the past few years reached an all-time high worldwide (17). A large number of refugees are being cared for in low and middle-income countries. Furthermore the large funding gap (difference between the actual funding needs of TB programs for TB prevention, diagnosis and treatment, and the actual amount of funds available) for the African Region was US\$ 0.4 billion in 2015 (12).

The WHO post-2015 global TB strategy aims to reduce global TB incidence by 90% before 2035 (18). However, the data in the 2015 WHO annual TB Report shows a bleak global TB situation. Dr. Lucica Ditiu, Executive Director of the Stop TB Partnership aptly summarized the situation recently by stating: "It is a global disgrace and human tragedy that TB—a curable disease—is killing around 1.5 million people per year and nobody speaks about ending it". "We know it can be done, we know how it can be done, we know how much it will cost us – we need to have the desire to do it and energy to move on. Ours can be the generation remembered as the one that turned the tide on this enormous yet treatable epidemic" (19).

The Global Plan to End TB 2016 -2020 launched by Stop TB Partnership (19) has three fundamental targets called 90-(90)-90:

Aim 1 is to have 90% of all people with TB diagnosed and treated,

Aim 2 (which is coupled to aim 1), is to ensure 90% of the most vulnerable populations (children, people living with HIV, miners, addictive substance users, prisoners, homeless, and migrants and others- we would like to include healthcare workers and patient carers in this list) in all countries (high or low income) are diagnosed and treated, and

Aim 3 is to ensure 90% of people diagnosed successfully complete treatment with services to ensure adherence and social support.

In addition the Global Plan calls for an additional US \$9 billion for research and development into improved diagnostics, treatment regimens and vaccines that are highly effective and non-toxic. The current funding trends for TB research have been rather disappointing (20). In the Africa Region, there is also an urgent need to seriously address the political, economic and social factors, apart from HIV, which influence host - M. tuberculosis interactions and increase the risk of developing active TB or re-activation of latent TB infection, and result in poor treatment outcomes (7-9). So what can researchers, healthcare workers, community groups, governments, private sectors, NGOs and funders do more to effect a major shift from the current status quo of global TB and TB/HIV control efforts in Africa? To achieve the laudable and ambitious 90-(90)-90 aims, the global scientific, political and funder communities seriously need to 'Unite to End TB', (21) and heed calls to action which have been regularly repeated on World TB Day (5-11) for scaling up of TB services for improved diagnosis, management and control of TB (22).

Recent political and funder initiatives provide new hope for the WHO Africa region to reduce the burden of TB and TB/HIV. Several novel and encouraging initiatives now present opportunities for the sub-Saharan African scientific and political communities to engage more proactively in galvanizing resources, conducting priority scientific and operational research, and facilitating national TB program control efforts, to take forward boldly the aims of the Global Plan to End TB in Africa: Examples of these are:

- 1) The European Union supported 'EDCTP2' programme (23) which provides unique opportunities for developing equitable, European-African partnerships (24) clinical research, capacity development and training on poverty related diseases which includes TB and TB/HIV TB (25).
- 2) The Global TB Caucus (26), a formidable network of parliamentarians and political representatives from over a 100 countries.
- 3) An African network called WARN-TB (27) which works with WHO-Tropical Disease Research Program (WHO-TDR) plans to develop new approaches that will increase the numbers of people diagnosed and treated, build capacity for TB operational research, and support resource mobilization for TB control.
- 4) A USA National Action Plan (28) for combating MDR-TB which aims to mobilize political will, financial commitments from donors and governments of MDR-TB endemic countries.

5) Expansion of Africa based grassroots community initiatives: a) The ENGAGE-TB approach (29) where the five founder countries (the Democratic Republic of the Congo, Ethiopia, Kenya, South Africa and the United Republic of Tanzania), have been joined by Burkina Faso, Côte d'Ivoire, Malawi, Namibia and Zimbabwe. b) Increasing activities of community TB groups like "TB PROOF" (30) which was founded in 2012 by African Health Care Workers and students after suffering multiple personal experiences with MDR-TB (31,32), and increased commitment from 90 non-governmental and other civil society organizations from 35 African to the WHO End TB Strategy (33).

6) The United States Agency for International Development (USAID) "Challenge TB Award" to Fight TB, a five-year cooperative agreement to implement the USAID global TB strategy (34).

These, and other initiatives, now offer unique opportunities and motivation for African scientists, healthcare workers and governments to 'Unite to End TB'. A book recently published entitled 'African Health Leaders – Making a Change and Claiming the Future' (35), contains important and relevant messages for the TB and TB/HIV fraternity in sub-Saharan Africa. Edited by Professor Francis Omaswa and Lord Nigel Crisp, Chairman of the UK All Party Parliamentary group on Global Health, a tireless advocate for global health and international development issues, and renowned for his commitment for improving health services in Africa, the book contains chapters are written by three generations of African leaders including the ex-Prime Minister of Mozambique, Dr Pascoal Mocumbi, and Rwandan Minister of health Dr Agnes Binagwaho, among others who have led health services transformation in Africa. They detail their experiences and vision for Africa health systems emphasizing that "African leaders and leadership in health have an enormous role to play in a new Africa, where Africans recognize that the responsibility for making Africa an equal player in the global community rests primarily with Africans." They address key global health issues and emphasize that there are lessons that other nations can learn from Africa. In addition they challenge Africans to take up the mantle and lead from the front. This supports the repeated calls for Africa to get independent from the dominance of research in Africa by western institutions (37,38), and to build infrastructure and capability that can be sustained long term.

