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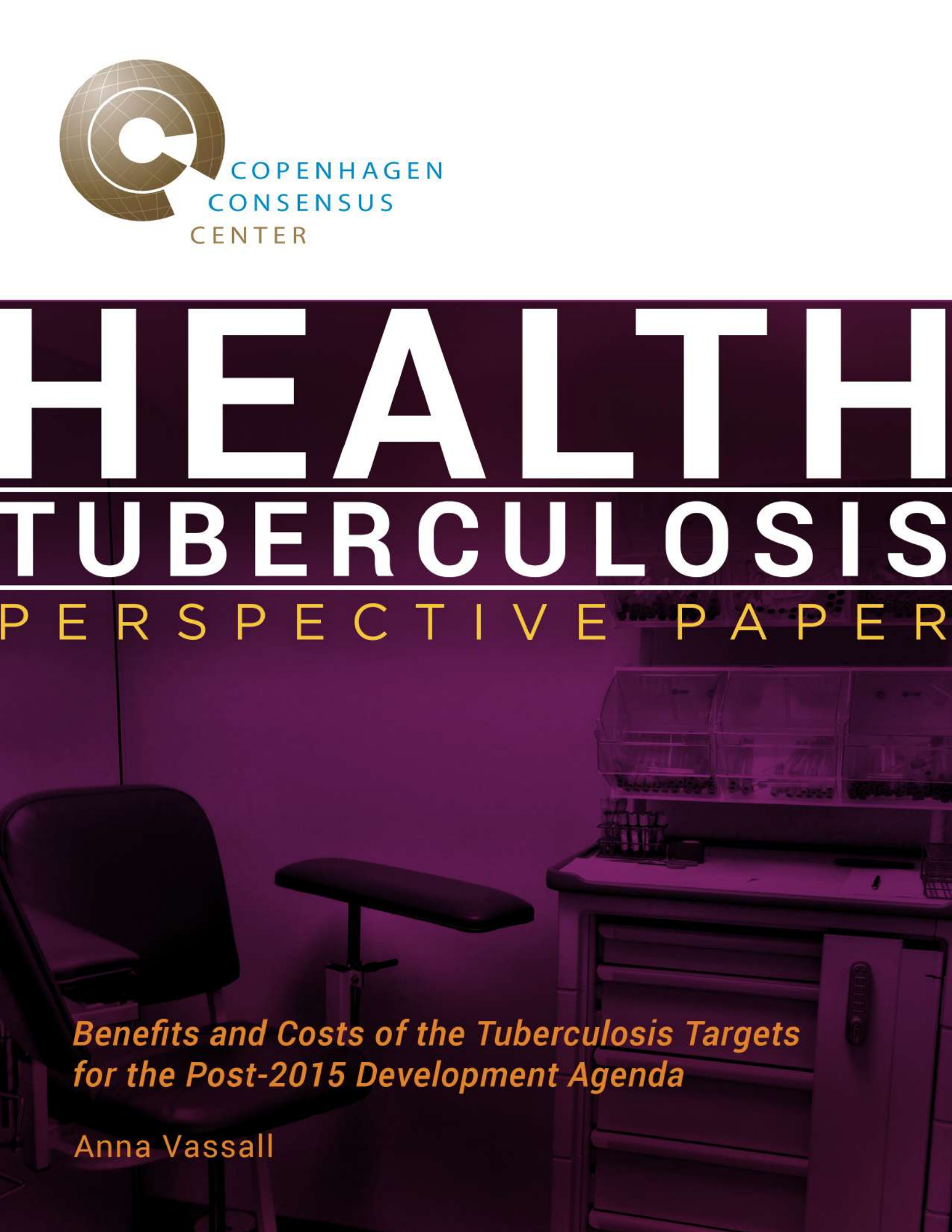

Benefits and Costs of the Tuberculosis Targets for the Post-2015 Development Agenda

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POST-2015 CONSENSUS

Benefits and Costs of the Education Targets for the Post-2015 Development Agenda

Post-2015 Consensus

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Introduction

The economic case for investment in tuberculosis (TB) control is compelling. TB control has been part of an essential package of health services for most low and middle income countries (LMICs) for decades, based on TB control's relatively high returns. The economic case, put simply, is that TB treatment is low cost and highly effective, and on average may give an individual in the middle of their productive life around 20 additional years of life, resulting in substantial economic and health return. Moreover, the delivery of high quality TB services can: prevent the spread of the disease to others; slow the emergence of drug- resistant forms of the disease, a dangerous and costly form of TB; and, disproportionately benefit the poor. Yet, to date, globally TB control is underfunded, both in relative and absolute terms [1]. The most recent global estimates suggest a resource gap of around US$ 2 billion per year [2], with TB receiving less than 4% of total development assistance for health (compared to HIV receiving 25%, and maternal and child health around 20%) in 2011 [3].

This report seeks to present a clear economic case for substantially increasing investment in TB control post 2015 from its current levels. The report first outlines the public health case for TB, highlighting the fact that TB remains one of the largest global killers. The report then highlights that, despite the low levels of funding, TB control to date has been a success story in terms of reaching the MDG targets, demonstrating that investment can achieve benefits at the population level. The report moves on to describe in detail the interventions that are key to TB control. While at the core of TB control is a cheap and effective treatment, the reality in many LMICs is that the complexity of identifying TB, weak health systems, the emergence of drug resistant forms of TB, and, co-infection with HIV; mean that in practice the TB response is multi-faceted. Rather than adopt a blunt advocacy approach, and assume that this 'real world' complexity does not exist, the paper takes an open approach and identifies these challenges and highlights the potential costs to address them. Finally the paper estimates the returns to investment in TB control. It reviews the current evidence to illustrate the cost and benefits of being identified, diagnosed and treated for and discusses what the need for renewed and increased investment in TB control at the global level.

Background

The global health burden of TB

In 2010, Tuberculosis (TB) was ranked 13 in terms of its contribution to the global burden of disease: a key component of the 47% of the global disease burden from communicable, maternal, neonatal, and nutritional disorders, which primarily impact LMICs and the world's poor [4]. Over 9 million individuals fell ill with TB in 2013, and TB remains a major cause of global mortality, with the annual number of deaths from TB being estimated at 1·4 million persons in 2013, which is on par with other major killers such as HIV and Malaria; and is a substantial (and primarily preventable) proportion of the 53 million deaths occurring globally per year [5]. Around 13% of the annual cases of TB and around 30% of all TB deaths are among persons living with HIV [6]. HIV increases the risk of mortality and the presentation of TB in those living with HIV is atypical meaning that TB, in those living with HIV, can be difficult to diagnose [6].

In simple terms the progression of TB has two stages. The first is *latent TB* infection. Over 2 billion people worldwide are latently infected with TB. Of those infected, approximately 5% develop *active TB* disease (become TB cases) within 18 months, followed by a further 5% risk of developing active TB disease over a lifetime [6]. The risk of developing active TB increases substantially following HIV infection [7]. Active TB can be broadly divided into two types: TB which is drug- sensitive – responding well to a standard combination first line treatment; and, multi-drug resistant TB (MDR-TB) which is resistant to two or more drugs (isoniazid and rifampicin) in the first line standard TB regimen. The treatment of MDR-TB is has poor outcomes, is complex and can be costly [8-10]. While MDR-TB can be spread and circulated among populations, its origins lie in the misuse, poor delivery and adherence of TB treatment [11]. Globally, between 1994 and 2010, multi-drug resistance was observed in 3.4% of all new TB cases and in 19.8% of previously treated TB cases [12]. It is estimated that, in 2013, there were almost half a million cases of MDR-TB globally. The pattern of MDR-TB varies considerably by region with some of the highest levels being reported in the Russian Federation (Murmansk oblast, 28.9%) and Eastern Europe. A particularly challenging form of MDR-TB, which is highly resistant to treatment to both first and some second-line drugs, is extensively drug resistant tuberculosis (XDR-TB). This form of TB is also now emerging in some settings, with four countries (former Soviet Union countries and South Africa) reporting that 10% of their MDR-TB cases were extensively drug-resistant [12].

Millennium Development Goals (MDG's) for TB

The global targets for TB, pre-2015, reflected in the MDGs, and supported by the several periodic Global Plans to Stop TB, were to detect at least 80% of TB cases and successfully treat at least 90% of these TB cases by 2015. Reaching these targets was estimated to cost around US$56 billion (between US$ 4-6 billion annually) between 2006 and 2015, and was anticipated to achieve a decreasing incidence of TB by 2015, and to ensure that prevalence and death rates should be halved, as compared with 1990 levels [13].

