Review

Advances in tuberculosis

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The review attempts to highlight recent advances in understanding the epidemiology, pathogenesis and treatment of tuberculosis. Strategies in the development of new tools should consider the needs of target populations that are dictated by the diversity in host and pathogen genetics.

Key words: Advances, tuberculosis, review.

INTRODUCTION

Despite the emergency measures in the last decade, tuberculosis (TB) remains one of the most serious global public health challenges. In 2009, the world saw the largest number of TB cases and deaths ever reported in history with 9.4 million incident cases and 1.68 million deaths in the year (World Health Organization, 2010). TB incidence rose rapidly and stabilized in sub-Saharan Africa peaking in 2004, strongly influenced by the human immunodeficiency virus (HIV) epidemic (Corbett et al., 2006, 2003). Prevalence increased more than threefold from 800,000 in 1990 to 2.8 million in 2006 (Kaufmann and Parida, 2008). TB remains the number one killer of HIV co-infected patients in Africa and is still the leading cause of death in the most productive age groups (World Health Organization, 2011; Lopez et al., 2006). Africa is the only WHO region that might not meet the STOP TB mortality target by 2015.

Drug resistance poses a serious challenge to TB control. In 2008, an estimated 440,000 patients (3.6% of all newly diagnosed cases) had multidrug resistant

(MDR) TB of whom only 7% were diagnosed and notified. In the same year, 963 cases of extremely drug resistant (XDR) TB were reported from 33 countries, a ~25% increase from the 772 cases reported in 2007. Over 40,000 cases of extremely drug resistant (XDR) TB have been reported from over 58 countries by 2010 (World Health Organization, 2010). In general, TB prevalence and incidence has been going down in the last decade. Nevertheless, TB is still out of control, particularly in Africa, with continued transmission complicated by the frightening menace of extreme drug resistance. This article attempts to provide an overview of recent advances in the understanding of TB from the perspective of control needs in Africa.

RECENT ADVANCES IN UNDERSTANDING TB

Genomics

The importance of understanding the biogeography of tuberculosis for the development of new tools is beginning to receive wider attention. The global population structure of *Mycobacterium tuberculosis*

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suggests its adaptation to specific human populations. The evidence of biological causality and relative contribution of social factors for such an association are of high interest in this regard (Hershberg et al., 2008).

Tuberculosis is an ancient disease that has probably evolved with ancestral humankind over several millions of years. The earliest evidence for TB disease in hominins dates back to about 500,000 years before present in Homo erectus fossils was found in Turkey (Kappelman et al., 2008). However, the strength of this bio-archaeological evidence is still disputed (Roberts et al., 2009). A more recent report of TB infection found in humans dates back to 9,000 years ago (Hershkovitz et al., 2008). *M. tuberculosis* complex (MTBC), the group of mycobacteria causing tuberculosis is estimated to have been present for over 3 million years (Gutierrez et al., 2005), diverged from its kin, *Mycobacterium leprae,* the causative agent of leprosy, over 33 million years earlier. Members of the MTBC are estimated to have differentiated much more recently. The highest diversity is found in Africa with all known lineages represented, three of which are still restricted to this continent suggesting that MTBC originated in Africa. Based on the results of DNA sequencing of 89 genes in each of the 108 strains of *M. tuberculosis* complex collected from different regions of the world, Hershberg et al. (2008) proposed "an out-of-Africa- and back" evolutionary scenario for MTBC. MTBC was first spread within Africa giving rise to two *Mycobacterium africanum* lineages. A phylogenetically "ancient" lineage (Lineage 1) accompanied the out-of- Africa migration of modern humans. Current distribution of lineage 1 appears to reflect the early routes modern humans might have followed in the spread out of Africa. Evolution of conducive ecological niches in centers of rapid population growth led to the development of three new "modern" lineages that further spread to different parts of the world, including back to Africa. Current global distribution of dominant lineages can be linked to historical routes of human migration by land and sea. The hypothesis postulates that modern strains became more virulent as they adapted to large host populations, with "ancient" lineages more likely to develop latency while more modern lineages tend to a faster disease progression. The implication of this process to the epidemiology of TB in the current environment of rapid population growth and urbanization is that more virulent strains are likely to emerge as large number of susceptible hosts become more readily available, particularly in Africa.

