REVIEW OF HIV/AIDS, TUBERCULOSIS AND MALARIA LANDSCAPE FOR THE GLOBAL FUND STRATEGY 2012-2016

EXECUTIVE SUMMARY

1. Progress in the treatment and prevention of HIV/AIDS, tuberculosis (TB) and malaria over the past decade have led to reductions in disease episodes and deaths, reversing the trends in the transmission of and the mortality due to the three diseases. The degree of progress varies between diseases, as do the epidemiology, efficacy of prevention and treatment interventions, and the amount of available funding.

2. Sustaining the gains made to date will require continued funding for programs, especially for services such as insecticide-treated nets (ITN) replacement for malaria or antiretroviral (ARV) treatment for HIV/AIDS, where the termination of funding would result in lost lives. Awareness of this so-called "mortgage" is important when accounting for future funding requirements.

3. Future plans by global partners (including UNAIDS, WHO and the Stop TB and Roll Back Malaria (RBM) partnerships) are ambitious and require substantial additional funds, in the face of the current austere funding environment. Since the Global Fund is a leading contributor to current programs, it will also be expected to help fund the required scale-up.

4. Recent developments are changing the approaches used against the diseases. Including:
- Proven new interventions and methods– e.g. treatment for prevention including discordant couples testing and treatment for HIV, improved MDR-TB diagnostic kits
- New targets set – e.g. 2011 Stop TB partnership target of 1 million HIV/TB lives saved by 2015
- Changes to guidance – e.g. reduction in treatment threshold for ARVs, anticipated test/treat/track guidance from WHO for malaria
- Operational research improving ease of scale-up– e.g. new devices for male circumcision

5. Other significant trends influencing treatment approaches and funding needs across a number of diseases include:
- Increased emphasis on diagnosis and surveillance to ensure activities focus on areas where the disease is active – e.g. RDT scale-up for malaria, MDR-TB detection
- Increased focus on most-at-risk populations (MARPs) – e.g. in concentrated HIV epidemics
- Diversification of channels used – e.g. increased private sector and community based approaches to implementation in all three diseases
- Addressing the threat of resistance – e.g. global plans to combat insecticide and artemisinin resistance in malaria

6. Also of note are discussions of frameworks to evaluate and prioritize interventions according to their effectiveness for a country's context—e.g. highlighted by the recent publication of the “Investment Framework for HIV”. This demonstrates the significant potential impact that a strategic, coordinated, prioritized approach to scale-up could have against the diseases in "breaking the trajectory of the epidemic".

7. Looking further ahead, there are no "magic bullets" anticipated from new technologies, but further additional incremental improvements on the horizon which will have to be incorporated into the Global Fund's programs as appropriate. These will also require flexibility and responsiveness from the funding model to scale-up once proven.

8. The implications for funding will be increased demands for a more diverse set of interventions requiring scale-up. Coupled with a risk of tightened funding in the economic climate, there is a real need to prioritize and fund the most effective interventions appropriate according to the country situation. The result is an urgent need to invest more strategically by focusing on the highest impact interventions appropriate to the context of a disease.

1. HIV/AIDS

1.a Executive Summary

1.1 The last decade has seen massive progress in scaling up treatment for HIV/AIDS, which has led to fewer deaths, but this progress has also resulted in more people living with the disease. There has been some improvement in prevention (aided by education, community mobilization, and condom distribution), with new HIV infections in overall decline worldwide.

1.2 Recent studies on discordant couple therapy and pre-exposure prophylaxis (PrEP) suggest the potential for further effective preventative interventions to join more established but not yet scaled-up interventions, such as male circumcision. These, alongside programs to eliminate vertical transmission from pregnant mothers offer significant opportunities to further prevent infections.

1.3 The development of effective antiretrovirals (ARVs) has transformed HIV from a death sentence to a chronic disease. While ARV prices will continue to decrease, this will be offset by increases in demand volumes driven in large part by greater prevalence, ambitious global targets, changes in treatment guidelines, and the use of treatment for prevention. The longer-term health effects of HIV are increasingly evident, and there will be added attention to both non-communicable diseases and co-infections for those receiving ARVs.

1.4 The net effect of these changes will be increased funding demands from a more diverse set of interventions requiring scale-up. Coupled with a risk of tightened funding in the economic climate, there is a real need to prioritize and fund the most effective interventions relevant to the disease situation. The recent publication of the “Investment Framework for HIV” has highlighted the benefit and potential impact of a coordinated, prioritized scale up of resources on a cost-effective, strategic set of interventions, claiming that the "prospect of overcoming the HIV/AIDS epidemic and decisively breaking its trajectory is realistically achievable".

1.b Estimated disease burden

1.5 New HIV cases have been declining steadily in the last decade, reaching 2.6 million per year in 2009.[1] This has been supported by increases in awareness of the disease within at-risk populations and safer sexual behavior. Deaths from AIDS have also declined from a peak of 2.1 million in 2004 to 1.8 million in 2009 as ARV treatments have become less expensive and more widely available.[2] Because death rates remain lower than the rate of new cases, the overall number of people living with AIDS has continued to increase, reaching 33.3 million people in 2009. Increased targeting of mother-to-child transmission has significantly reduced (by 24 percent in five years) the number of children born with HIV.[3]

1.6 Africa suffers from the largest share of the disease burden, comprising 68 percent of new HIV infections and 72 percent of all deaths from AIDS. Eight of the top ten high-burden countries are in Africa, with one country (South Africa) containing almost 18 percent of the total number of people living with the disease.[4]

[1] UNAIDS Report on the Global AIDS Epidemic 2010.
[2] Ibid.
[3] Ibid.
[4] Ibid.

Exhibit 1: *HIV/AIDS – Estimated incidence and prevalence by country (2009)*

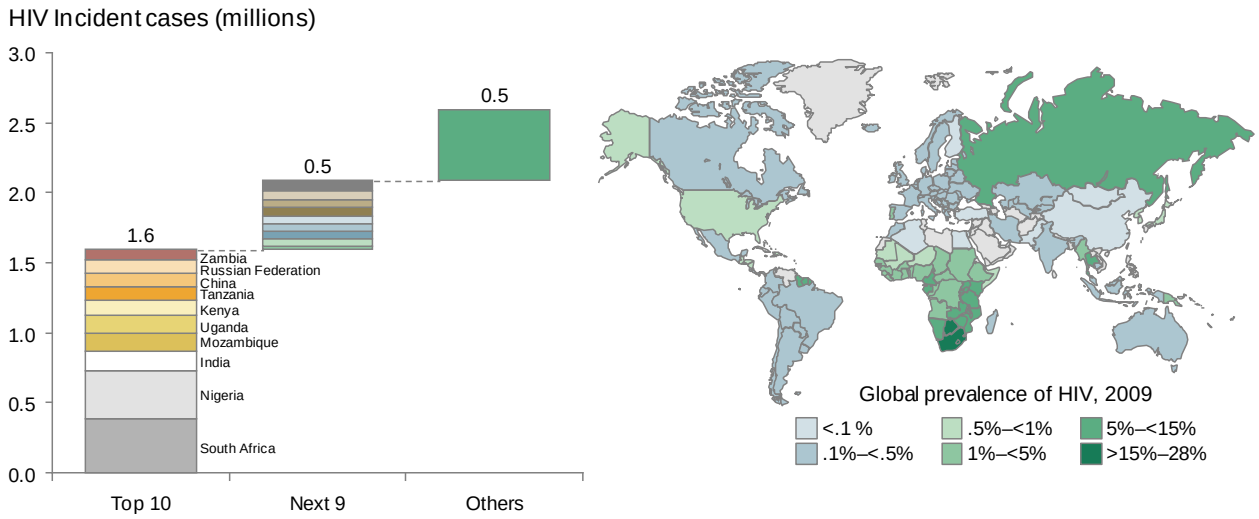
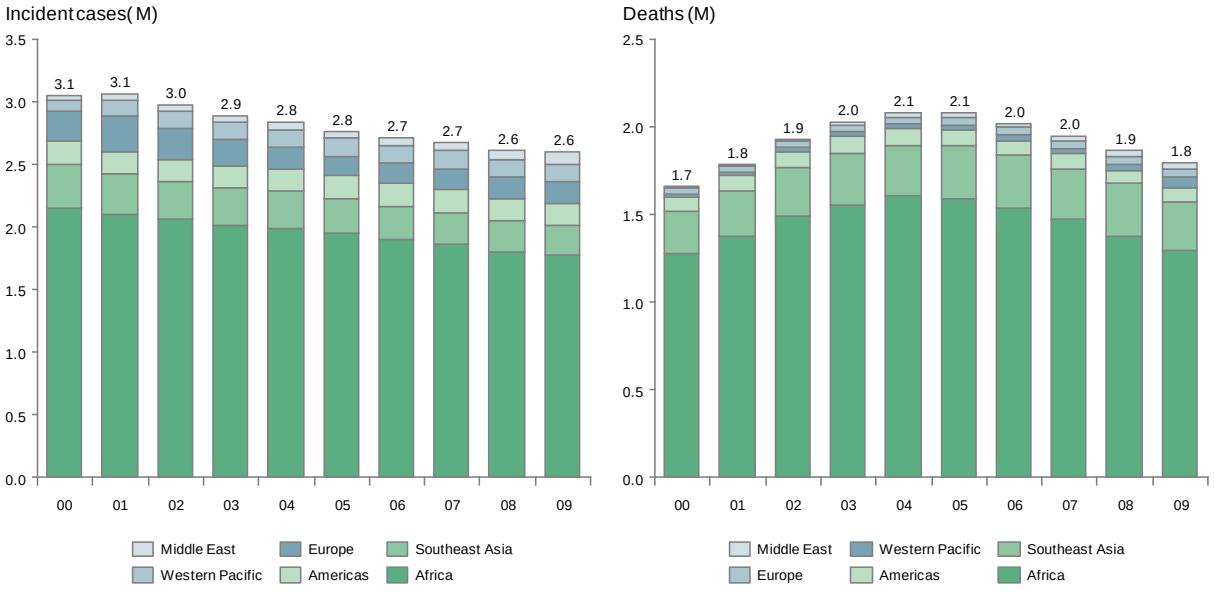
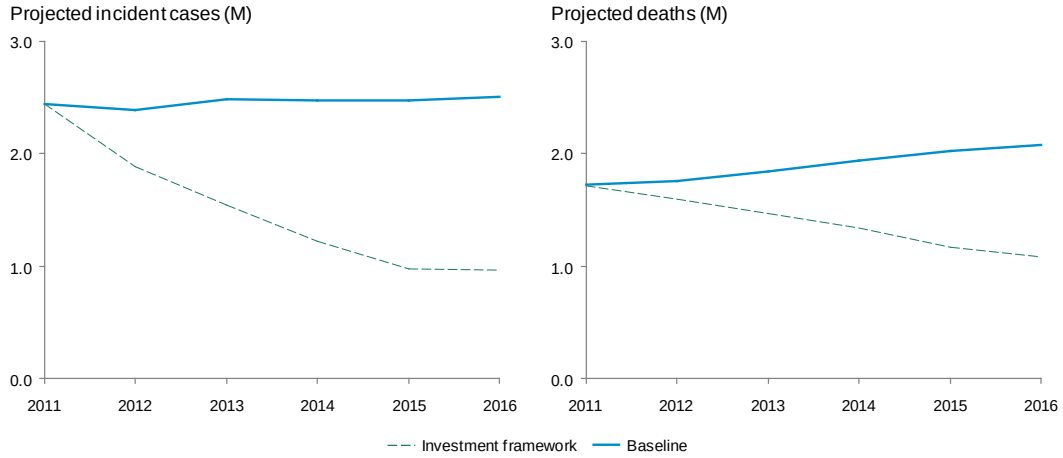