While TB remains an important global health issue, there is cause for optimism concerning the achievement of the MDGs. The over-arching objective of the MDGs targets, to halt and reverse the spread and impact of TB, is beginning to be met. A combination of TB control strategies, social and economic development and health systems improvements have positively impacted TB incidence, prevalence and mortality. Between 1990 and 2010 there was a 38% reduction in the disease burden from TB (per 100,000 population) [14]. Since 1995 it is estimated that 37 million lives have been saved [15]. Deaths from tuberculosis in individuals who are HIV-negative have decreased from 1·8 million in 1990 to 1·3 million in 2013, a -1·4% annual reduction [5]. When examining mortality rates (age adjusted[1]), the rate of decrease has risen over time from a decline of -3.3% per year between 1990 and 2000 to -3.7% annually between 2000 and 2013[5]. The World Health Organisation (WHO) estimates that overall the TB mortality rate has fallen by 45% between 1990 and 2013, almost reaching the MDG of a halving the death rate from TB globally [2].

[1] (TB has rising incidence and mortality rates with age which mean that ageing of the world's population in the absence of other changes will naturally lead to higher
numbers of cases and deaths)

However, the absolute number of TB cases globally however continues to rise. The number of incident cases for tuberculosis in individuals who are HIV-negative has increased from 5·0 million in 1990 to 7·1 million in 2013 - a 1·5% annual increase. However the rate of TB incidence (age-adjusted) in individuals who are HIV-negative has improved, from being stable between 1990 and 2000, to reducing -0.6% annually between 2000 and 2013[5]. As a consequence of shortened duration of disease through improved treatment and declining incidence rates, the World Health Organisation estimates that prevalence of the TB has fallen worldwide by 41%[2] [2]. However, this remains still somewhat below the MDG target of 50% reduction by 2015.

Post-2015 goals

The goals adopted in this report at those ratified by the World Health Assembly. In May 2014, the World Health Assembly, passed a resolution approving with full support the post-2015 Global TB Strategy with its ambitious targets in May 2014. The strategy aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and new TB cases by 90% between 2015 and 2035, (with interim targets in 2025) and to ensure that no family is burdened with catastrophic expenses due to TB[15]. The 'End TB' strategy accelerates the rate of decrease in both TB mortality and incidence substantially compared to the MDG targets. The targets also highlights the importance of placing TB in the context of broader developmental objectives, in particular the ambition of universal health coverage and financial protection of the poor from the catastrophic expenses associated with TB. The full resolution also highlights the importance of tackling the problem of MDR-TB and promoting collaboration across international borders.

TB control interventions required to reach post-2015 goals

Although progress in the last two decades suggests that TB control is beginning to work, an effective TB response has been hampered by weak health systems, poverty and sub-optimal medical technologies. This section summarises the current interventions available to control TB, and highlights the potential role of both strengthened health systems, development interventions and new clinical technologies to accelerate TB control.

Identifying individuals to be screened or diagnosed for TB

Identifying those infected (or at a high risk of infection) and/or with active TB is complex. Latent TB is asymptomatic. The symptoms of (active) pulmonary TB include cough, fever, night sweats and weight loss, many of which are similar to symptoms of common diseases. Pulmonary TB in those with HIV may be asymptomatic or may present with a lesser range and intensity of symptoms. Extra-pulmonary TB can affect any organ of the body with varied symptoms and manifestations; and these symptoms may also present differently in those with HIV [6]. These complexities mean that to date around 30% of all cases of active TB go unrecognised [15]. The WHO also estimates that currently around half a million people with latent TB are on preventative therapy, far below the numbers that could potentially benefit from it, primarily due to difficulties in reaching populations with latent TB [2].

[2] It should be noted that the WHO estimates differ from those from reference [2], due to different the use of different methods and assumptions about TB case detection rates (from which back calculations of true incidence are made)

Most TB programmes rely on primarily on 'passive case finding' to identify cases of active TB. This strategy is based on the expectation that those with TB symptoms will present at health services for their symptoms, and that health professionals are sufficiently skilled to recognise and act on them. Passive case detection is also considered the mainstay of preventing transmission, given that infection is airborne, and symptomatic patients tend to be more infectious than non-symptomatic ones. However, in many LMICs health system access is poor. In some cases even, when geographical access is sufficient, there may also be limited capacity within health providers to recognise symptoms, particularly in health systems with high levels of unregulated private providers or very fragmented health systems. Moreover, the yield of passive case detection in settings with high numbers of asymptomatic or atypical TB (for example in populations with high numbers of individuals living with HIV) may be insufficient.

The limits of passive case finding, and the low case detection rate globally, has provoked some countries to use more active forms of case detection. This more active form of case finding can also be used to reach and treat those populations with a high risk of re-activating latent TB. In countries like South Africa, with high levels of HIV, a policy of 'intensified TB case finding' has been adopted [16]. This requires that all people living with HIV, wherever they receive care, should be regularly screened for TB using a clinical algorithm (commonly a symptom screen, but also some times including x-ray) at every visit to a health facility or contact with a health worker [17]. Those without TB symptoms may be provided with treatment for latent TB, while those with symptoms may go onto the (active) TB diagnostic clinical algorithm.

For some 'high risk' populations screening for both latent and active TB may move out of health facilities and be brought to the community [18]. In some settings, like Bangladesh, with a strong community infrastructure, community health workers (CHWs) may be used to identify those at risk of TB [19]. In other communities with very high levels of HIV, mobile units may be used to deliver a range of services including screening for TB [20]. For contacts of those recently diagnosed with TB, contract tracing may be adopted [21], either using a community based infrastructure or outreach workers. TB screening services may also be brought into prison and mining populations. Health workers may also be subjected to routine TB screening. In settings with high levels of private provision, TB programmes may support private providers notify (and possibly go on to diagnosis and treat) TB either by supplied essential equipment and supplies, regulation or provider payments [22-29].

Screening and treatment of latent TB

Providing preventative TB treatment in those populations with a high risk of developing active TB is recommended by the WHO [2, 17, 30]. High - risk population include contacts of those with active TB, persons living with HIV and those with other co-morbidities such as diabetes. Latent infection can be diagnosed using two main methods: tuberculin skin test (TST) or interferon-gamma release assay (IGRA), the latter being more expensive but more specific than the former [31-34].

For those in high risk groups who have latent TB, (and for those with HIV with unknown latent TB status), preventative treatment may be provided where active TB has been ruled out. The optimal treatment regimen for latent TB is still being evaluated, but currently the WHO recommends a 6-9 months treatment of one TB drug (isoniazid) [35]. Alternative or

complementary strategies for some population groups are 36 months to lifelong treatment for persons living with HIV [36], or shorter course combined therapies (for example a 3 month combination of two TB drugs isoniazid and rifapentine [37]). Longer regimens are considered important for some groups, particularly where high population levels of TB may cause re-infection. Shorter regimens may be easier to adhere to, but this needs to be balanced with increased drug toxicity [6].

Diagnosis of active TB

There are a number of different methods available to diagnose active TB. Smear microscopy is recommended by the WHO and is a widely used, often 'point of care', low cost, method of TB diagnosis. Those who have positive smear test, are described as having 'smear positive' TB. However, it is far from a perfect test, and may miss substantial numbers of those with active TB, particularly in settings with high numbers of individuals living with HIV [38, 39]. Those who have the form of TB that cannot be diagnosed by smear microscopy are described as having 'smear negative' TB. The WHO also recommends the Xpert MTB/RIF assay for widespread use in the diagnosis of TB. This test increases sensitivity [40], however the per test unit cost is considerably higher than that of smear microscopy [41].

Beyond these initial rapid tests, there are a number of tests that are more accurate. Culture in liquid medium is considered the gold standard TB test. Culture based tests however take time to provide results, and can require substantial investments in laboratory infrastructure [42]. As a consequence these tests are often not available or when they are they are either too slow (in the case of those co-infected with TB and HIV health status can worsen quickly) or a high rate of default is observed as patients do not come back for test results. In many settings, particularly in populations with high rates of HIV, clinicians often use a combination of x-ray (a sensitive, but not very specific test in the case of TB) and 'empirically' treat patients [43]. There is little known about the sensitivity and specificity of empirical treatment in different settings, and it is likely that the success of this approach depends on the training of clinicians, and their exposure to large numbers of TB cases [44].