It is possible that additional MTBC lineages might be added to the list as isolates of more areas of the world are scanned by molecular typing. A new lineage, the "Woldeya lineage", or Lineage 7 was recently identified in the northern part of Ethiopia with genetic roots that date further back in time than with the other modern lineages (unpublished data). This lineage is restricted to the Horn of Africa with all isolates in the global database so far linked to Ethiopia or recent Ethiopian emigrants. It is postulated that lineage 7 might have survived from the period of the ancient human migration out of Africa. Currently, this lineage constitutes less than 5% of strains identified from clinical cases in the area. With increasing globalization, it is possible that the population structure of *M. tuberculosis* will become homogenized as evidenced by the relative decline of *M. africanum* in West Africa (Groenheit et al., 2011) possibly due to a competitive advantage of the re-introduced modern lineages in transmission efficiency.

Selection of mycobacterial antigens for the development of diagnostic tests therefore needs to consider the phylogeography of *M. tuberculosis*. Gambians infected with Lineage 6 (*M. africanum*) were found to have an attenuated response to ESAT-6 antigen, an important component in several vaccines and diagnostic tools under development. Progression to active disease was found to be lower in *M. africanum* subtype 2 compared to *M. tuberculosis* despite similar transmission efficiency (de Jong et al., 2008) suggesting attenuation of the genotype for the West African host. The sensitivity of the Capilia TB assay may for example be lower in West Africa because the dominant TB lineage (lineage 5) in the region harbors mutations in the *mpb64* gene that the test depends on.

Effectiveness of drugs or vaccines could be similarly affected. Several studies from different geographical areas have suggested that the Beijing genotype is associated with an increased risk of multi drug resistance (MDR) and XDR (Dheda et al., 2008; Dheda et al., 2010). This is particularly true in areas where the prevalence of this lineage is increasing (Hanekom et al., 2011). Special attention will be needed where this genotype is present in terms of rapid diagnosis, treatment adherence and infection control, among other things, to reduce the possibility of spread of drug resistance. A recent study from Ghana that compared the proportion of phenotypic drug resistance between the different *M. tuberculosis* lineages reported that *M. africanum* was less likely to be drug (particularly streptomycin) resistant than the *M. tuberculosis (sensu stricto)* prevalent there*,* which predominantly belongs to Lineage 4, also known as the Euro-American lineage (Yeboah-Manu et al., 2011). Understanding the impact of genetic diversity in clinical settings and its role in the emergence of MDR and XDRTB may be essential to predict which way MDR TB might evolve in the future.

In a study that compared the panel of cytokine responses induced during infection of human macrophages with strains of different lineages of *M. tuberculosis*, it was noted that relative to ancient lineages, modern lineages induced lower levels of pro-inflammatory responses, and thus lower induction of the adaptive response (Rakotosamimanana et al., 2010). This was interpreted as reflecting the evolutionary differential adaptation to host density with a predominant strategy of latency (ancient) or an increased ability to cause early progressive disease (modern). This again

illustrates the significance of host-pathogen co-evolution in the pathogenesis of TB.

One reason for the variable efficacy of BCG in different geographic regions (Colditz et al., 1994) could be due to differences in strain genetics (Hart, 1967). It has been postulated that the Beijing genotype is less vulnerable to BCG-induced immunity (perhaps because of increased virulence) and that widespread BCG vaccination might have actually offered it an evolutionary advantage, although the evidence for this remains inconclusive (Hanekom et al., 2011). Efficacy of BCG vaccination in mice was altered when mice were challenged with the Beijing rather than H37Rv laboratory strain (Grode et al., 2005; Lopez et al., 2003). It is important to note that most of the vaccine strains currently under development seem to belong to Lineage 4 (Gagneux and Small, 2007) although Lineages 1 (East African Indian), 2 (Asian or Beijing) and 3 (Central Asian) account for a much higher share in global burden of TB disease. Ahmed and Hasnain (2011) have suggested that the success of the TB program in India could in part be due to the predominance of the ancestral lineage (Lineage 1) which tends to be more "protective", "less rapidly disseminating at the population level" and "less prone to acquisition of drug resistance" than Lineage 2 that is dominating in East Asia. Although much work is still needed to confirm these assumptions, the possible implications of strain genetics to disease control are evident.