Exhibit 2: *HIV/AIDS – Estimated incidence and deaths by WHO regions[5] (2000-2009)*



[5] UNAIDS data 2010

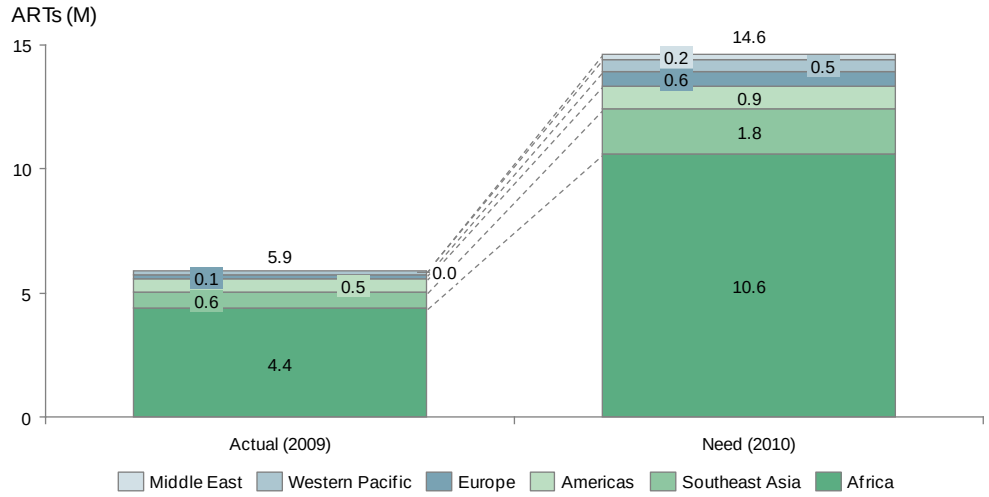
Exhibit 3: *HIV/AIDS – Projected incidence and deaths (2011-2016)*[6]



1.c Unmet needs

1.7 Of the 14.6 million people in need of antiretroviral (ARV) therapy in 2009, 60 percent or (8.7 million) did not receive it.[7] Unmet needs for **EMTCT (Eliminating Mother to Child Transmission)** of HIV are lower, with 47 percent (or 670,000) of all pregnant women in need going without treatment.[8] WHO guidelines introduced in 2010 recommend that **ARV treatment commence earlier (at a CD4 count of 350)**, increasing the number of people in need of treatment. The START study is investigating the effects of commencing treatment even earlier, although any resulting guideline changes would not be expected until 2013 at the earliest. Another significant unmet need remains with respect to most-at-risk populations[9] (**MARPs**) — who often lack access to prevention and treatment options.

Exhibit 4: *HIV/AIDS – Unmet needs by region*[10]



[6] Schwartlander, Bernhard, *et al.*. "Towards an improved investment approach for an effective response to HIV/AIDS." *The Lancet*. Vol 377 June 11, 2011
[7] Global Fund Results Report 2011.
[8] Ibid.
[9] Including, for example, sex workers, men who have sex with men (MSM), transgendered persons, injecting drug users (IDUs), prisoners, migrants, and sex workers and their clients
[10] Global Fund data adjusted to match 2011 Global Fund Results Report

1.8 While the absolute unmet need is highest in Africa, with 6.2 million people not receiving treatment, percentage needs remain above 50 percent in other regions as well.

1.9 Disease progression: Overall disease prevalence (the number of people living with AIDS) will likely continue to increase as ARV treatment becomes more accessible. Patients who otherwise would have died will survive but will continue to live with the disease and require ARVs. HIV incidence is expected to decrease due to safer sexual behavior and improved disease awareness.

1.10 Resistance: Recent WHO surveys have shown ARV resistance levels of less than 5 percent in low and middle-income countries, reaching levels as high as 10 percent to 20 percent in Europe and the US.[11] The overall impact of resistance on the epidemic and the cost of treatment from more expensive second-line therapies are not yet known.

1.d Key advancements (new approaches and innovations)

Exhibit 5: HIV/AIDS – Likelihood and impact of new interventions[12]

Type	Existing	Anticipated	Timing	Likelihood	Impact
Vaccine	N/A	RV144, HVTN 505	2020+		
Prevention	Condoms, Male Circumcision	Treatment as Prevention (discordant couples)	2011		
		Oral PReP (for MSMs)	2011		
		Male circumcision devices	2012		
Treatments	ARV	Treatment. 2.0	2011		
Diagnostics	CD4, viral load	Point of care	2011		
		Couples testing	2011		

1.11 Vaccine: There is currently no vaccine for HIV. While an HIV vaccine does appear theoretically possible, and while several candidates have been considered in clinical trials, positive results remain elusive—the RV144 trial concluded in 2009 and showed modest efficacy by reducing infection rates by 31 percent. A follow-up study to RV144 will likely go into Phase IIb/III trials in 2014 but would probably not be registered until after 2020, in a best-case scenario. There are currently only two Phase IIb trials underway, both for HVTN 505.

[11] UNAIDS Report on the Global AIDS Epidemic 2010

[12] "Likelihood" refers to the chance that the new intervention is developed and taken-up within the period of the strategy (2011-2015). "Impact" refers to the magnitude of health impact from the intervention. Increased shading denotes higher likelihood/impact.

1.12 Prevention: Besides condoms and **male circumcision** (which has been proven effective but suffers from limited uptake despite advances in circumcision devices and operations research), the main prevention focus for HIV/AIDS is shifting towards combination prevention, which includes biomedical and behavioral interventions.[13]

1.13 On the biomedical front, "**treatment as prevention**" involves providing ARVs for the purpose of preventing transmission. Various studies have shown reduced transmission risk when oral ARV treatment was provided to HIV-positive individuals or those who are HIV-negative but at high risk of infection. One study found that the approach reduced transmission between **discordant couples** by as much as 96 percent[14] recommended that ARVs be taken by the HIV-positive partner even at CD4 counts above 350**.** Additionally, **pre-exposure prophylaxis** (**PrEP**) has also been shown to be effective in two trials of oral treatments: for men who have sex with men[15] and for heterosexual couples, prompting interim CDC guidance in early 2011. [16] WHO guidance on discordant couples is anticipated. A key challenge will be to scale-up and fund ARV treatment as prevention for those most at risk of HIV transmission.