The diagnosis of MDR-TB provides additional challenges. Microscopy cannot identify new drug- resistant TB, but Xpert MTB/RIF can identify cases of rifampcin-resistant TB, a strong indication that a patient has MDR-TB. Culture based tests also are used to diagnose MDR-TB and can offer confirmation to those tested using Xpert MTB/RIF; and identify the specific drugs the patient is susceptible too, facilitating treatment. However as with standard culture, these tests take considerable time (up to 3 months) and in many LMIC settings are not available, given the laboratory infrastructure requirements.

Finally, in many LMIC settings, even very short gaps in between the patient providing sputum for testing, receiving result, and starting on treatment can result in high levels of default during the diagnostic process [45]. This has led to increased interest in interventions such as patient support and enablers to encourage patients to adhere and return for tests results.

Treatment of active TB

The treatment of drug susceptible TB is involves delivering a standard low cost (around US$ 21 per person for drugs only) regimen of TB treatment usually for six months, divided into

two phases, and intensive phase for two months and a four month continuation phase. During both phases treatment must be adhered to maximise treatment success and prevent drug resistance developing. Treatment is monitored using the same smear microscopy test as used for diagnosis. For those who are 'smear positive' at the start of treatment, sustained conversion to a 'smear negative' result is essential for the patient to be defined as cured. For 'smear negative' TB case full completion of treatment is seen as treatment success. Twenty years ago, most countries hospitalised TB patients to ensure treatment adherence, but this was expensive and did not result in high success rates [46, 47]. In the last twenty years the WHO has recommended the Directly Observed Treatment Strategy (DOTS). This is a wide ranging strategy, but at its centre is a recommendation of ambulatory treatment approaches with high levels of adherence monitoring. LMICS have implemented DOTS in different ways, with some countries requiring daily visits by the patient in the intensive phase to a health facility, and others adopting more community based methods of adherence support [19, 48]. In some countries, treatment adherence is supported through the provision of social or nutritional support [47]. With good treatment adherence, treatment is very successful, with over a 90% cure rate in most settings.

The treatment of MDR-TB is far more complex than first-line treatment and can take 24 months or longer. It is also much less effective [9, 10]. Treatment can be provided using standardised or individualised drug regimens, with the latter tailored to the individual's drug resistance profile. The latter may be more expensive, but also has a higher cure rate [9]. The cost of MDR-TB treatment is also high, with drugs in the thousands of dollars[8]. As many countries still provide MDR-TB using long periods in hospital, the non-drug costs are also considerable and may increase the drugs costs several fold [49]. In some LMICs ambulatory models of care are being explored[50], in other settings these high costs mean that to date access to MDR-TB treatment remains low [2].

Programmatic/ health system interventions

The above highlights the fact that strengthening TB control to achieve the post- 2015 targets requires investment both in technology, but also the health systems that support the delivery of services [51]. In order to identify TB cases, the health system has to be strengthened to recognise symptomatic patients quickly, even if patients are visiting clinics for other diseases or symptoms. Beyond this, the reach of the 'public' system may be insufficient, and investment will be required in either broadening out to involve private providers and communities, or extending the system through further physical infrastructure including mobile services and outreach teams [52, 53]. Strengthening diagnosis capability also requires substantial support to laboratories and all the systems that support them, including systems to transport samples and quality control services. For treatment, ensuring a high quality of adherence support remains essential, and the treatment of MDR-TB may require substantial infrastructure investment. Both the funding of drugs and ensuring sound drugs supply systems are key to TB control. Programmatic, management and information support to all these services needs to have the capacity to enable and support these investments; and ensure that funding flows and is spent in an efficient manner [52, 53]. Finally, the provision of social protection and cash transfer, may enhance the adherence and address any perverse economic incentives inherent in TB control [54] [55].

New technologies

Despite the availability of screening, diagnostic and treatment technologies for TB, there remains substantial scope for improvement. Investment in new diagnostic and treatment technologies may both substantially improve the efficacy of TB control, and help address some of the numerous health system and patient side barriers to deliver service. Xpert MTB/RIF was the first new TB technology in twenty years, and has renewed interest in investments in new TB diagnostics, including similar technologies to identify resistance to other drugs [56, 57]. Investment in new drugs has also increased in previous years, with 2 new drugs recently seeking WHO approval for the treatment of MDR-TB [58-62]. A plethora of other new drugs and regimens with the aim of shortening both first line and MDR-TB treatment are also currently being trialled, although to data the results of early trials have been negative[62-64]. Finally, there is also considerable interest in a TB vaccine, and there are several trials on-going [65]. Although it is unlikely many of these potential new technologies will substantially impact TB control by 2025, if trials are successful they may well play a key role in TB control by 2035.

Method for Estimating the BCRs of TB control

This paper takes the following simple approach to assessing the BCR of reaching the TB control targets. It first summarises up the recent literature on the cost-effectiveness of the main TB control interventions. This review is based on four previous systematic review efforts: 1) a review of modelling of TB diagnostics [66]; 2) a review treatment costs (Laurence Y, Griffith U, Vassall A, in submission); review of cost-effectiveness of MDR-TB treatment[8]. These reviews contain over 100 references, and for simplicity only recent studies since 2006 in LMICs were selected for inclusion here. It should be noted, that the methods for cost-effectiveness analysis differ widely by study. There are a range of studies collecting robust evidence of cost-effectiveness used trial based approaches, other studies use a variety of decision analytical models to synthesise evidence to predict cost-effectiveness in different populations; and finally some studies focus on the cost-effectiveness of TB using models that predict disease transmission.

From these studies, a very broad cost per Disability Adjusted Life Year averted (DALY) (across all studies) is calculated for three main areas of intervention required to achieve the post-2015 goals: the identification and treatment of latent TB; the diagnosis and treatment of drug-susceptible TB; and the diagnosis and treatment of MDR-TB. This cost per DALY is then valued using the recommendations by the Copenhagen Consensus, with adjustments made for both a 3 and 5% discount rate. It is conservatively assumed that this captures the value of all health and non-health benefits accrued through TB control. It should be noted that this approach is very blunt; but has been chosen as the majority of the literature on the economics of TB control focuses on cost-effectiveness; to focus only on literature that estimates cost-benefit, would be extremely limited both in terms of scope and quality.

Working out one BCR that summarises the overall cost-benefit of reaching the post-2015, is complex. The populations in need receiving each of these interventions will change as the epidemic recedes, both between those with TB, HIV and MDR-TB, and geographically. Moreover, differences in TB prevalence substantially influence the cost-effectiveness of different approaches to screening and diagnosis; as the numbers of individuals needing

screening will vary widely. The costs of treatment will depend highly on to local approach to MDR-TB; as well as the modality used for adherence support for first line treatment. Finally, this approach implicitly assumes that the target can be reached at scale merely though the scale up of current interventions; at constant cost. Although this is unlikely to be achievable in practice, there is little evidence on the economies or dis-economies of scale of TB control, and for this type of broad exercise this simplification is made. But in reality, while some economies of scale may be achieved initially it may cost more to reach and treat the whole population in need, at the speed required to reach both the mortality and incidence reduction in the target. These complexities mean that it is not possible to estimate precise cost-effectiveness without an extensive country level modelling exercise.[3]

Other papers in the Copenhagen Consensus series which face this challenge and require multiple and complex interventions, have addressed this challenge either by concentrating on one aspect of the intervention or restricted the analysis to specific population to provide an illustration of the potential BCR, leaving it to the expert panel to decide how much this may apply globally and over time – or a wider service package. This paper instead estimates a weighted BCRs based on the relative population in need if each intervention in 2013, implicitly assuming that the range of cost per DALY averted from the studies to date is representative of this population and at the scale required to reach the targets, and that the balance of the different populations in need does not evolve as scale-up progresses. In summary the approach used in this report provides blunt but transparent estimates of range of the BCR of TB control, the strength of the estimate being that the report describes above the complexity of 'real TB response' that is multi-faceted for the experts, the weakness being that in doing so it highlights that simple calculations made from setting specific cost per DALY averted at specific points in time may not be representative of the true BCR globally or highly robust over time as the TB epidemic recedes – pending the results of the current on-going modelling exercises to be realised in 2015.