Pathogenesis

M. tuberculosis complex interacts with the human immune system in a way that leads to latent infection that may reactivate later. Unlike with several other pathogens that develop antigenic diversity as a mechanism for immune evasion to escape destruction by the host, the epitope regions of the *M. tuberculosis* antigen genes or T cell epitopes are actually under strong selective pressure to be maintained (Comas et al., 2010). The pathogen needs recognition by the host T cell immune response in order to establish itself in latency or induce destruction of host tissue to facilitate transmission. The fact that *M. tuberculosis* is limited in its sequence diversity in T cell antigens may benefit development of diagnostic tools that can be used across different geographical regions. On the other hand, its strategy of exploiting the immune system for its dissemination at the population level raises the possibility that vaccine induced immunity could inadvertently increase transmission, if it worsens pathology without improving bacterial control – a consideration that vaccine research cannot afford to overlook.

A recent review (Dorhoi et al., 2011) has identified key areas of progress but also listed key issues to address regarding the immune response to TB in humans. Not much detail is known regarding the role of the tubercle and caseation in TB as well as factors involved in resolution of inflammation within granulomas. More data are emerging on how mycobacteria exploit the granuloma to their own advantage. The pathogen appears to accumulate host cholesterol (probably to use as energy source) and activates a large number of genes to help fight oxidative stress. The role of neutrophils in unresolved inflammation and potential involvement in reactivation is yet to be clarified. Likewise, the role of B cells, which are regularly seen in considerable numbers within granulomas, remains far from clear.

Macrophages are probably the first cells to encounter *M. tuberculosis*, particularly alveolar macrophages in the lung. Much is yet to be learned about the regulation of inflammation at the macrophage level during the acquired response to TB. Among the recent areas of research interest is the effort to further understand the surface and intracellular molecular mechanisms and consequences of this encounter. An example is autophagy, a process of intracellular degradation of host cellular components, often for homeostatic purposes. Recently, autophagy has been described as a major pathway for control of intracellular proliferation of mycobacteria and it clearly plays a role in the host's immune response (Kleinnijenhuis et al., 2011).

The antibacterial effects of IFN-γ, a critical cytokine for control of mycobacterial growth, are mediated at least in part through the induction of a GTPase IRGM1 that translocates to mitochondria where it also regulates autophagy. The balance between autophagy and apoptosis which dampens inflammation, and pyroptosis, which stimulates it, is suspected to determine the outcome of mycobacterial infection. Interestingly, a polymorphism in IGRM has recently been described to protect against "modern" *M. tuberculosis* (or *M. tuberculosis* sensu stricto) but not *M. africanum* in a West African population (Intemann et al., 2009). The cross regulation between the pathways of inflammasome activation and autophagy is thus a current area of research interest (Huynh et al., 2011). A mycobacterial gene that enhances intracellular bacterial survival is reported to inhibit autophagy.

Biomarkers

Another area of intense research is based on the need to better understand disease processes in TB. Tuberculosis is a dynamic continuum of host pathogen interaction with multiple types and degrees of pathological processes going on within the same host simultaneously resulting in a spectrum of immune responses. Activities to characterize these immune responses in terms of the disease spectrum fall under the umbrella description of "biomarker studies". Unlike diagnostics, which describe the condition of an individual at a point in time, it is hoped that biomarkers might also provide prognostic information (Wallis et al., 2010) allowing us to differentiate TB infection, disease, and latency, and providing information

on the likelihood of cure, protection, relapse or reactivation of disease. Success in biomarker discovery is thus obviously closely linked with progress in understanding host pathogen interactions in TB.