1.14 Finally, the first evidence was presented in 2010 that vaginal microbicides could be an effective part of the combination prevention approach, reducing HIV infection risk by 39 percent.[17].

1.15 Treatments: ARV therapy is the standard treatment for HIV today. While new drugs are being evaluated in clinical trials, no revolutionary breakthroughs are expected. The focus instead seems to be on simplifying and reducing the cost of existing treatments, under the WHO's "Treatment 2.0," which involves optimizing drug regimens, expanding point-of-care (POC) diagnostics, reducing costs, adapting delivery systems, and mobilizing communities. Commodity prices for ARVs have decreased due in larget part to patent expiries, changes to licensing arrangements, negotiations and increased competition, although the rate of price reduction is likely to slow for first-line treatments.[18]

1.16 Diagnostics: Advances in diagnostics also appear to be concentrated on simplifications rather than technological breakthroughs. Expansion of POC and couples testing seem to be most promising, the former allowing tests to take place in the same location that health services are delivered and the latter encouraging couples to be tested jointly, thus reducing risky behavior and asymmetric information. Within the next five years, HIV incidence assays may be available and would be able to provide more accurate measures of disease incidence, with implications for improved surveillance, modeling, and evaluation.

1.17 Demand implications: Given that existing treatments ensure the survival, but not the cure, of people with AIDS, the number of people living with the disease will almost certainly continue to increase. Advances in diagnostics will make it easier to identify those in need of treatment, and the most promising prevention options will involve ARV treatments. All of these factors should increase demand for ARVs in the future.

[13] Coates TJ et al. *Behavioural strategies to reduce HIV transmission: how to make them work better*. The Lancet 2008; 372:669-684

[14]Cohen MS et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;365:493-505

[15] Grant RM. Antiretroviral agents used by HIV-uninfected persons for prevention: pre- and postexposure prophylaxis. *Clin Infect Dis.* 2010;50(Suppl 3):S96-S101

[16] Partners PrEP Study Team: http://www.avac.org/ht/a/GetDocumentAction/i/35459

[17] Abdool Karim Q et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science.* 2010;329:1168-74.

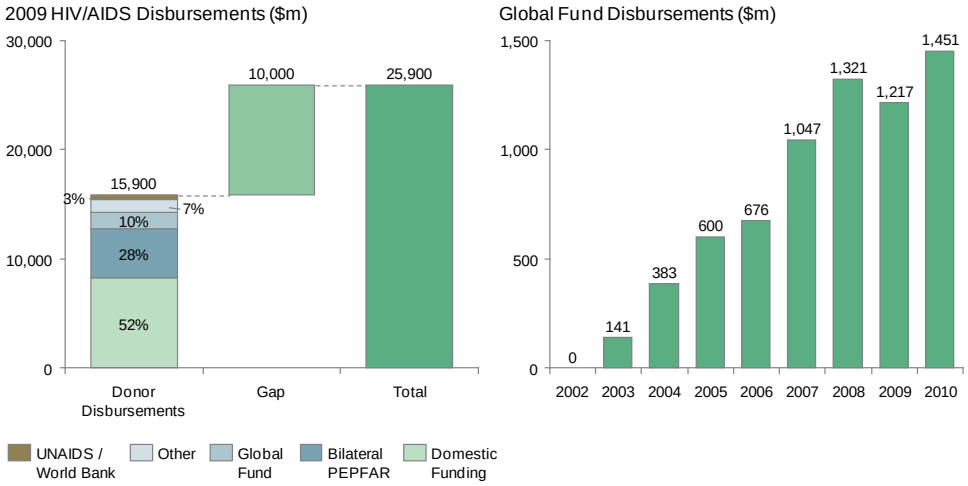
[18] http://www.aids2031.org/pdfs/the%20cost%20of%20antiretrovirals_28.pdf

1.18 The publication of a recent article concerning an **"Investment Framework"** for HIV has prompted recent debate in the field. The authors of the paper call for a more strategic approach to funding, with a targeted set of interventions appropriate to the context of the epidemic in each country, and demonstrate the potential impact of a coordinated, prioritized scale-up in terms of both health and cost impacts – modelling the prevention of more than 12 million new infections and 7 million deaths between 2011 and 2012.[19] Similar prioritization and cost-effectiveness considerations are being examined as part of the RethinkHIV, with a focus on sub-Saharan Africa, and due for full publication in 2012.[20]

1.e Partner landscape and funding environment

1.19 The United States' PEPFAR (President's Emergency Plan for AIDS Relief) is by far the largest AIDS funder globally, having spent US$4.4 billion bilaterally (not including money donated to the Global Fund) in 2009, comprising 58 percent of all international spending.[21] The Global Fund is the next-largest international donor, disbursing 21 percent of international AIDS funding in 2009.[22]

Exhibit 6: *HIV/AIDS – Funding summary*[23]



1.20 Besides the US$7.6 billion spent by donors, an additional US$8.3 billion was provided primarily from domestic sources, either public or private. The total amount spent, US$15.9 billion, is still US$10 billion short of the need in 2010.[24] Funding needs will continue to grow as more patients require ARV therapy. In 2011, the international community set a target of placing a total of 15 million people on ARV treatment by 2015. Reaching this goal will require continued increases in funding. Donor disbursements will be affected by the worsening economic climate, risking continued increases to the funding gap. Key partners for HIV/AIDS include the Gates Foundation, Clinton Global Initiative, UNAIDS, Partners in Health, Esther, MSF, and PEPFAR.

[19] Schwartlander, Bernhard, *et al.*. "Towards an improved investment approach for an effective response to HIV/AIDS." *The Lancet*. Vol 377 June 11, 2011.
[20] http://www.rethinkhiv.com/index.php/about
[21] UNAIDS Report on the Global AIDS Epidemic 2010 and PEPFAR website.
[22] Global Fund Results Report 2011.
[23] Triangulated from 2011 Global Fund Results Report, UNAIDS 2010, and funder websites.
[24] UNAIDS Report on the Global AIDS Epidemic 2010.

1.f Key issues and implications for the Global Fund

Discussion/Issue within HIV/AIDS community	**Implication for the Global fund**
Publication and discussion of **Investment Framework** for HIV/AIDS, which illustrates a tool to help guide funding decisions towards more effective interventions in response to the epidemics	Demonstration of the impact and importance of a prioritized, coordinated response that accounts for the context of an epidemic within each country
2010 WHO guidelines **reduced treatment threshold** to start at a higher CD4 count of 350. START study examining benefits of further reducing treatment threshold (earliest updated WHO treatment guidance 2013)	Increased demand on funding for ARVs if treatment guidelines increase the treatment threshold further
Increasing focus on elimination of maternal-to-child transmission (**EMTCT**) by 2015	Increased funding demands for ARVs and need for additional coordination with MNCH
New prevention methods receiving more attention, including treatment for prevention (for example discordant couples therapy); as well pre-Exposure prophylaxis (PrEP) and topical microbicides	Increased funding demands for both ARTs and microbicides for the purposes of prevention of HIV transmission
Recognition of insufficient allocation of resources and poor coverage for **MARPs** in certain epidemics	Increased focus on MARPs required to improve impact and effectiveness of funding
Male circumcision recognized as effective, onetime intervention for prevention, and made easier by the development of new circumcision devices that will aid rapid scale-up	Increased demand for programs providing male circumcision. Potential need to encourage scale-up of this proven intervention
Non-communicable diseases (NCD) such as diabetes and CVS, and **co-infections** (TB and hepatitis C) gaining prominence as PLHIV surviving for increasingly long periods	Increased demand for treatment of non-communicable diseases and co-infections in PLHIV. Especially for TB in light of Stop TB HIV/TB 2015 target (see TB section)

2. TUBERCULOSIS

2.a Executive summary

2.1 Global tuberculosis (TB) control has improved through the implementation of the Stop TB Strategy and the Global Plan to Stop TB, although reductions in the disease incidence rate since 2004 have been consistent but modest.