Evidence on the cost-effectiveness of TB Control

Cost-effectiveness of case finding (including the treatment of latent TB)

The cost-effectiveness of screening and treatment of latent TB in those with HIV is long established with over a dozen studies [34, 67-78] finding this intervention cost-effective: a selection of the more recent studies is provided in Table 1 below. Studies have typically arrived at estimates between US$100 and US$ 200 per QALY or DALY averted for intensified case finding among those with HIV (or testing for HIV) in a range of LMICs settings, depending on the population group screened and the method used. There is much less known about the cost-effectiveness of more active forms of case detection, for example reaching out to communities with high levels of HIV using mobile services. One study from South Africa finds a cost of over US$2500 per TB case cured examining a cohort of attendees of mobile HIV testing services [20]. This finding cannot be translated into a cost per DALY averted, as the study design does not compare case detection with a control group seeking care for TB symptoms at health facilities. A recent modelling study examining active case detection more

[3] Both Stop TB (www.**stoptb**.org*)* and the TB-MAC modelling consortium (***tb-mac****.org)* have on-going exercises with multiple models estimating both these costs and outcomes globally that take into account these setting specific factors, however these will not report until mid- 2015. Readers are advised to consult both organisations websites for updates.

generally, and including transmission benefits however finds that even at these high levels of cost, active screening services may still be cost-effective using WHO thresholds [79]. There is also little known about the cost-effectiveness of screening household contacts in LMICs, as most of the evidence in this area focuses in contact tracing in high income countries, but a recent study suggests that screening young household contacts in high burden settings may also be highly cost-effective strategy of active case detection [21].

Table 1 – Summary of recent studies on intensified and active case finding, screening and the treatment of latent TB

Setting	Population group	Primary result*	Approach used	Source
Uganda	HIV-infected adults	Compared to no program, the incremental cost-utility of the targeted testing program was US$102/QALY gained	Empirical cohort study	Shrestha, R K. 2007 [75]
South Africa	All those being tested for #HIV	Costs of US$ 81-166 for detecting a TB case compared to 'do-nothing'	Empirical cohort study	Hausler, H. P. 2006 [70]
Sub-Saharan Africa	All those testing positive with HIV	Screening all those testing positive with HIV with sputum microscopy, compared to a 'do nothing' base case is US$149 per QALY. At prevalence higher than 10%, other strategies become cost-effective	Hypothetical modelled cohort of sub-Saharan Africa population parameterised from literature	Maheswaran, H. et al 2012 [71]
South Africa	All those starting HIV treatment	The incremental cost of intensive screening including culture was $360 per additional tuberculosis case identified.	Empirical cohort study	Bassett, I. V. 2010 [80]
South Africa	All those visiting mobile services in community with high HIV prevalence	The cost of the intervention was US$1,117 per tuberculosis case detected and US$2,458 per tuberculosis case cured.	Empirical cohort study	Kranzer, K., 2012 [20]
Mexico	Individuals at high risk for HIV infection over 20 years	The incremental cost per case of LTBI detected was US$730, cost per active TB averted was US$529 and cost per QALY gained was US$108.	Markov model for parameterised for Mexico	Burgos, J. L. 2009 [81]
Population in a high burden country	Young household contacts	The discounted societal cost of care per life year saved ranged from US$237 (no-testing) to US$538 (IGRA only testing).	A decision analysis model was developed to estimate health and economic outcomes of five TB infection screening strategies in young household contacts	Mandalakas, A.M. 2013 [21]
Population of India, China, and South Africa	General population using a combination of discrete (2-year) campaigns and as continuous activities integrated into ongoing TB control program	Discrete campaigns costing up to $1,200 per case actively detected and started on treatment in India, $3,800 in China, and $9,400 in South Africa were all highly cost-effective (using WHO thresholds)	Transmission model	Azman, A.2014 [82]

** results reported in the dollar years reported by each study*

Cost-effectiveness of the treatment of drug-susceptible TB

The cost-effectiveness and affordability of first line regimens for TB treatment is long established. The World Development Report in 1993 identified TB treatment as one of the most cost-effective components of a basic package of health care; using evidence from early studies of short course regimens in Tanzania and Mozambique[83]. Since then, attention has focused on exploring the most cost-effective way to deliver treatment. For those countries which provide TB treatment through hospitals, a number of analyses were conducted examining relative cost-effectiveness of ambulatory treatment [46, 47, 84]. For other settings, the focus of economic analysis has been on delivery through community structures [48, 85-87] and ensuring effective co-operation with the private sector [22, 23, 25].

Currently the cost-effectiveness of TB treatment (including costs of passive case detection and diagnosis) is estimated at between US$20 and US$ 270 per DALY, depending on the income level of the settings; and the cost of the health system. One of the few cost-benefit studies for an LMIC setting conducted for TB (examining 10 years investing in TB control in India) finds a BCR of 115: 1.

There are also a wide range of studies explore the incremental cost-effectiveness of different diagnostic approaches and technologies; that are too numerous to review in detail here [88-101]. Most of the treatment studies above include the costs of diagnosis with smear microscopy; and thus are included in the cost per DALY averted figures above. In addition, studies by Menzies et al., which uses a transmission model to examine the cost-effectiveness impact of introducing Xpert MTB/RIF in 5 southern African settings, and Vassall et al., which uses a decision analytical model with the same aim for a cohort of those suspected of having TB, find Xpert MTB/RIF to be cost-effective [102, 103]. There is however much current debate on whether and how improved diagnostics can improve patient outcomes, given recent trial results from South Africa that show limited impact on health outcomes in practice, due to the extent empirical diagnosis [43, 44].

Table 2 – Summary of key recent studies the diagnosis of treatment of drug susceptible TB

Setting	Population group	Primary result*	Approach used	Source
India	TB control in the general population	The cost of TB control averaged just US$26 per DALY gained over 1997-2006 and generated a return of US$115 per dollar spent.	Economic modelling based on country-level programme and epidemiological data from 1997 to 2006	Goodchild, M. 2011
Ethiopia	TB patients	The cost per successfully treated patient was US$161.9 and US$60.7 depending on whether health facility or community DOT was used	Community randomised trial	Datiko, D. G. 2012[104]
Ukraine	TB patients	The cost per DALY was US$ 55 using an ambulatory model of care	Empirical cross sectional study	Vassall, A. 2009[47]
India	TB patients in public private mix project	Average societal cost per patient successfully treated fell from US$154 to US$132 in the 4 years following the initiation of PPM	Empirical cross sectional study	Pantoja A. 2009[23]
South Africa	TB patients in public private mix project	Cost per case cured ranges from (US $354-979) in private providers and public sites (US $700-1000)	Empirical cross sectional study	Sinanovic, E. 2006[26]
Five southern African settings	Presumptive TB cases	Xpert has an estimated cost-effectiveness of US$959 (633-1,485) per disability-adjusted life-year averted over 10 y. Across countries, cost-effectiveness ratios ranged from US$792 (482-1,785) in Swaziland to US$1,257 (767-2,276) in Botswana.	Transmission model	Menzies, N. A. 2012[102]
India, South Africa, Uganda	Presumptive TB cases	Average cost per DALY of TB diagnosis and treatment ranges from US$25 per DALY to US$ 85 per DALY (for a range of algorithms (including culture) and with and without Xpert)	Decision analytic cohort model	Vassall, A. 2011[103]

** results reported in the dollar years reported by each study*

Cost-effectiveness of the diagnosis and treatment of MDR-TB

Given the high cost of MDR-TB treatment and lower outcomes, concerns have been raised about the high opportunity cost of investment in this area when other TB control priorities and health systems investments are not being achieved [105, 106]. However, while diagnosing and treating MDR-TB may be more costly than treating drug-susceptible TB, it has still been found to be cost-effective. A systematic review by Fitzpatrick and Floyd, summarises the evidence on the cost-effectiveness of treatment MDR-TB[8]. It finds that the best estimates of the cost per DALY averted were US$ 598, $163, $US143 and $ US 745, from studies in Estonia, Peru, the Philippines and Russia respectively. When these results are extrapolated to other settings systematic review finds cost per DALY averted was lower than GDP per capita in all 14 WHO sub-regions considered, ranging from US$187 per DALY in parts of the eastern Mediterranean region to up to 1891 per DALY in parts of the Western pacific region for outpatient based models of care. MDR-TB treatment costs can however increase more than two-fold where countries chose to use hospitalised models of care [8]. A generic model based study examining drug-susceptibility testing (including the costs of treatment) in moderate prevalence setting supports this systematic review and found a cost per DALY averted of drug-susceptibility testing and follow-on treatment of around US$ 744 per DALY averted [107].