Correlates of risk and protection are required for rapid screening of candidate TB vaccines. In particular there is a need to provide clinically relevant surrogate endpoints for TB vaccine trials (Ottenhoff, 2009). Correlates of protection can only be confirmed through randomized clinical trials that establish the effectiveness of a vaccine. However, comparison of the immune response of individuals who develop disease or not following exposure to TB can identify correlates for risk of tuberculosis (Walzl et al., 2011) and therefore possibly for failure to control the disease or develop immunity.

Although vaccine immunogenicity is currently measured based on the prototypic TH1 cell cytokine (IFN γ) responses from cells in peripheral blood, recent data raise concern that these parameters may not correlate with risk of disease (Kagina et al., 2010). Th1 specific cytokine responses, including of polyfunctional T cells, measured at 10 weeks post-immunization did not correlate with risk of disease in BCG vaccinated newborns followed for two years. CD4+ T cell expression of IFN γ, co-expression of IFN γ, TNF α and IL 2 (by polyfunctional CD4+ T cells) or CD8+ T cell responses did not correlate with risk of disease during the first 2 years of life. The susceptibility to mycobacterial infection of patients with defects in the IFN-γ pathway affirms the importance of this cytokine but the study cited above indicates the inadequacy of relying on a single effector response in a process that involves a number of other players (including $\gamma\delta$ T cells, CD1-restricted T cells and regulatory T cells (Tregs).

Biomarkers have also found their place in diagnosis. The tuberculin skin test (TST) is perhaps the oldest immunodiagnostic and it remains in use a century after its introduction, although the limitations of TST as a marker for active tuberculosis are well recognized. In the last decade, T-cell based interferon gamma release assays (IGRAs) using more specific antigens than TST have been employed for the diagnosis of latent TB. Although IGRAs are more sensitive and specific than TSTs, they may be no more suitable for differentiating between active and latent infection (except probably when samples originate from lesions, an unlikely situation in most TB diagnostic set ups). A recent meta-analysis suggested that IGRAs do not have high predictive value for development of active tuberculosis ((Rangaka et al., 2011) and concluded that the identification of better predictive markers was essential. Promising results have been reported in this regard with the use of poly-cytokine bio-signatures (Chegou et al., 2009) and measurement of expression levels of mRNA transcripts for IL-8, FOXp3 and IL-12 β in ESAT-6 stimulated polymorphonuclear cells (Wu et al., 2007). T cells secreting only TNFα have recently been proposed as indicators for active TB (Harari et al., 2011). T cells secreting only IFN γ were

also reported to be more frequent in patients with ongoing disease (Casey et al., 2010).

The quest for specific and sensitive serological tests has so far failed (Steingart et al., 2011; Steingart et al., 2007). An innovative approach with high throughput screening for antibodies against the entire *M. tuberculosis* proteome has recently identified a small pool of antigens that are recognized in sera of patients with active tuberculosis (Kunnath-Velayudhan et al., 2010). Such a systems immunology approach is likely to take centre stage in the search for biomarkers in the next years.

Markers that can predict risk of relapse in an individual at baseline are also critically needed, for example markers that may reflect the extent of disease. Current indicators of disease severity such as chest X ray reading or bacterial load as measured by time to positivity in liquid culture are difficult to standardize and scale up.

Sputum culture conversion at 2 months after TB treatment is at present recognized as the most reliable predictor of non-relapse and is used as a surrogate end point in clinical trials to accelerate approval of new TB drugs. Its prognostic value at the individual patient level has however been questioned (Mitchison, 1993), but at any rate a marker of potential treatment outcome that gives an answer earlier than 2 months into treatment is desperately needed. Another drawback is that the test relies on sputum collection, which is particularly difficult in children. Changes in cytokine ratios (IFN-γ/IL-10 or IL4/IL-4δ2) in PBMC stimulation assays are receiving attention as potential alternative predictors of treatment outcome. Bactericidal activity in whole blood culture is another promising test that could prove to be useful in identifying effective drug regimens. The comparison of changes in frequencies of certain T cell types secreting cytokines (either IFN γ only, or combinations with IL-2 and TNF α) might help to predict cure. With successful treatment, the pattern has been observed to shift to that seen during latency.