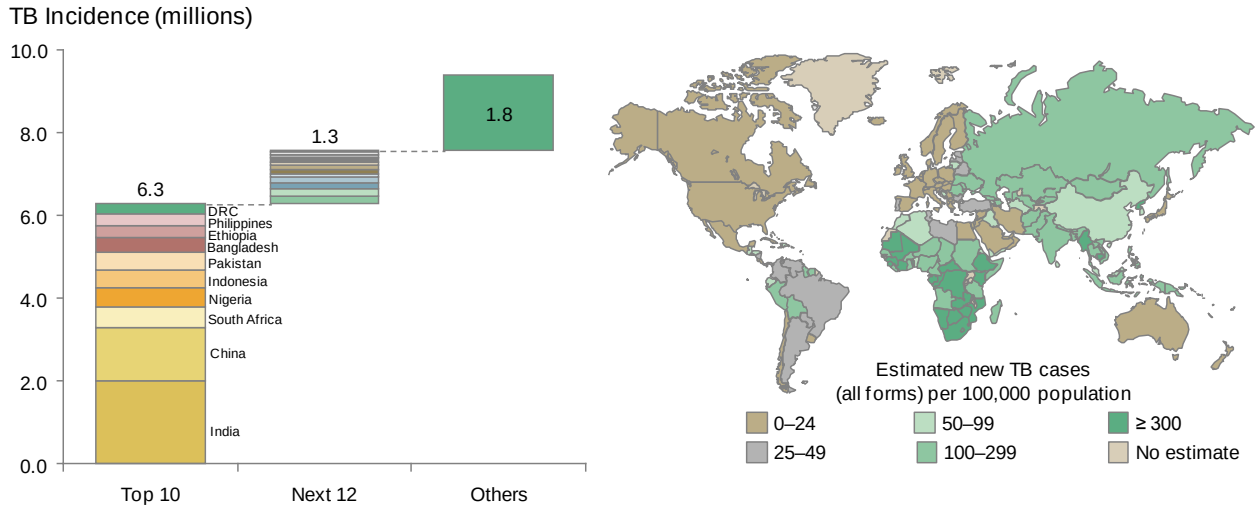
2.2 With no vaccine on the short-term horizon, upcoming improvements in treatment and diagnostics will have an incremental impact on disease burden. Multi-Drug Resistant Tuberculosis (MDR-TB) is expensive to treat and may become a growing threat for local health systems in some regions of the world. HIV/TB co-infection has become increasingly prominent and will remain an issue especially in African countries for years to come.

2.3 Given these dynamics, as well as an increasingly challenging funding environment, tuberculosis will continue to pose a major challenge to global health. A coordinated effort (both within the TB community, and with the HIV community) will be required to continue progress against the disease, and to reach the targets set.

2.b Estimated disease burden

2.4 The region with the greatest share of tuberculosis burden (incidence) is Southeast Asia, accounting for almost one-third of all incident cases in 2009. The problem of HIV-related tuberculosis is largely concentrated in sub-Saharan Africa, with 80 percent of all new HIV/TB cases occurring in this region.[25]

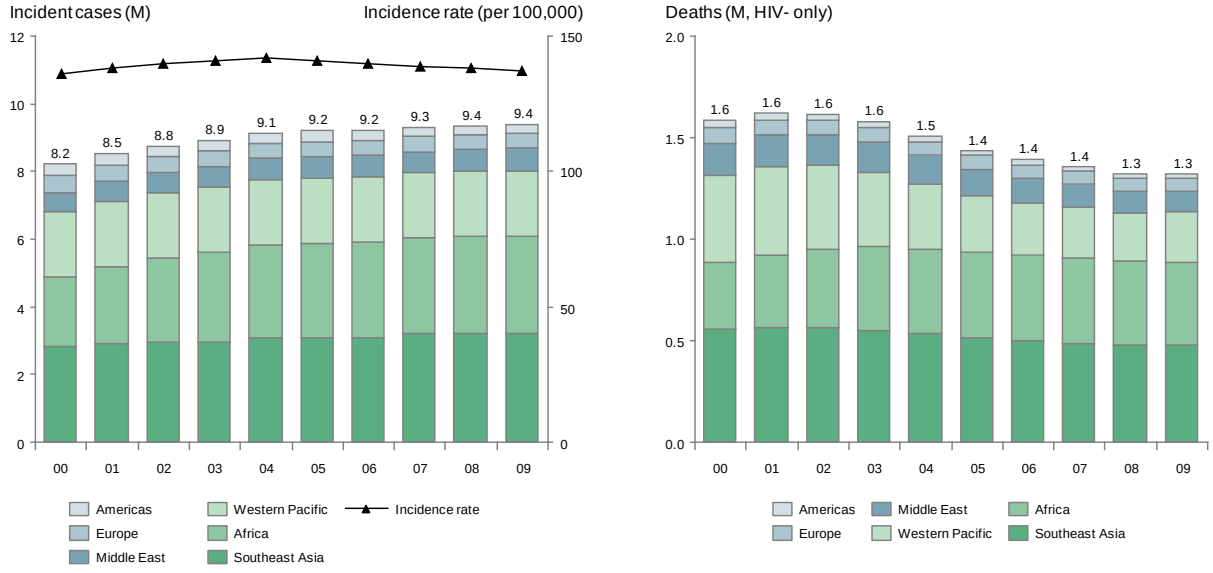
Exhibit 7: *Tuberculosis – Estimated incidence by country[26] (2009)*



[25] WHO. World Tuberculosis Control Report 2010.
[26] Ibid.

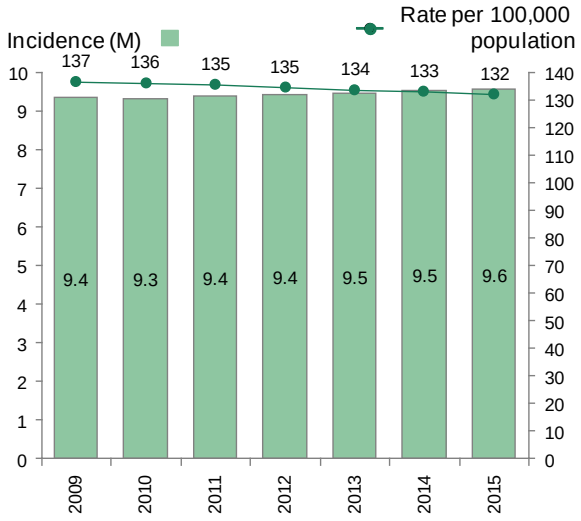
2.5 The global tuberculosis incidence rate is falling slowly at around 1 percent per annum following a peak at just over 140 per 100,000 populations in 2004. Due to the interplay between population growth and incidence, the absolute number of cases continued to increase from 8.2 million cases in 2000 to 9.4 million cases in 2009, offsetting the per capita decline.[27] Decreases in mortality have come mostly from the scale-up of the DOTS/Stop TB strategy, with improvements in case detection rates, from 46 percent in 1995 to 63 percent in 2009, and in treatment success rates, from 57 percent in 1995 to 86 percent in 2009 for new smear-positive cases. Although precise estimates are difficult to obtain since many countries still lack adequate surveillance, approximately 440,000 MDR-TB cases occur annually worldwide (around 3 percent of new and 21 percent of retreated TB cases). HIV-positive cases make up about 12 percent of all incident cases and 23 percent of all TB deaths.[28]

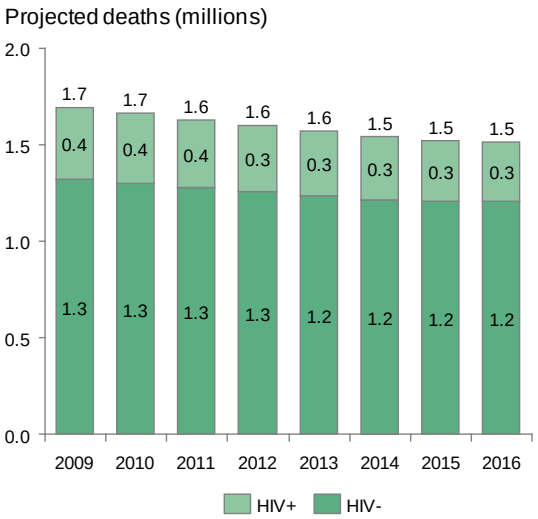
Exhibit 8: *Tuberculosis – Estimated incidence and deaths by WHO region (2000-2009)*[29]



[27] Ibid.
[28] Ibid.
[29] Ibid.

Exhibit 9: *Tuberculosis – Projected incidence and deaths (2010-2015)*[30]

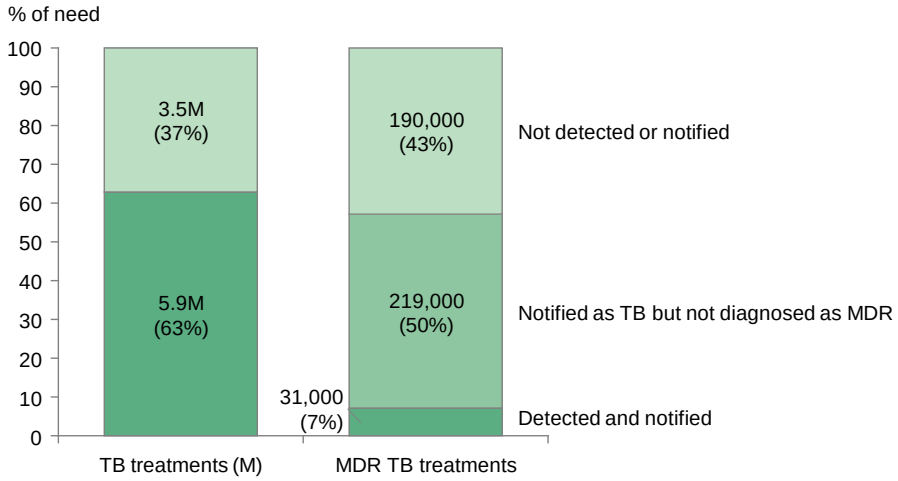




2.c Unmet needs

2.6 Of the 9.4 million new patients estimated to need treatment in 2009, 3.5 million (37 percent) were not detected. Of the 250,000 cases of MDR-TB that could have been diagnosed, only 31,000 were diagnosed and notified.[31] Unmet needs tend to be more concentrated among the poor in countries that lack health system capacity to properly implement TB control programs. Poor people and special risk groups (including migrant, homeless, and marginalized populations) in middle-income and wealthier countries, however, are also less likely to be detected or receive adequate treatment. **Community-based** approaches to detection and treatment are important to address these currently unmet needs.