Cost-effectiveness of investment in selected new technologies

The focus of most-investigations into new drugs has focused on drugs that achieve treatment shortening. Examining first-line treatment, Salomon et al use a transmission model and finds that a non-inferior 2-month first line regimen would prevent around 13%-20% of all new TB cases and 19%-25% of TB deaths depending on assumptions made around the scale-up of current regimens [108] over an 18 year period. Furthermore, the study suggests that if the cost savings generated by treatment shortening were invested in TB case detection 2 or 3 fold reductions in incidence may be possible. A more recent effort by Forfana et al. remains positive, but suggest a more modest impact, estimating a 3% reduction in incidence from a 4 month regimen and 7% from a 2 month regimen [109] over a ten year period.

The analysis of the economic gains from treatment shortening has focused on using decision analytic models of patient cohorts. A study by Owens et al. examined a hypothetical novel non-inferior first line regimen and explored trade-offs between drug price, treatment duration and health systems treatment costs for a cohort of new TB patients. This study found that a novel regimen with a 4 month duration costing US$1 per day would be at worst highly cost-effective and at best cost saving, depending on the current level of treatment costs [110].

There has been much less work conducted on the potential cost-effectiveness and impact of new MDR-TB regimens. In the last few years, two new MDR-TB drugs (Bedaquiline and Delamanid) have come up for regulatory authority and programmatic approval by the World Health Organisation. As part of the latter process, an exploratory cost-effectiveness analysis using a decision analytic model of a cohort of new MDR-TB cases was conducted [60, 111]. This analysis found both drugs to be potentially cost-effective; when their impact on efficacy is considered; although, the lack of strength of evidence from the clinical trials (in the case of Bedaquiline uncertainty around its impact on mortality, in the case of Delamanid the lack randomization when assessing long term outcomes) was raised as a concern[60, 111].

In the case of Bedaquiline, the impact on cost-effectiveness of a shortened MDR-TB regimen was also examined, given that the trial results suggested that time to sustained sputum conversion may be reduced. Examining a reduction in treatment shortening of two months, the cost-effectiveness analysis found cost savings, at current drug prices, however the extent of which was highly dependent on the level of hospitalization during treatment. Further trials, with an integrated economic analysis, are on-going that test the use of Bedaquiline as part of a nine-month MDR-TB regimen (the STREAM trial)[112].

Finally, a recent study examining the potential cost-effectiveness of new TB vaccine find that that over 2024-2050, a vaccine targeted to adolescents/adults could have a greater impact than one targeted at infants. In low-income countries, a vaccine with a 10-year duration and 60% efficacy targeted at adolescents/adults was considered cost-effective at $149 (cost saving to $387) per DALY averted. If targeted at infants, 0.89 (0.42-1.58) million TB cases could be prevented at $1,692 ($634-$4,603) per DALY averted [65].

Summary of Benefit Cost Findings

Using the studies on cost-effectiveness outlined above (selected studies referenced in Table 3, and adjusted to 2013 US$), and then simply valuing health benefits using the Copenhagen Consensus methods, this report finds BCRs for TB diagnosis and treatment ranging from 11 – 192:1, depending on the cost and valuation of benefit used.

The **BCR for the diagnosis and treatment of TB** based on current screening practices is likely to be somewhere in the range of **11-192: 1, depending on how the DALY is valued.**

For countries adopting **intensified case detection and treatment of latent TB for those living with HIV** to reach the post-2015 goals (most likely countries with high levels of HIV co-infection) this additional investment has a BCR of **6-47:1.**

Finally, for countries, also needing to **diagnosis and treat MDR-TB** this additional investment has a **BCR of 0-5:1.**

Table 3 – Summary of Benefit Cost Ratios for key TB strategies

Intervention	Cost per DALY range (2013 US$)		Benefit Cost Ratio (low range DALY) (2013 US$)		Benefit Cost Ratio (high range DALY) (2013 US$)	
Intensified case finding and treatment of latent TB [71, 75]	107	156	9	6	47	32
TB diagnosis and treatment (drug sensitive TB)[103, 113]	26	89	38	11	192	56
TB diagnosis and treatment (MDR-TB) [8, 107]	217	2192	5	0	23	2

Even though the BCRs for both drug susceptible TB diagnosis and treatment and intensified case finding and treatment of latent TB for those living with HIV show an extremely high benefit cost ratio, the following caveats have to be taken into account when assessing these estimates that on the whole demonstrate that these BCRs are likely to be conservative estimates:

1. Some of the studies from which they are derived do NOT fully take into account transmission benefits, which will substantially improve the positive economic impact of TB control.

2. For comparability this paper adopts the Copenhagen consensus approach to assigning a value of economic benefit to DALYs. However, it should be noted that this approach does not account for any welfare gain from reducing poverty or improving equity. These gains are becoming increasingly important in TB strategy post- 2015 reflected in the adoption of goal to ensure that no family is burdened with catastrophic expenses due to TB. The relationship between TB and poverty is well established with TB both directly affecting the physical capacity to work, but also the costs of seeking and accessing care exposing households to financial difficulties [114]. Conversely other studies show a strong association between factors such as over-crowding, poor nutrition and alcoholism may impact the risk of being infecting and developing TB [114]. Therefore either preventing TB, or ensuring that TB treatment is conducted in as effective and low cost manner, is key to ensure that possibly already poor individuals and households do not fall into further economic decline. Finally, two recent systematic reviews that document the economic and poverty impact of TB on the poor, find that for many households in sub-Saharan Africa TB is a financially catastrophic event, with a burden of more than 10% of annual per capita income [114, 115]. One of the review reports that, on average, the cost of TB was found to be 39% of reported household income (4-148%)[115].

a) These estimates may underestimate the costs of strengthening and expanding health systems to support TB control. Most the costing studies included in this analysis cost the full costs of TB control interventions at the delivery site level, and some programme support activities. However, it is likely that any rapid scale of TB control will require broader health system investment [52, 53, 106], particularly in those countries where the health system does not physically reach all the population in need. These costs are not included here, but this paper on TB control should be seen as complement and not a substitute for any other Copenhagen Consensus paper examining the benefit costs ratios of health systems strengthening.

b) These costs assume that there are no new advances in terms of the shortened duration of TB treatment, new diagnostics and the development of TB vaccines up until 2035. The evidence above shows that treatment shortening could have substantial cost savings; and should a vaccine become available at the right price, then the BCR for reaching the post-2015 target could dramatically improve

Using the weighted average, based on 2013 global TB incidence and HIV co-infection, the following overall BCR is estimate for reaching the post -2015 TB control goals. **It should be noted that costs and benefits here represent total, not incremental benefits of TB control from the current baseline. It should also be noted that annual total costs and DALYs are top end, and assume full coverage from year 1 at incidence levels in 2015. Both cost and DALYs are likely to change over the next twenty years. The overall level of intervention and therefore total costs are likely to be lower at many points, either due to the time it takes to reach full coverage, or later on in the period due to the transmission impact of the interventions. The level of total DALYs may also vary, with earlier efforts having a greater transmission impact, but in the absence of country level this cannot be determined in the analysis.**

	Annual cost for first year (US$ millions)	**Benefits ($millions)**				**Benefit for Every Dollar Spent**			
		Discount rate = 3%		Discount rate = 5%		Discount rate = 3%		Discount rate = 5%	
Target		DALY = $1000	DALY = $5000	DALY = $1000	DALY = $5000	DALY = $1000	DALY = $5000	DALY = $1000	DALY = $5000
Reduce TB deaths by 95% and TB incidence by 90% between 2015 and 2035	$8,092	$132,856	$664,279	$111,288	$556,438	**$16**	**$82**	**$14**	**$69**

Conclusion

The WHO estimates that between 2002 and 2011, 43 million people were successfully treated for TB at a unit cost of between US$100-500 per person[1]. This report argues the case that this continuing this effort may result in a return of up to US$56 per dollar spent. This benefit will primarily accrue to the very poorest globally. TB control continues to be chronically under-funded, yet the costs of addressing TB are not substantial compared to other development and health investments. The economic case for strengthening the health systems and services to support TB control presented here is therefore one of the most convincing in the area of public health today – and must be a core part of the post-2015 development effort.