Future approaches to biomarker discovery will certainly make use of "omics" (transcriptomics, proteomics and metabolomics). Unique transcriptional profiles that could differentiate between active and cured (Mistry et al., 2007) or active and latent tuberculosis (Maertzdorf et al., 2011) have been described. Proteomic fingerprinting of serum identified two serum markers (serum amyloid A and transthyretin) that could distinguish tuberculosis from other differential diagnoses (Agranoff et al., 2006). Although no such data have emerged for TB yet, metabolomics is another approach that future biomarker discovery is likely to explore (Walzl et al., 2011).

Diagnostics

The WHO has recently endorsed a number of tests for use in disease endemic countries. These include commercial liquid culture systems and the rapid nucleic

acid based line-probe assay for species and drug sensitivity confirmation in smear positive patients. Less expensive non-commercial culture and drug susceptibility testing options are still very relevant for resource limited settings in the context of reference laboratories or other laboratories with sufficient culture capacity. WHO endorses the microscopically observed drug susceptibility test (MODS), nitrate reductase assay and indirect colorimetric redox indicator methods for rapid detection of MDR as interim solutions until automated systems are affordable and available (Wallis et al., 2010)

One recent advance in the rapid diagnosis of TB is the introduction of the Xpert MTB/RIF automated system (Cepheid, Sunnyvale, USA) recently endorsed by the WHO (Boehme et al., 2010). This integrated sample processing and nucleic acid amplification system can detect M. tuberculosis from sputum in less than 2 h with high sensitivity and specificity in smear positive, and a moderate sensitivity (around 71-72%) but high specificity in smear negative cases. It is less subject to contamination or infection risk and easy to use although it still requires adequate laboratory infrastructure and training (Theron et al., 2011b; Van Rie et al., 2010). Even though it is highly suited for rapid diagnosis and MDR screening at the peripheral health facility level, its current price tag, including the running cost per patient, exclude its extended applicability for use in disease control programs of resource limited countries, at least as it stands today. Its inability to detect INH resistance is another disadvantage. Operational research is necessary to determine its performance in different populations with various levels of HIV prevalence, mycobacterial strain diversity and drug resistance mutations. Its impact on adherence and patient related outcomes requires further investigation (Theron et al., 2011a).

Important gaps remain in the currently expanding global TB diagnostic pipeline. Point of care (POC) diagnostics that do not add much to the cost of TB care and do not require running sophisticated equipment are desperately needed. Additional shortcomings include the absence of reliable diagnostic tests for detection of TB in children, in smear negative tuberculosis and in HIV co-infected individuals. The sensitivity of nucleic acid based techniques in smear negative and extra-pulmonary cases, needs improvement (Miller et al., 2011).

Meantime, existing tools can be optimized for better impact. Compelling evidence has recently emerged to support the concept that same day diagnosis of tuberculosis with two on-the-spot sputum specimens can reduce the risk of default (Cuevas et al., 2011b). WHO stop TB and country efforts are underway to replace conventional microscopy with expanded use of LED microscopy in TB control programs. LED microscopes can exploit the increased sensitivity of fluorescence microscopy under routine conditions at low cost, with longer use times between bulb replacement and without the need of a dark room while offering the same specificity (Cuevas et al., 2011a).

Vaccines

Neonatal vaccination with BCG does not prevent pulmonary TB in adults or stop TB transmission. Although it protects against severe forms of TB in children (the most susceptible age), it has variable efficacy hampered by a number of factors including prevalent helminthic infestation. Its safety is compromised in HIV infected individuals. Nevertheless, it remains the only vaccine against TB to date. Two strategies are being employed to develop a new TB vaccine. One strategy is to replace BCG with a whole organism (recombinant improved BCG or attenuated M. tuberculosis) and a second one is to enhance the protective efficacy of BCG with booster vaccines as either protein-adjuvant or a recombinant viral vector. The main vaccine targets are infants, adolescents and HIV-infected individuals.