Exhibit 10: *Tuberculosis – Unmet needs in detection*[32]



[30] Forecast expected values were predicted by fitting log-linear model of time-series for the years 2005-2009. Mortality projections from Glaziou, P et al. " Lives saved by tuberculosis control and prospects for achieving the 2015 global target for reducing tuberculosis mortality." *Bull World Health Organ* 2011;89:573–582

[31] WHO. World Tuberculosis Control Report 2010.

[32] Global Fund Results Report 2011. Number of cases in need of treatment includes only those notified.

2.7 Disease progression: Continuation and acceleration in the recent declines in global TB incidence, prevalence, and mortality rates can be achieved by early case detection and improvement in treatment success rates from ongoing TB initiatives. Nevertheless, the long incubation period of tuberculosis means that rapid changes in disease burden (as well as in the regional distribution of burden) are unlikely to take place over short periods of time.

2.8 Resistance: Continued growth in the **resistance to current therapies** poses a threat. Countries with weak health systems will be especially at risk, since resistance often arises from inadequate treatment regimens. Treatment and care for MDR-TB is at least 10 times more expensive per patient than standard TB treatment[33]. These countries will find it difficult to fund the more complex and expensive MDR-TB treatments and will require additional assistance from external donors.

2.d Key advancements (new approaches and innovations)

Exhibit 11: *Tuberculosis – Likelihood and impact of new interventions[34]*

Type	Existing	Anticipated	Timing	Likelihood	Impact
Vaccine	BCG	Mtb72F, MVA85A, H56	2020		
Treatments	Rifampicin/ Isoniazid/ Pyrazinamide/ Ethambutol	Moxifloxacin, Gatifloxacin, PA 824, TMC 207, OPC-67683	2013		
Diagnostics	Sputum smear Culture (solid/liquid)	Xpert MTB/RIF	2011		
TB/HIV	ART/3Is	NA	NA		

2.9 Vaccine: The existing vaccine against tuberculosis BCG (Bacillus Calmette-Guérin) has variable efficacy, being less effective in tropical regions and in adults. Despite promising research in finding substitutes for BCG (at least three candidates are currently in early stage clinical trials: MVA85A, Mtb72F and H56), an effective vaccine remains unlikely in the near to medium term.

2.10 Treatments: The WHO Stop TB Strategy comprises six components (including high-quality DOTS expansion and enhancement) and involves standardized treatment with supervision and patient support, which includes a variety of drugs and a treatment duration of at least six months. Efforts to improve existing regimens are primarily focused on reducing the length of treatment. Moxifloxacin and gatifloxacin, both currently in Phase III trials, could reduce treatment regimens to four months. Both are expected to become available in late 2012-2013. Some new anti-TB drugs that are currently in phase II trials and could become available by 2013 are PA 824 (for drug-susceptible TB) and TMC 207 and OPC-67683 (for drug-resistant TB).

2.11 Diagnostics: Sputum smear microscopy is the standard procedure for diagnosing TB in most developing countries, but case detection remains suboptimal. Culture is the standard method of confirming the disease and detecting resistance. Liquid culture results may be

[33] Global Fund Results Report 2011, page 73 *"In the 22 high TB–burden countries, most estimated costs for DOTS per patient ranged between US$ 139 and US$ 313 between 2007 and 2009"*

[34] "Likelihood" refers to the chance that the new intervention is developed and taken up within the period of the strategy (2011-2015). "Impact" refers to the magnitude of health impact from the intervention. Increased shading denotes higher likelihood/impact

obtained in 1-2 weeks, whereas solid culture results may take as long as 4-12 weeks to obtain conclusive results. A new test developed by Cepheid and FIND, called Xpert MTB/RIF, can produce results in as few as 100 minutes, but its cost (US$17,000 per machine and US$16.86 per cartridge as negotiated by FIND) may limit scale-up in developing countries.

2.12 HIV/TB: No new technologies specific for the treatment or prevention of HIV/TB are expected over the medium term. The main challenge will be to expand existing interventions such as antiretroviral therapy and the three I's: Isoniazid preventive therapy (IPT), intensified TB case-finding among people with HIV, and infection control to prevent the spread of TB in health facilities.

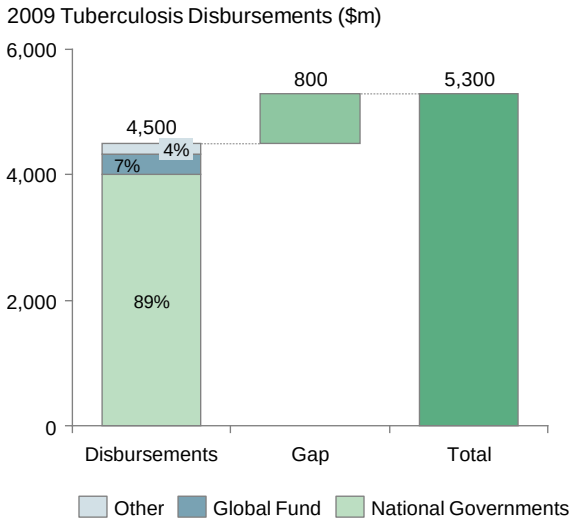
2.13 Demand implications: With a viable vaccine still years away, primary advancements will focus on incremental improvements to – and expansion of – existing treatment and diagnostic options. The WHO believes that **advances in TB diagnostics,** while shortening diagnostic and treatment delays in general, will triple the number of **MDR-TB cases** identified and double **HIV/TB** cases identified, thus producing a growing demand for treatment of more complex forms of TB.

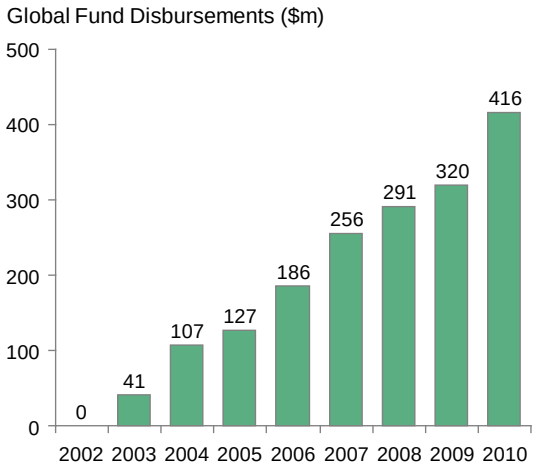
2.e Partner landscape and funding environment

2.14 National governments are the major source of funding for TB control activities, making up approximately 87 percent of all TB funding globally as of 2009. The Global Fund is by far the largest international donor, comprising 65 percent of international funding in 2009. Of the US$2.8 billion in funding available to National TB programs in the 22 high-burden countries by 2011, approximately 45 percent went to Russia, 14 percent to China, 10 percent to South Africa, and 5 percent to India.[35]

2.15 Out of an estimated need of US$5.3 billion in 2009, only US$4.5 billion was made available, leaving a funding gap of US$0.8 billion.[36]

Exhibit 12: *Tuberculosis – Funding summary*[37]





[35] Ibid.
[36] The Global Plan to Stop TB 2006-2015.
[37] Triangulated from TB Control Report 2010 and Global Fund Results Report.

2.16 During the period 2011-2015, US$37 billion of funding will be required for TB control, in order to reach Stop TB Partnership goals of cutting prevalence and deaths in half by 2015, as compared with 1990. A recent additional target calls for **1 million lives saved from HIV/TB by 2015**. **Domestic funding** (increasing at the level of GDP growth) would contribute US$23 billion of the required amount, leaving the remaining US$14 billion to be funded by international donors. This would require a six-fold increase from current levels of international funding (from ~US$ 0.5 billion to 2.8 billion on average per year).

2.17 Key partners in TB include national governments; international organizations such as the WHO, WB, UNAIDS, the International Union against TB; bilaterals such as USAID and DFID; and many other NGOs such as Partners in Health, Médecins Sans Frontières, KNCV, and the Red Cross, many of which belong to the Stop TB Partnership.