References

1. Floyd K, Fitzpatrick C, Pantoja A, Raviglione M: **Domestic and donor financing for tuberculosis care and control in low-income and middle-income countries: an analysis of trends, 2002-11, and requirements to meet 2015 targets.** *Lancet Glob Health* 2013, **1:**e105-115.

2. Organisation WH: **Global Tuberculosis Report 2014.** Geneva, Switzerland: World Health Organisation; 2014.

3. **Financing Global Health** [http://vizhub.healthdata.org/fgh/]

4. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al: **Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.** *Lancet* 2012, **380:**2095-2128.

5. Murray CJ, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, Dansereau EA, Graetz N, Barber RM, Brown JC, et al: **Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.** *Lancet* 2014, **384:**1005-1070.

6. Zumla A, Raviglione M, Hafner R, von Reyn CF: **Tuberculosis.** *N Engl J Med* 2013, **368:**745-755.

7. Wells CD CJ, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al: **HIV infection and multidrug-resistant tuberculosis: the perfect storm.** *J Infect Dis* 2007, **196 Suppl 1:**S86-107.

8. Fitzpatrick C, Floyd K: **A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis.** *Pharmacoeconomics* 2012, **30:**63-80.

9. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, Gandhi NR, Galvani AP: **Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis.** *Lancet Infect Dis* 2009, **9:**153-161.

10. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM: **Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis.** *PLoS One* 2009, **4:**e6914.

11. Dye C WB: **Criteria for the control of drug-resistant tuberculosis.** *Proc Natl Acad Sci USA* 2000 **97(14):**8180-8185.

12. Zignol M, van Gemert W, Falzon D, Sismanidis C, Glaziou P, Floyd K, Raviglione M: **Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007-2010.** *Bull World Health Organ* 2012, **90:**111-119D.

13. Partnership ST: **Global Plan to Stop TB 2006-2015.** Geneva, Switzerland: Stop TB Partnership; 2006.

14. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, et al: **Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.** *Lancet* 2012, **380:**2197-2223.

15. **Factsheet: Post 2015 Global Tuberculosis Strategy** [http://who.int/tb/post2015_TBstrategy.pdf?ua=1]

16. Kranzer K, Houben RM, Glynn JR, Bekker LG, Wood R, Lawn SD: **Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis.** *Lancet Infect Dis* 2010, **10:**93-102.

17. Organisation WH: **Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings.** World Health Organisation; 2011.

18. Kranzer K, Afnan-Holmes H, Tomlin K, Golub JE, Shapiro AE, Schaap A, Corbett EL, Lonnroth K, Glynn JR: **The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review.** *Int J Tuberc Lung Dis* 2013, **17:**432-446.

19. Islam MA, Wakai S, Ishikawa N, Chowdhury AM, Vaughan JP: **Cost-effectiveness of community health workers in tuberculosis control in Bangladesh.** *Bull World Health Organ* 2002, **80:**445-450.

20. Kranzer K, Lawn SD, Meyer-Rath G, Vassall A, Raditlhalo E, Govindasamy D, van Schaik N, Wood R, Bekker LG: **Feasibility, Yield, and Cost of Active Tuberculosis Case Finding Linked to a Mobile HIV Service in Cape Town, South Africa: A Cross-sectional Study.** *PLoS Med* 2012, **9:**e1001281.

21. Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E: **Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting.** *Thorax* 2013, **68:**247-255.

22. Pantoja A, Floyd K, Unnikrishnan KP, Jitendra R, Padma MR, Lal SS, Uplekar M, Chauhan LS, Kumar P, Sahu S, et al: **Economic evaluation of public-private mix for tuberculosis care and control, India. Part I. Socio-economic profile and costs among tuberculosis patients.** *Int J Tuberc Lung Dis* 2009, **13:**698-704.

23. Pantoja A, Lonnroth K, Lal SS, Chauhan LS, Uplekar M, Padma MR, Unnikrishnan KP, Rajesh J, Kumar P, Sahu S, et al: **Economic evaluation of public-private mix for tuberculosis care and control, India. Part II. Cost and cost-effectiveness.** *Int J Tuberc Lung Dis* 2009, **13:**705-712.

24. Ferroussier O, Kumar MKA, Dewan PK, Nair PKJ, Sahu S, Wares DF, Laserson K, Wells C, Granich R, Chauhan LS: **Cost and cost-effectiveness of a public-private mix project in Kannur District Kerala, India, 2001-2002.** *International Journal of Tuberculosis and Lung Disease* 2007, **11:**755-761.

25. Floyd K, Arora VK, Murthy KJ, Lonnroth K, Singla N, Akbar Y, Zignol M, Uplekar M: **Cost and cost-effectiveness of PPM-DOTS for tuberculosis control: evidence from India.** *Bull World Health Organ* 2006, **84:**437-445.

26. Sinanovic E, Kumaranayake L: **Financing and cost-effectiveness analysis of public-private partnerships: provision of tuberculosis treatment in South Africa.** *Cost Eff Resour Alloc* 2006, **4:**11.

27. Sinanovic E, Kumaranayake L: **The motivations for participation in public-private partnerships for the provision of tuberculosis treatment in South Africa.** *Glob Public Health* 2010, **5:**479-492.

28. Sinanovic E, Kumaranayake L: **Sharing the burden of TB/HIV? Costs and financing of public-private partnerships for tuberculosis treatment in South Africa.** *Trop Med Int Health* 2006, **11:**1466-1474.

29. Sinanovic E, Kumaranayake L: **Quality of tuberculosis care provided in different models of public-private partnerships in South Africa.** *Int J Tuberc Lung Dis* 2006, **10:**795-801.

30. Nunn P, Williams B, Floyd K, Dye C, Elzinga G, Raviglione M: **Tuberculosis control in the era of HIV.** *Nat Rev Immunol* 2005, **5:**819-826.

31. Kerkhoff AD, Kranzer K, Samandari T, Nakiyingi-Miiro J, Whalen CC, Harries AD, Lawn SD: **Systematic review of TST responses in people living with HIV in under-resourced settings: implications for isoniazid preventive therapy.** *PLoS One* 2012, **7:**e49928.

32. Marra F, Marra CA, Sadatsafavi M, Moran-Mendoza O, Cook V, Elwood RK, Morshed M, Brunham RC, FitzGerald JM: **Cost-effectiveness of a new interferon-based blood assay, QuantiFERON-TB Gold, in screening tuberculosis contacts.** *International Journal of Tuberculosis and Lung Disease* 2008, **12:**1414-1424.

33. Pooran A, Booth H, Miller RF, Scott G, Badri M, Huggett JF, Rook G, Zumla A, Dheda K: **Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis.** *BMC pulmonary medicine* 2010, **10:**7.

34. Shrestha RK, Mugisha B, Bunnell R, Mermin J, Hitimana-Lukanika C, Odeke R, Madra P, Adatu F, Blandford JM: **Cost-effectiveness of including tuberculin skin testing in an IPT program for HIV-infected persons in Uganda.** *International Journal of Tuberculosis and Lung Disease* 2006, **10:**656-662.

35. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, McIntyre JA, Gray GE, Chaisson RE: **New regimens to prevent tuberculosis in adults with HIV infection.** *N Engl J Med* 2011, **365:**11-20.

36. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, Mosimaneotsile B, Motsamai OI, Bozeman L, Davis MK, et al: **6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial.** *Lancet* 2011, **377:**1588-1598.

37. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, Hamilton CD, Menzies D, Kerrigan A, et al: **Three months of rifapentine and isoniazid for latent tuberculosis infection.** *N Engl J Med* 2011, **365:**2155-2166.

38. Davis JL, Cattamanchi A, Cuevas LE, Hopewell PC, Steingart KR: **Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis.** *Lancet Infect Dis* 2013, **13:**147-154.

39. Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, Urbanczik R, Perkins M, Aziz MA, Pai M: **Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review.** *Lancet Infect Dis* 2006, **6:**570-581.

40. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR: **Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis.** *Eur Respir J* 2014, **44:**435-446.

41. Pantoja A, Fitzpatrick C, Vassall A, Weyer K, Floyd K: **Xpert MTB/RIF for diagnosis of tuberculosis and drug-resistant tuberculosis: a cost and affordability analysis.** *Eur Respir J* 2013, **42:**708-720.