The second program of the European and Developing Countries Clinical Trials Partnership (EDCTP2) (23,38) now provides unique opportunities over the next 10 years for African scientists to take up leadership of poverty related diseases including TB and develop equitable north-south clinical trials research and training partnerships based on priority issues. EDCTP2 has substantial funding for clinical trials research, training and capacity development on TB as one of the major poverty-related disease in sub-Saharan Africa (25). Three funding schemes or 'actions' are supported under the EDCTP2 program



(38): 1) Research & Innovation Actions (RIA), 2) Coordination & Support Actions (CSA), and 3) Training & Mobility Actions (TMA). Research & Innovation Actions (RIAs) are primarily clinical research activities and clinical trials conducted in partnership between European and Sub-Saharan African (SSA) countries aiming at increasing the number of new or improved interventions for TB, HIV malaria and other poverty-related diseases. Coordination & Support Actions (CSAs) are primarily accompanying measures, such as activities to develop, strengthen and extend clinical research capacities in SSA. They aim to maximize the public health impact of research results by promoting their translation and supporting their uptake in policy-making, health systems and clinical practice at local, national, regional and international levels. Training & Mobility Actions (TMAs) are activities which foster career development (fellowships) of individual junior and senior researchers from SSA, support training and mentorship of researchers, and promote mobility of individual researchers. Between 2009 and 2014, EDCTP supported four African (South, East, West and Central) regional networks of excellence (39) which enabled African scientific leadership to develop and address capacity development and training needs, identify gaps for tackling TB and develop locally relevant solutions. Progress made under the first EDCTP program requires to be consolidated and research capacity built strengthened further.

It is important that alongside EDCTP2 and other current donor initiatives, African governments must seriously commit to, and set aside a specific budget, for TB research, capacity development and control initiatives in their own countries. Furthermore the conventional and longstanding focus on promoting development of new TB drugs, diagnostics and vaccines (40) must be supplemented by novel innovations which can focus on host-factors which are responsible for, and drive, the poor treatment outcomes of MDR-TB treatment. This includes the neglected issue of long term functional disability which arises from permanent lung damage suffered by a significant proportion of TB patients who recover after treatment but are unable to lead normal lives or go back to work (41,42). A whole range of Host-directed therapies are now becoming available which will require evaluation in clinical trials for their impact when used as adjunct therapy, on shortening the duration of TB treatment, improving treatment outcomes of MDR-TB and preventing pulmonary damage and functional disability (43). These will be taken forward by a recently formed Host-Directed Therapies consortium (HDT-NET) (44), a consortium of partners from all Africa regions in collaboration with institutions in Europe, Australia and USA (45).

TB control programs in sub-Saharan Africa can only succeed if appropriate mechanisms for close engagement of national scientists, healthcare workers, patient groups, governments and policy makers are put in place. Furthermore, scaling up sustainable interventions for TB care and treatment requires high-level political commitment and adequate financial and human resources (46). Central coordination

under the national government's stewardship will be essential. African governments must step up current efforts to further improve the quality of proactive TB screening and identification of all missed, sub-clinical and undiagnosed cases of TB (47,48), improve health services to provide quality TB treatment, and provide follow up care. Efforts must also be stepped up to improve capacity for rapidly diagnosing MDR-TB to address this deadly and growing epidemic in Africa (12). We also re-iterate that it is only through empowerment of indigenous younger generation scientists, program managers, and healthcare workers, that the current status quo can be changed significantly.

The only way forward to achieve the aims of The Global Plan to End TB 2016 -2020 is for researchers, funders, national governments, industry, pharma and community groups to 'Unite to End TB' and promote the four WHO sub-themes for World TB Day, March 24th 2016: 1) Together we can better test, treat, and cure TB, 2) Together we can end TB stigma and discrimination, 3) Together we can drive TB research and innovation, and 4) Together we can prevent TB by ending poverty. All national governments, funder and donor investments into TB in Africa should be aligned in parallel with international efforts at improving social and living conditions, and the 'one health' initiative with a holistic approach to managing poverty related diseases (49). Only then will significant progress be made in achieving WHO post-2015 End TB strategy goals, and gains in achieving TB control will be enhanced and sustained.

#### AUTHOR CONTRIBUTIONS

All authors conceived the idea of a World TB Day viewpoint. All authors contributed equally to the writing and editing of content of this article.

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