2.f Key issues and implications for the Global Fund

Issue	Implication for the Global Fund
Global targets for 2015 – aligned with MDGs (Global Plan to Stop TB)	Increased demand for funding in order to fill gaps towards universal coverage and to reach targets
Additional 2011 Stop TB Partnership goal is to save **1 million lives from HIV/TB** by 2015	Additional target beyond original Global Plan to Stop TB. The Global Fund will be asked to dedicate additional resources for treatment and diagnosis across HIV and TB – such as ART and 3Is
Domestic funding to play increasingly important role, especially in middle-income countries	Global Fund expected to further engage in policy shaping and advocacy, especially in Asia and Europe
Increased focus on **MDR-TB** detection will increase need to diagnose and properly treat MDR-TB cases	Increased funding demands for diagnostics, expensive MDR-TB treatments, and to the effective implementation of first-line treatments that will limit MDR-TB development
Increased focus outside of national programs – such as **private**, and **community sector** participation in TB care and control	Increased demand for funding of public/private schemes, and of community-based approaches, particularly for vulnerable populations
Early and improved case detection can lower transmission, especially in vulnerable populations	Additional funding demands for new diagnostic tools

3. MALARIA

3.a Executive summary

3.1 Recent progress in the treatment and prevention of malaria has led to declines in disease episodes and deaths. Sustaining this progress will require the periodic replacement of insecticide-treated nets (ITNs) nearing their expiry date, as part of a broader strategy of integrated vector management (IVM), case management, surveillance, elimination, and intermittent preventative treatment (IPT). The Global Malaria Action Plan (GMAP) has set out a strategy to reach ambitious targets, including achieving universal coverage by 2015.

3.2 No new treatments are likely to significantly change the disease landscape over the next five years, however the ramp-up of rapid diagnostic tests will reduce treatment needs and feed investments in improved surveillance systems that allow for a better calibrated response to malaria. The threat of resistance to existing insecticides and treatments remains a substantial challenge to future progress against the disease, and WHO plans against the former were published in 2011, with the latter anticipated in early 2012.

3.3 Overall, the factors above will add to the substantial unmet funding needs, which will only be slightly offset by recent donor commitments. The Global Fund, which currently contributes a majority of international funding, will remain a major contributor to the fight against malaria.

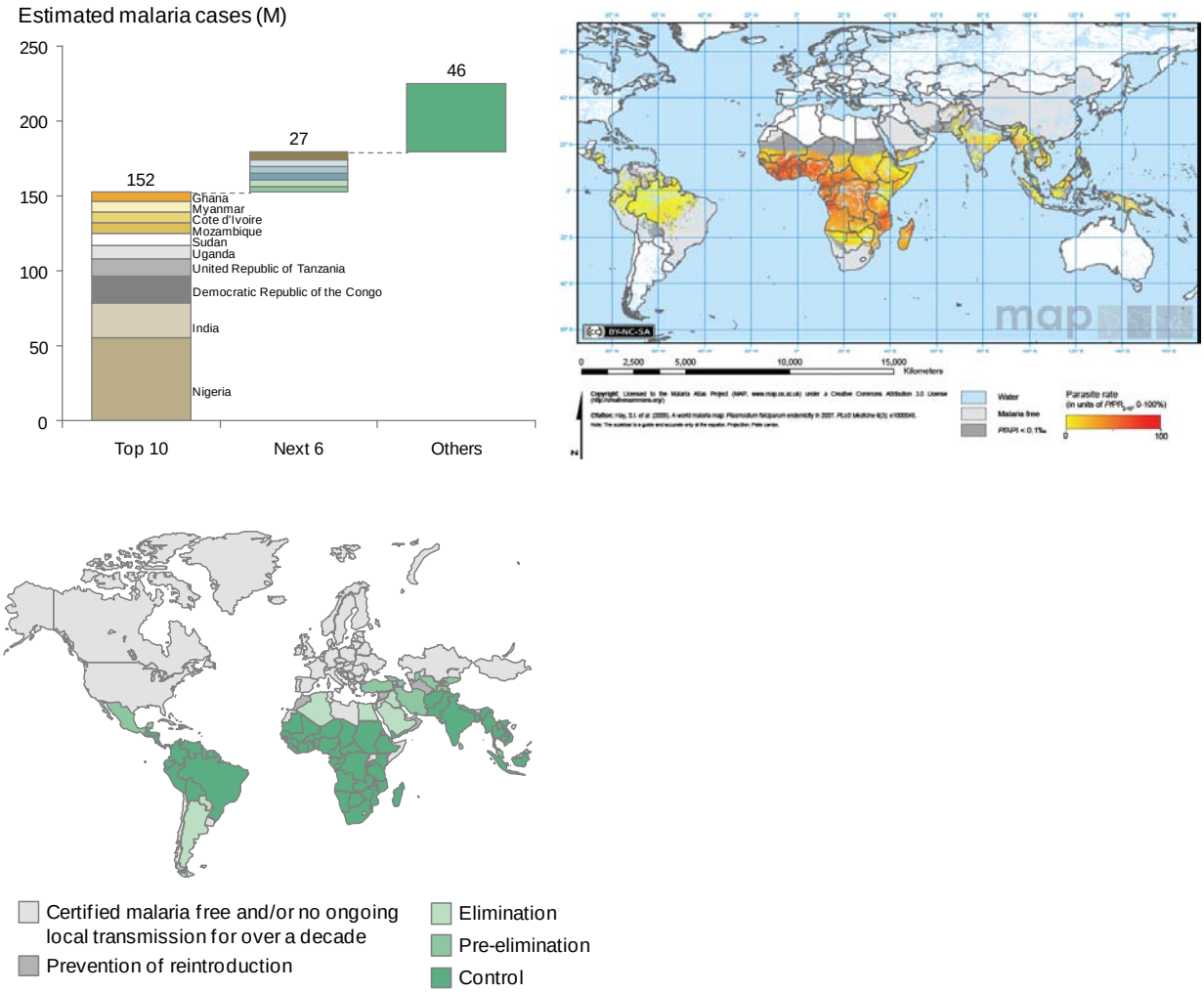
3.4 In the context of resource constraints set against the ambitious plans for increased coverage, surveillance, and the challenges of resistance, there is a continued need to prioritize and coordinate efforts in malaria

3.b Estimated disease burden

3.5 Malaria today is primarily concentrated in tropical regions, with 78 percent of all cases and 91 percent of all deaths occurring in Africa in 2009.[38] The disease is even further concentrated in certain African countries, with the two countries—Nigeria and the Democratic Republic of Congo (DRC)—making up approximately one-third of cases and deaths. Of the most common two species of malaria, *P. vivax* is predominantly located in Asia, whereas *P. falciparum* is concentrated in Africa. The increased mortality associated with *P. falciparum* accounts for the differential between the distribution in cases and deaths.

[38] WHO, World Malaria Report 2010

Exhibit 13: *Malaria – Estimated incident cases[39] and intensity status by country[40,41] (2009)*



3.6 Malaria cases and deaths have shown gradual declines over the past several years, reaching an estimated 225 million cases and 781,000 deaths in 2009.[42] These declines are partly attributable to the rapid expansion of vector control. As of the end of 2010, sufficient ITNs were supplied to cover up to 76 percent of the 765 million at-risk people in sub-Saharan Africa.[43]

3.7 Diagnostic and treatment coverage has also increased. The percentage of reported suspected malaria cases receiving a parasitological test has grown to 73 percent worldwide, but coverage varies widely by region, with Africa trailing the rest of the world significantly. Of the 42 African countries that report testing statistics, 21 show that less than 20 percent of cases are tested.[44] Since most cases of presumptive treatment of malaria are in the private sector, achieving universal access to RDTs requires universal coverage in the private sector. This means learning more about making development assistance work through the formal and less formal parts of the commercial private sector.[45] The distribution of artemisinin-based combination therapies (ACTs)

[39] WHO, World Malaria Report 2010 – country level data
[40] ATLAS project (http://www.map.ox.ac.uk/)
[41] WHO, World Malaria Report 2010
[42] Ibid
[43] Ibid. Includes 66% as of the end of 2009 and an additional 10% added in 2010.
[44] Ibid
[45] Consultation on the economics and financing of universal access to parasitological confirmation of malaria, 31 May – 1 June 2011. Final Report

is also believed to have increased, although actual numbers are incomplete and vary significantly by country.