42. Lu C, Liu Q, Sarma A, Fitzpatrick C, Falzon D, Mitnick CD: **A systematic review of reported cost for smear and culture tests during multidrug-resistant tuberculosis treatment.** *PLoS One* 2013, **8:**e56074.

43. Theron G, Zijenah L, Chanda D, Clowes P, Rachow A, Lesosky M, Bara W, Mungofa S, Pai M, Hoelscher M, et al: **Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial.** *Lancet* 2014, **383:**424-435.

44. Theron G, Peter J, Dowdy D, Langley I, Squire SB, Dheda K: **Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings?** *Lancet Infect Dis* 2014, **14:**527-532.

45. Rao NA, Anwer T, Saleem M: **Magnitude of initial default in pulmonary tuberculosis.** *J Pak Med Assoc* 2009, **59:**223-225.

46. Vassall A, Bagdadi S, Bashour H, Zaher H, Maaren PV: **Cost-effectiveness of different treatment strategies for tuberculosis in Egypt and Syria.** *Int J Tuberc Lung Dis* 2002, **6:**1083-1090.

47. Vassall A, Chechulin Y, Raykhert I, Osalenko N, Svetlichnaya S, Kovalyova A, van der Werf MJ, Turchenko LV, Hasker E, Miskinis K, et al: **Reforming tuberculosis control in Ukraine: results of pilot projects and implications for the national scale-up of DOTS.** *Health Policy Plan* 2009, **24:**55-62.

48. Floyd K, Skeva J, Nyirenda T, Gausi F, Salaniponi F: **Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi.** *Int J Tuberc Lung Dis* 2003, **7:**S29-37.

49. Pooran A, Pieterson E, Davids M, Theron G, Dheda K: **What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa?** *PLoS One* 2013, **8:**e54587.

50. E S, L R, A V, V A, L W, N N, K M, G C, H C: **Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in South Africa.** *International Journal of Tuberculosis and Lung Disease* 2014, **In press**.

51. TB S: **Contributing to health systems strengthening: guidence to National Tuberculosis Programmes.** Geneva, Switzerland: World Health Organisation; 2008.

52. Atun R, Lazarus JV, Van Damme W, Coker R: **Interactions between critical health system functions and HIV/AIDS, tuberculosis and malaria programmes.** *Health Policy Plan* 2010, **25 Suppl 1:**i1-3.

53. Atun R, Weil DE, Eang MT, Mwakyusa D: **Health-system strengthening and tuberculosis control.** *Lancet* 2010, **375:**2169-2178.

54. Jack W: **The public economics of tuberculosis control.** *Health Policy* 2001, **57:**79-96.

55. Boccia D, Hargreaves J, Lonnroth K, Jaramillo E, Weiss J, Uplekar M, Porter JD, Evans CA: **Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications.** *Int J Tuberc Lung Dis* 2011, **15 Suppl 2:**S37-49.

56. Denkinger CM, Kampmann B, Ahmed S, Dowdy DW: **Modeling the impact of novel diagnostic tests on pediatric and extrapulmonary tuberculosis.** *BMC Infect Dis* 2014, **14:**477.

57. Denkinger CM, Pai M, Dowdy DW: **Do we need to detect isoniazid resistance in addition to rifampicin resistance in diagnostic tests for tuberculosis?** *PLoS One* 2014, **9:**e84197.

58. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, Gao M, Awad M, Park SK, Shim TS, et al: **Delamanid for multidrug-resistant pulmonary tuberculosis.** *N Engl J Med* 2012, **366:**2151-2160.

59. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, Cirule A, Leimane V, Kurve A, Levina K, et al: **Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis.** *Eur Respir J* 2013, **41:**1393-1400.

60. A V: **Cost-effectiveness of introcuding bedaquiline in MDR-TB regiments - an exploratory analysis.** 2013.

61. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, Leimane V, Andries K, Bakare N, De Marez T, et al: **Multidrug-resistant tuberculosis and culture conversion with bedaquiline.** *N Engl J Med* 2014, **371:**723-732.

62. Dooley KE, Nuermberger EL, Diacon AH: **Pipeline of drugs for related diseases: tuberculosis.** *Curr Opin HIV AIDS* 2013, **8:**579-585.

63. Dawson R, Diacon A: **PA-824 , moxifloxacin and pyrazinamide combination therapy for tuberculosis.** *Expert Opin Investig Drugs* 2013, **22:**927-932.

64. Diacon AH, Dawson R, Von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, Conradie A, Erondu N, Ginsberg AM, Egizi E, et al: **Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis.** *Antimicrob Agents Chemother* 2013, **57:**2199-2203.

65. Knight GM, Griffiths UK, Sumner T, Laurence YV, Gheorghe A, Vassall A, Glaziou P, White RG: **Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries.** *Proc Natl Acad Sci U S A* 2014, **111:**15520-15525.

66. Zwerling A, White RG, Vassall A, Cohen T, Dowdy DW, Houben RM: **Modeling of novel diagnostic strategies for active tuberculosis - a systematic review: current practices and recommendations.** *PLoS One* 2014, **9:**e110558.

67. Baltussen R, Floyd K, Dye C: **Cost effectiveness analysis of strategies for tuberculosis control in developing countries.** *BMJ* 2005, **331:**1364.

68. Currie CS, Floyd K, Williams BG, Dye C: **Cost, affordability and cost-effectiveness of strategies to control tuberculosis in countries with high HIV prevalence.** *BMC Public Health* 2005, **5:**130.

69. Foster S, Godfrey-Faussett P, Porter J: **Modelling the economic benefits of tuberculosis preventive therapy for people with HIV: the example of Zambia.** *AIDS* 1997, **11:**919-925.

70. Hausler HP, Sinanovic E, Kumaranayake L, Naidoo P, Schoeman H, Karpakis B, Godfrey-Faussett P: **Costs of measures to control tuberculosis/HIV in public primary care facilities in Cape Town, South Africa.** *Bulletin of the World Health Organization* 2006, **84:**528-536.

71. Maheswaran H, Barton P: **Intensive case finding and isoniazid preventative therapy in HIV infected individuals in Africa: economic model and value of information analysis.** *PLoS One* 2012, **7:**e30457.

72. Masobe P, Lee T, Price M: **Isoniazid prophylactic therapy for tuberculosis in HIV-seropositive patients--a least-cost analysis.** *S Afr Med J* 1995, **85:**75-81.

73. Pho MT, Swaminathan S, Kumarasamy N, Losina E, Ponnuraja C, Uhler LM, Scott CA, Mayer KH, Freedberg KA, Walensky RP: **The cost-effectiveness of tuberculosis preventive therapy for HIV-infected individuals in southern India: a trial-based analysis.** *PLoS One* 2012, **7:**e36001.

74. Rose DN: **Short-course prophylaxis against tuberculosis in HIV-infected persons. A decision and cost-effectiveness analysis.** *Ann Intern Med* 1998, **129:**779-786.

75. Shrestha RK, Mugisha B, Bunnell R, Mermin J, Odeke R, Madra P, Hitimana-Lukanika C, Adatu-Engwau F, Blandford JM: **Cost-utility of tuberculosis prevention among HIV-infected adults in Kampala, Uganda.** *Int J Tuberc Lung Dis* 2007, **11:**747-754.

76. Sutton BS, Arias MS, Chheng P, Eang MT, Kimerling ME: **The cost of intensified case finding and isoniazid preventive therapy for HIV-infected patients in Battambang, Cambodia.** *International Journal of Tuberculosis and Lung Disease* 2009, **13:**713-718.

77. Terris-Prestholt F, Kumaranayake L, Ginwalla R, Ayles H, Kayawe I, Hillery M, Godfrey-Faussett P: **Integrating tuberculosis and HIV services for people living with HIV: Costs of the Zambian ProTEST Initiative.** *Cost Effectiveness and Resource Allocation* 2008, **6:**2.

78. Uhler LM, Kumarasamy N, Mayer KH, Saxena A, Losina E, Muniyandi M, Stoler AW, Lu Z, Walensky RP, Flanigan TP, et al: **Cost-effectiveness of HIV testing referral strategies among tuberculosis patients in India.** *PLoS One* 2010, **5**.

79. Azman AS, Golub JE, Dowdy DW: **How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and India.** *BMC Med* 2014, **12:**216.