There are at least 14 candidate vaccines currently in clinical trials. (http://www.stoptb.org/wg/new_vaccines, accessed 11.11.2011). Two recombinant strains of BCG have been evaluated in humans and shown to be potentially more potent than BCG. The first was rBCG30 over-expressing the 30 kDa major secreted antigen from *M. tuberculosis.* A recombinant BCG strain engineered to secrete listeriolysin leading to antigenic escape into the cytoplasm is currently in a Phase IIa trial in South Africa (clinicaltrials.gov trials identifiers NCT00749034; NCT01113281). Attenuated strains of M. tuberculosis are still in the pre-clinical phase. Several BCG-booster vaccines have entered human trials. M72 recombinant protein delivered with AS01 and AS02 GlaxoSmith-Kline adjuvants showed a relatively reactogenic profile when tested in PPD-negative volunteers in a Phase I study in Europe. This vaccine is currently in Phase IIa in South Africa (clinicaltrials.gov identifiers:NCT00600782; NCT00950612). A fusion protein of ESAT-6 and antigen 85B (Hybrid I) administered in IC31 adjuvant has completed three phase I trials, including one in PPD positive volunteers in Ethiopia (clinicaltrials.gov trial identifier NCT01049282). HyVAC IV, the next generation of this vaccine where ESAT-6 was replaced with TB10.4 to avoid interference with diagnostic tests based on ESAT-6, is now undergoing Phase I study in Sweden and South Africa ((http://www.aeras.org/portfolio/clinical-trials.php?id=19). The newest of the recombinant protein vaccines is H56, a vaccine designed to provide protection in both uninfected and latently-infected individuals: this vaccine contains antigens (ESAT-6 and Ag85B) which are expressed in early infection and another (Rv2660) which is expressed primarily in chronic/latent infection. Among the recombinant viral vectors, Aeras 402/Ad35-85B-TB10.4 is in Phase II trial in South Africa (clinicaltrials.gov identifier NCT01198366). Modified vaccinia virus Ankara 85A (MVA) has undergone 12 human trials so far with another four currently underway, including in HIV-infected individuals in Senegal and South Africa. (clinicaltrials.gov trial identifiers NCT00395720, NCT00480558 and NCT00731471).

In the absence of validated correlates of protection or animal models, efficacy studies remain a challenge for rapid vaccine development because of cost and the time needed for completion. Although clinical trial sites are being established and strengthened in high TB burden sites, raising enough resources to ensure that adequate numbers of such sites in diverse geographic regions are well prepared and have the funds for large scale efficacy trials appears to be the daunting and yet critical task of the next years. The WHO STOP TB estimate of the cost of a TB vaccine to be licensed by 2015 is approximately 3.5 billion USD (Kaufmann et al., 2010). It should be appreciated however that in the long run, the return on investment in vaccines is very likely to greatly outweigh its original cost (Kaufmann et al., 2010).

Further screening of other vaccine candidates in the preclinical pipeline to select which should go into further development may benefit from in vivo and in vitro models that might be developed in the course of efficacy trials of the current leading vaccines. Most of the current candidate vaccines in the pipeline are pre-exposure intended to replace BCG or boost it. Post exposure vaccines that prevent disease progression, therapeutic vaccines that could achieve sterile cure or reduce duration of treatment as well as vaccines that prevent infection are much needed. Whole heat-killed Mycobacterium vaccae (an environmental saprophyte) has undergone extensive evaluation to supplement chemotherapy although publicly available data do not allow definitive conclusions about the benefits of this approach (Kaufmann et al., 2010). Much less advanced are vaccine strategies to prevent infection. Such an approach may develop from better understanding and exploitation of processes that take place in the pulmonary tissues and B cell compartment as well as lessons from better designed models for studies in TB.

Treatment and new drug development

Effective treatment of MDR remains a challenge. WHO treatment guidelines for MDR TB have recently been updated by an expert group (Falzon et al., 2011) based on best available evidence to recommend implementation in national programs. Emphasis is placed on wider availability of drug sensitivity testing using molecular techniques and monitoring of sputum with culture for early detection of treatment failure. Treatment for an intensive phase of more than 8 months and a total of at least 20 months is recommended, preferentially as ambulatory. The guideline recommends ART for all patients with HIV and drug-resistant TB requiring second-line anti-TB drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment.