Exhibit 14: *Malaria – Estimated cases and deaths by WHO regions (2000-2009)*[46]

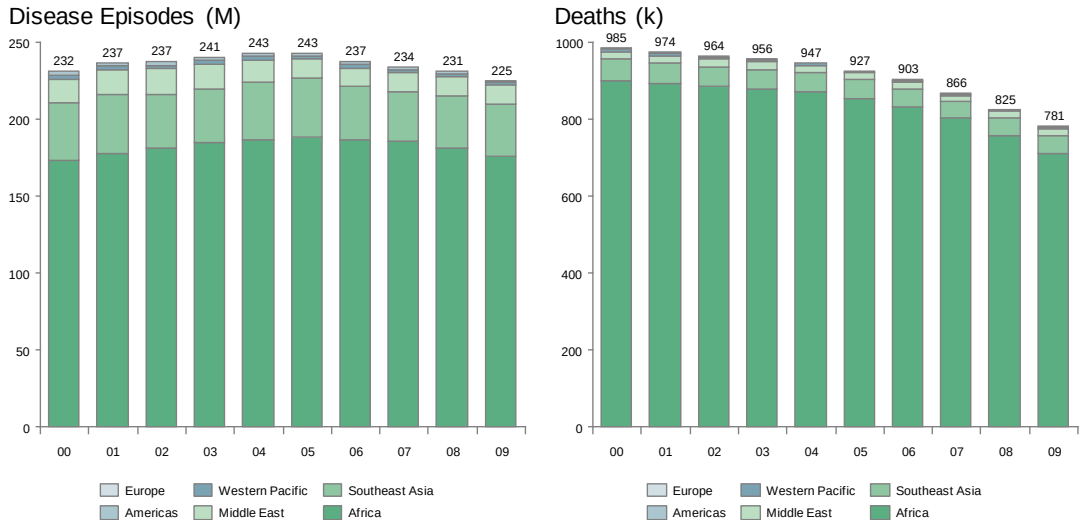
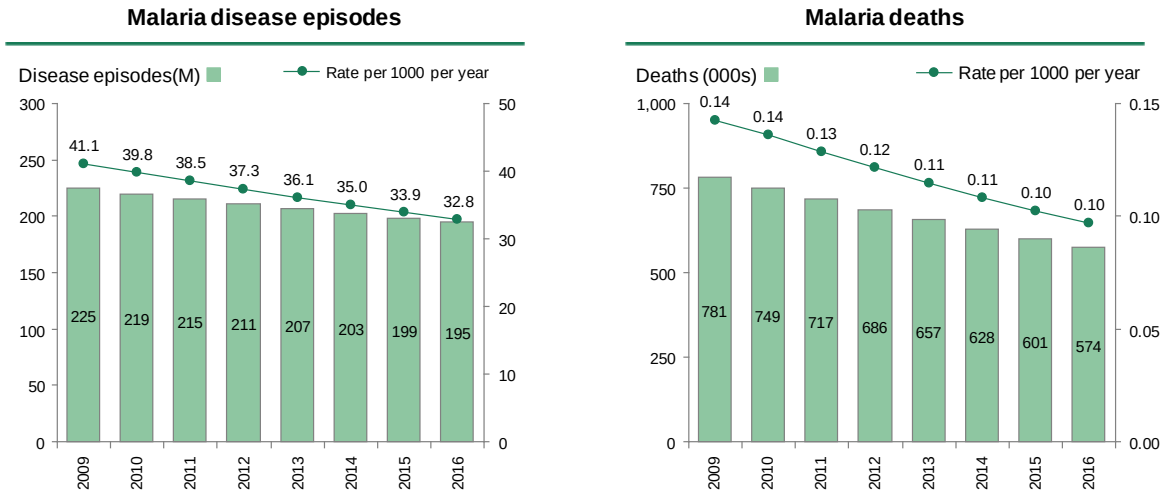


Exhibit 15: *Malaria – Projected cases and deaths (2010-2015)*[47]



3.c Unmet needs

3.8 In 2009, 158 million ACT courses were procured, compared with an estimated 225 million disease episodes. The actual unmet is even greater than the difference, since many of the ACT courses were used on patients who did not have malaria due to false diagnoses. The availability of ACTs varies widely between countries, but tends to be much lower in Africa.

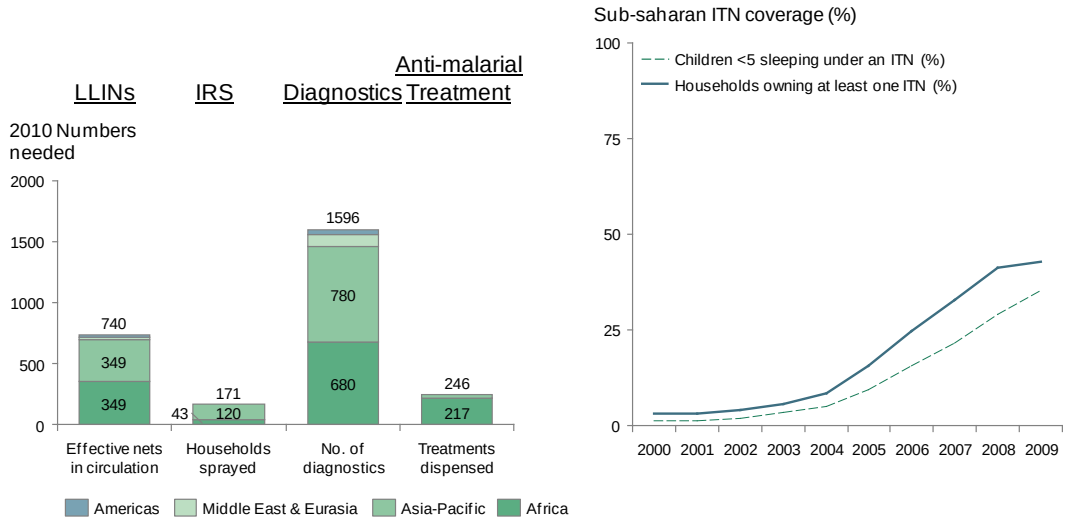
[46] Ibid

[47] Global Fund estimates: forecast expected values were predicted by fitting log-linear model of time-series for the years 2005-2009, so extrapolated forward based on a continuation of previous evolution

3.9 Unmet needs for ITNs are also largely concentrated in Africa, where despite rapid scale-up since 2004, only 42 percent of households own an ITN, and only 35 percent of children under the age of five sleep under an ITN at night as of 2009.[48] Even with widespread vector control distribution, appropriate education needs to be provided to ensure that ITNs and other tools are used effectively.

3.10 Specific populations with unmet needs include migrants and seasonal workers, who often fall outside the reach of mainstream distribution systems.

Exhibit 16: *Malaria – Projected needs by region (2010)*[49]



3.11 Disease progression: As universal coverage targets for vector control are approached, malaria disease episodes are likely to decrease accordingly. **Ramp-up of rapid diagnostic test (RDT)** usage will lead to more accurate diagnoses and epidemiological data as well as better utilization of existing treatments. Due to the natural lag between vector control distribution and incidence impact, the recent large scale-up of ITN distribution will likely yield incidence decreases in the coming years.

3.12 Resistance: Artemisinin resistance to date has been largely limited to the low transmission countries of Southeast Asia. Nevertheless, continued use of oral artemisinin-based monotherapies in the high transmission countries of Africa risks triggering broader resistance to ACT treatment. In the past, **resistance to drugs**, such as chloroquine, resulted in increased child mortality and a reversal of gains in disease control. In 2011, the WHO published the global plan for artemisinin resistance containment (GPARC) to address this threat, and called for more rational usage of ACTs – i.e. based on a confirmed diagnosis of malaria. The threat of artemisinin resistance may also be somewhat mitigated by non-ACT treatments currently in early stage trials.

3.13 **Insecticide resistance** will also begin to pose a substantial threat. Resistance to pyrethroids, the only insecticide class licensed for ITN use, has already been detected in Africa. Without additional insecticide classes beyond the four currently licensed for indoor residual spraying (IRS), insecticide resistance may threaten the effectiveness of existing approaches to vector control. Improved monitoring and increased use of multiple vector control interventions will also mitigate the risk of insecticide resistance. A global plan for insecticide resistance management is due for publication by the WHO in early 2012.

[48] WHO World Malaria Report 2010.
[49] GMAP for regional needs 2010, World Malaria Report 2010 for ITN coverage in sub-Saharan Africa

3.d Key advancements (new approaches and innovations)

Exhibit 17: *Malaria – Likelihood and impact of new interventions*[50]

Type	Existing	Anticipated	Timing	Likelihood	Impact
Vaccine	N/A	RTS,S	2015		
Prevention	ITN, LLINs, IRS	Durable wall linings	2013-14		
		New classes of insecticide	2016+		
		IPTc, IPTi	2011-2012		
Treatments	ACT	Formulations for children and pregnant women	2012-2014		
Diagnostics	RDTs	LAMP	2012?		

3.14 Vaccine: There has been a great deal of research into the possibility of a malaria vaccine, however none has been made available to date. The most promising candidate, RTS,S, entered Phase III trials in May 2009. Developed via a public-private partnership between GSK and PATH Malaria Vaccine Initiative (MVI), RTS,S targets infants and young children, but is only expected to provide short-term immunity and up to 50 percent to 60 percent efficacy. Full data from clinical trials is expected in 2014, and WHO expects to make a policy recommendation in 2015, but even if the vaccine is successful, it is unlikely to replace existing prevention measures such as vector management and control techniques.