80. Bassett IV, Wang B, Chetty S, Giddy J, Losina E, Mazibuko M, Bearnot B, Allen J, Walensky RP, Freedberg KA: **Intensive tuberculosis screening for HIV-infected patients starting antiretroviral therapy in Durban, South Africa.** *Clinical Infectious Diseases* 2010, **51:**823-829.

81. Burgos JL, Kahn JG, Strathdee SA, Valencia-Mendoza A, Bautista-Arredondo S, Laniado-Laborin R, Castaneda R, Deiss R, Garfein RS: **Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico.** *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2009, **13:**962-968.

82. Azman AS, Dowdy DW: **Bold thinking for bold results: modeling the elimination of tuberculosis.** *Int J Tuberc Lung Dis* 2014, **18:**883.

83. Murray CJ, DeJonghe E, Chum HJ, Nyangulu DS, Salomao A, Styblo K: **Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries.** *Lancet* 1991, **338:**1305-1308.

84. Floyd K, Wilkinson D, Gilks C: **Comparison of cost effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: experience from rural South Africa.** *BMJ* 1997, **315:**1407-1411.

85. Moalosi G, Floyd K, Phatshwane J, Moeti T, Binkin N, Kenyon T: **Cost-effectiveness of home-based care versus hospital care for chronically ill tuberculosis patients, Francistown, Botswana.** *Int J Tuberc Lung Dis* 2003, **7:**S80-85.

86. Nganda B, Wang'ombe J, Floyd K, Kangangi J: **Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Machakos District, Kenya.** *Int J Tuberc Lung Dis* 2003, **7:**S14-20.

87. Okello D, Floyd K, Adatu F, Odeke R, Gargioni G: **Cost and cost-effectiveness of community-based care for tuberculosis patients in rural Uganda.** *Int J Tuberc Lung Dis* 2003, **7:**S72-79.

88. Dowdy DW, O'Brien MA, Bishai D: **Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis.** *Int J Tuberc Lung Dis* 2008, **12:**1021-1029.

89. Hughes R, Wonderling D, Li B, Higgins B: **The cost effectiveness of Nucleic Acid Amplification Techniques for the diagnosis of tuberculosis.** *Respiratory Medicine* 2012, **106:**300-307.

90. Roos BR, van Cleeff MR, Githui WA, Kivihya-Ndugga L, Odhiambo JA, Kibuga DK, Klatser PR: **Cost-effectiveness of the polymerase chain reaction versus smear examination for the**

diagnosis of tuberculosis in Kenya: a theoretical model. *Int J Tuberc Lung Dis* 1998, **2:**235-241.

91. Scherer LC, Sperhacke RD, Ruffino-Netto A, Rossetti ML, Vater C, Klatser P, Kritski AL: **Cost-effectiveness analysis of PCR for the rapid diagnosis of pulmonary tuberculosis.** *BMC Infect Dis* 2009, **9:**216.

92. Shah M, Dowdy D, Joloba M, Ssengooba W, Manabe YC, Ellner J, Dorman SE: **Cost-effectiveness of novel algorithms for rapid diagnosis of tuberculosis in HIV-infected individuals in Uganda.** *AIDS* 2013, **27:**2883-2892.

93. van Cleeff M, Kivihya-Ndugga L, Githui W, Ng'ang'a L, Kibuga D, Odhiambo J, Klatser P: **Cost-effectiveness of polymerase chain reaction versus Ziehl-Neelsen smear microscopy for diagnosis of tuberculosis in Kenya.** *Int J Tuberc Lung Dis* 2005, **9:**877-883.

94. Anderson C, Inhaber N, Menzies D: **Comparison of sputum induction with fiber-optic bronchoscopy in the diagnosis of tuberculosis.** *Am J Respir Crit Care Med* 1995, **152:**1570-1574.

95. Albert H: **Economic analysis of the diagnosis of smear-negative pulmonary tuberculosis in South Africa: incorporation of a new rapid test, FASTPlaqueTB, into the diagnostic algorithm.** *International Journal of Tuberculosis and Lung Disease* 2004, **8:**240-247.

96. Andrews JR, Lawn SD, Rusu C, Wood R, Noubary F, Bender MA, Horsburgh CR, Losina E, Freedberg KA, Walensky RP: **The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy: a model-based analysis.** *AIDS* 2012, **26:**987-995 910.1097/QAD.1090b1013e3283522d3283547.

97. Chihota VN, Grant AD, Fielding K, Ndibongo B, van Zyl A, Muirhead D, Churchyard GJ: **Liquid vs. solid culture for tuberculosis: performance and cost in a resource-constrained setting.** *Int J Tuberc Lung Dis* 2010, **14:**1024-1031.

98. Dowdy DW, Lourenco MC, Cavalcante SC, Saraceni V, King B, Golub JE, Bishai D, Durovni B, Chaisson RE, Dorman SE: **Impact and cost-effectiveness of culture for diagnosis of tuberculosis in HIV-infected Brazilian adults.** *PLoS One* 2008, **3:**e4057.

99. Dowdy DW, Maters A, Parrish N, Beyrer C, Dorman SE: **Cost-effectiveness analysis of the gen-probe amplified mycobacterium tuberculosis direct test as used routinely on smear-positive respiratory specimens.** *J Clin Microbiol* 2003, **41:**948-953.

100. Dowdy DW, van't Hoog A, Shah M, Cobelens F: **Cost-effectiveness of rapid susceptibility testing against second-line drugs for tuberculosis.** *Int J Tuberc Lung Dis* 2014, **18:**647-654.

101. Mueller DH, Mwenge L, Muyoyeta M, Muvwimi MW, Tembwe R, McNerney R, Godfrey-Faussett P, Ayles HM: **Costs and cost-effectiveness of tuberculosis cultures using solid and liquid media in a developing country.** *Int J Tuberc Lung Dis* 2008, **12:**1196-1202.

102. Menzies NA, Cohen T, Lin HH, Murray M, Salomon JA: **Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation.** *PLoS Med* 2012, **9:**e1001347.

103. Vassall A, van Kampen S, Sohn H, Michael JS, John KR, den Boon S, Davis JL, Whitelaw A, Nicol MP, Gler MT, et al: **Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis.** *PLoS Med* 2011, **8:**e1001120.

104. Datiko DG, Lindtjorn B: **Cost and cost-effectiveness of smear-positive tuberculosis treatment by Health Extension Workers in Southern Ethiopia: a community randomized trial.** *PLoS One* 2010, **5:**e9158.

105. Khan MS, Coker RJ: **Tuberculosis control: hard questions - Authors' reply.** *Lancet* 2014, **384:**1744-1745.

106. Khan MS, Coker RJ: **How to hinder tuberculosis control: five easy steps.** *Lancet* 2014, **384:**646-648.

107. Oxlade O, Falzon D, Menzies D: **The impact and cost-effectiveness of strategies to detect drug-resistant tuberculosis.** *Eur Respir J* 2012, **39:**626-634.

108. Salomon JA L-SJ, Getz WM, Resch S, Sánchez MS, Porco TC, et al: **Prospects for advancing tuberculosis control efforts through novel therapies. .** *PLoS Med* 2006 **3(8)**.

109. Fofana MO, Knight GM, Gomez GB, White RG, Dowdy DW: **Population-level impact of shorter-course regimens for tuberculosis: a model-based analysis.** *PLoS One* 2014, **9:**e96389.

110. Owens JP, Fofana MO, Dowdy DW: **Cost-effectiveness of novel first-line treatment regimens for tuberculosis.** *Int J Tuberc Lung Dis* 2013, **17:**590-596.

111. A V: **Cost–effectiveness of introducing Delamanid in MDR-TB regimens: an exploratory analysis.** 2014.

112. Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PP, Chiang CY, Squire SB, Madan J, Meredith SK: **Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial.** *Trials* 2014, **15:**353.

113. Goodchild M, Sahu S, Wares F, Dewan P, Shukla RS, Chauhan LS, Floyd K: **A cost-benefit analysis of scaling up tuberculosis control in India.** *Int J Tuberc Lung Dis* 2011, **15:**358-362.

114. Barter DM, Agboola SO, Murray MB, Barnighausen T: **Tuberculosis and poverty: the contribution of patient costs in sub-Saharan Africa--a systematic review.** *BMC Public Health* 2012, **12:**980.

115. Tanimura TJ, E. Weil, D. Raviglione, M. Lonroth K.: **Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review.** *European Respiratory Journal* 2014**:**1763-1775.

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