Ten compounds have progressed into the clinical development pipeline in the last 10 years among which six are specific for TB. There is however much unmet need in TB drug development. First line treatment is still too long and involves a number of drugs with potentials for severe side effects and risk of increasing drug resistance. Pediatric treatment regimens and formulations are not optimal. Existing drugs are inadequate for successful cure of MDR and particularly of XDR patients. Less than 69% of MDR cases are cured after 18 months of directly observed treatment. The drugs are poorly tolerated and too expensive for control programs to scale up for universal access. Only 1% of MDR cases were estimated to have received adequate WHO-recommended treatment in 2008 (World Health Organization 2010). Treatment of TB in HIV infected patients is complicated by the interaction with antiretroviral drugs, often requiring individualized treatment for best results. Shorter and safer treatment options than isoniazid or rifampicin are needed for treatment of latent tuberculosis. Progress is unfortunately delayed by financial shortage, estimated at over 75% (Ma et al., 2010) the lengthy, expensive and risky nature of drug development and low market incentives for the private sector, as well as inadequacies in the capacity to conduct controlled clinical trials to support registration of new drugs.

TB/HIV

Despite the high risk of mortality and relapse after treatment of HIV associated TB, co-infection treatment regimens are still not fully sorted out. A recent meta-analysis highlighted the paucity of evidence on HIV-TB co-infection treatment, including optimal dosing schedule and duration of rifamycin as well as timing of ART (Khan et al., 2010). Duration of treatment with daily rifamycin of over more than 6 months was associated with lower risk of failure and relapse suggesting that the currently recommended duration is inadequate in co-infection (Nahid et al., 2007).

CONCLUSION

More understanding of the basics in tuberculosis is essential and one methodology that has received particular attention in recent years is the use of a "systems" approach ("systems biology", "systems immunology", or "systems epidemiology") to generate hypotheses and test them through mathematical models. The knowledge gained could inform development of better tools for diagnosis, treatment and prevention of tuberculosis.

Key downstream research questions include operational targets of how to maximize the yield from existing tools in resource-constrained settings. Building capacity for effective partnership within networks to carry out good quality vaccine and diagnostic trials in high burden settings is necessary. National initiatives can

promote knowledge of international principles of research ethics in high burden countries to facilitate clinical trial site development. Functional ethics review committees and national regulatory authorities are critical components of a sustainable research structure in endemic countries. International collaboration should encourage empowerment of local institutions to generate quality data specific to the operational requirements at site and improve program performance based on best available evidence.

Some progress has been made in the control of tuberculosis. The incidence rate of TB is falling albeit at a very slow rate of less than 1%/year (World Health Organization, 2010). This is low compared to the drop in incidence in Western Europe of 4-5%/yr before chemotherapy and of 7-12%/year after the introduction of effective drugs (Borgdorff et al., 2002). Although prevalence is falling globally, the WHO target of halving the prevalence of TB by 2015 is unlikely to be achieved. New tools are definitely required to reduce the TB burden and eventually achieve the elimination target of less than 1 incident case per million by 2050 (Lonnroth et al., 2010). On the other hand, not all currently available tools are being utilized to their limits, particularly in areas where the TB burden is high. In 2008, 1.6 million or 39% of all new sputum smear positive cases were missed by the DOTs programs. Among the 1.37 million TB HIV co-infected patients, only 7.3% received ART. Limitations in implementation of the STOP TB strategy for TB control have recently been outlined by Marais B et al (Marais et al., 2010). Key among them is lack of adequate commitment by national governments to control TB compounded by allocation of meager national funds to competing priorities.

New technologies will not be sufficient on their own if there is no system in place to make effective use of them in patient care. A weak health system is increasingly recognized as one important impediment in meeting TB and other MDG targets (Atun et al., 2010). Measures to strengthen systems in governance, financing, health workforce, information management, procurement and supplies and in service delivery must complement all the other efforts for success in TB control, a process which can only be realized within the context of the national systems of countries when owned, sustained and scaled up.

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