3.15 Prevention: Besides existing vector control technologies, renewed focus has been placed on discovering new alternatives to counter the risk of insecticide resistance. One promising vector control innovation is the durable lining, an insecticide-treated plastic sheeting hung on interior walls. Durable linings have proven effective in limited studies, but will need to pass through WHO testing procedures before being recommended for large-scale implementation. New classes of insecticide are being developed but are unlikely to be tested and approved within the next five years. The Global Plan for Insecticide Resistance Management (GPIRM) is being developed at the WHO in order to manage the threat of resistance to existing insecticides. Long-lasting insecticidal nets (LLINs), which last more than five years, have also been considered. Despite their greater cost-effectiveness on a per-year basis, uptake of such LLINs will be slowed by their higher up-front price point. Beyond traditional vector control, intermittent preventive treatment (IPT), a full therapeutic course of an anti-malarial drug provided to the whole of a population at risk has

[50] "Likelihood" refers to the chance that the new intervention is developed and put into use within the period of the strategy (2011-2015). "Impact" refers to the magnitude of health impact from the intervention. Increased shading denotes higher likelihood/impact

shown positive results in children (IPTc) and infants (IPTi), but has yet to be widely adopted and scale-up will likely be focused on the Sahel.

3.16 Treatments: Expected short-term treatment innovations are limited primarily to new applications of existing ACT treatments. The WHO in 2011 recommended an artesunate injection for severe cases of malaria, when patients are unable to swallow oral medicines. Treatments more suitable for pregnant women and child-friendly formulations are expected in 2012-2014. Single-dose treatments (OZ 439 and NITD 609) could be game-changing, but remain in early-stage clinical trials. New synthetic compounds are also in the pipeline and will be indispensible to fighting ACT resistance. The Affordable Medicines Facility for malaria (AMFm) is currently in its first phase, conducting nine pilots in eight countries, and aims to enable countries to increase the provision of affordable ACTs through the public, private, and NGO sectors. Early results indicate that the innovations in the AMFm have increased availability and lower retail prices of ACTs[51]. These findings suggest that in addition to the government and private not-for-profit sectors, which are the traditional channels for development assistance - and which the AMFm also supports, the commercial private sector is a viable channel for getting donor-financed ACTs to people in malaria endemic countries.

3.17 Diagnostics: Rapid diagnostic tests have been developed, although effectiveness varies by test and location. New developments are focused mainly on simplifying ease-of-use and improving accuracy in low-prevalence settings. Loop-mediated isothermal amplification (LAMP) of DNA for malaria is one such example, which can be used in basic laboratories to detect low parasite densities. The continued scale-up of RDTs will be a higher priority for resources, but should reduce the antimalarial treatments used on patients without malaria, and will also highlight the need for provision of treatment for non-malarial fevers. Surveillance is increasingly important - WHO is anticipated to issue **guidance to Test/Treat/Track** cases – with an aim to record and report every case.

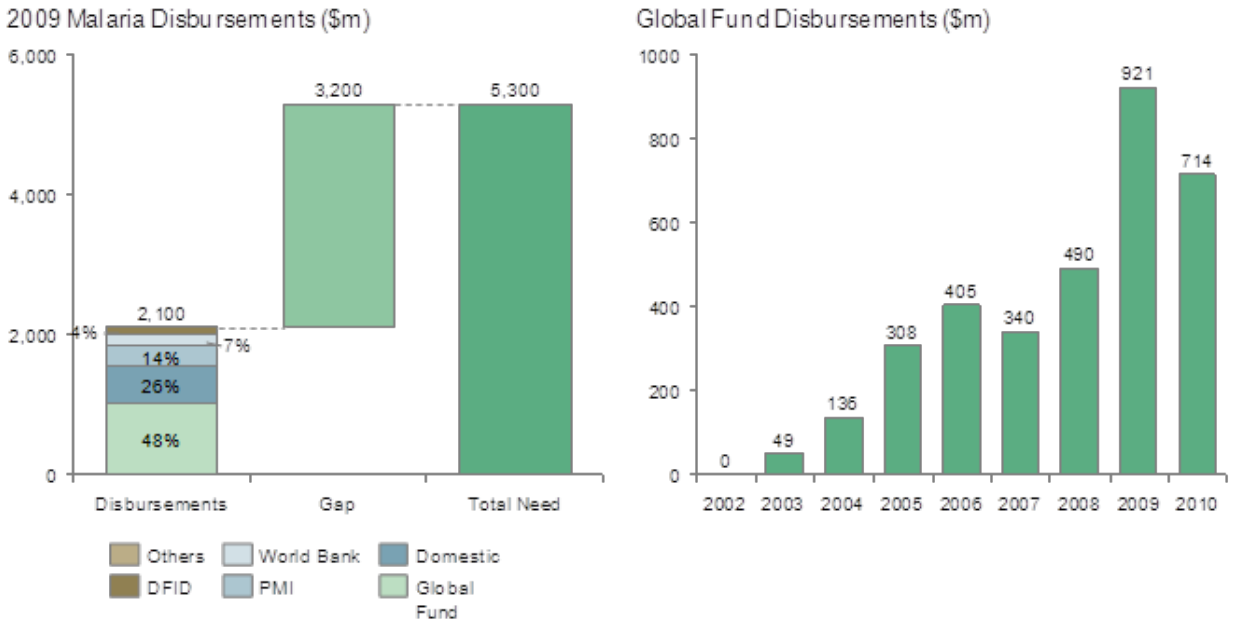
3.18 Demand implications: With revolutionary advancements in vaccines, prevention, treatment, and diagnostics unlikely over the short to medium term, the need for malaria control will remain high. Continued scale-up of existing diagnostics is likely to reduce malaria treatment needs.

3.e Partner landscape and funding environment

3.19 The Global Fund is the largest international donor to malaria control efforts, having provided approximately 65 percent of all international disbursements.[52] Other international donors include the President's Malaria Initiative (PMI), World Bank, and DFID.

[51] Health Action International. Retail prices of ACTs co-paid by the AMFm and other antimalarial medicines in Ghana, Kenya, Nigeria and Tanzania. June 2011
[52] Global Fund website

Exhibit 18: *Malaria – Funding summary*[53]



3.20 Of the estimated US$5.3 billion required for malaria control in 2009, only US$2.1 billion was available, leaving a funding gap of approximately US$3.2 billion. Funding needs will continue to be at least US$5 billion per year through 2015, according to the Global Malaria Action Plan (GMAP), which aims to achieve a global reduction in incidence by 75 percent and near-zero mortality. The RBM partnership in 2008 set the target to eliminate malaria by end-2015 in ten additional countries and in the WHO Europe Region.

3.21 The World Bank is expected to maintain existing funding levels (of US$150-200 million), while the PMI has increased funding from US$300 million in 2008 to US$620 million in 2011, with a similar appropriation expected in 2012. Significant increases are also possible from DFID, which may reach over US$500 million per year by 2015. Other major partners in malaria include Roll Back Malaria and the UN Secretary General's Special Envoy for Malaria.

[53] Triangulation from World Malaria Report 2010, PMI website, UN and Global Fund website.

3.f Key issues and implications for the Global Fund

Debate/Issue within malaria community	Implication for the Global Fund
Global Fund is **leading provider of funding**, for a disease with substantial unmet needs and , ambitious partner goals	Expectation that the Global Fund will continue its substantial contributions to malaria funding, and potentially grow this in line with partner plans
Large number of **ITNs** distributed in recent years will **need to be replaced** as their expiry date nears .	A large part of malaria funding is "mortgaged" and will need to be dedicated to the replacement of existing nets.
WHO anticipated to issue **guidance to Test/Treat/Track** cases - aim to record and report every case.	Increased demand for funding for provision of RDTs and building and maintenance of surveillance systems, leading to more effective use of ACTs through a focus on confirmed malaria cases.
Scale-up of **rapid diagnostic tests** to meet targets means fewer patients will receive a diagnosis for malaria, but there will be additional incremental costs for diagnostics.	A fundamental implication of RDT use is the unmet provision of treatment for non-malarial fevers once diagnosed. This creates the opportunity for synergistic provision of non-malarial treatments
The roles of **public, NGO and private sectors** in expanding access to prevention, diagnostics and treatment.	Analyzing which combination of channels is most suitable for each country, depending partly on the current mix of service delivery channels.
Increased focus on **community sector participation** in malaria care to reach marginalized populations and to ensure effective distribution and replacement of LLINs	Increased demand for funding for community-based projects
Potential for **drug** (especially artemisinin and partner medicines) and **insecticide resistance** to threaten gains made thus far in malaria prevention and treatment	Expected demands for new interventions for treatment and vector control. Will be asked to co-finance implementation of containment strategies (consistent with the GPARC and GPIRM) in order to ensure value for money