Report of the First Meeting of the expert panel on health impact of Global fund investements

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Executive Summary

The key objective of the Global Fund Strategy 2012 to 2016 is to maximize the impact of its investments. However, there are methodological and policy limitations regarding the current methods used by The Global Fund to estimate and measure impact. In response to a request by the Board of The Global Fund (1), an expert panel comprising key Global Fund partners and leading experts in this area, was convened in Geneva on 10 to 11 July 2014. The group agreed on a set of recommendations for Global Fund on how best to improve its current methods for measuring impact. These are listed by disease and are differentiated by short- and long-term perspective:

HIV

- Short-term: continue using Spectrum/AIM for estimating lives saved from ART and use it to start reporting on infections averted by PMTCT. Remove 'double-counting' of lives saved between DOTS and ART by lives saved from treating HIV-positive TB patients from DOTS count.
- Long-term: measure the impact of other key interventions using transmission models such as Spectrum/Goals or AEM models preferably through existing UNAIDS-led processes.

TB:

- Short-term: revise the current method (service-based multiplier) to WHO current method which is applying the case fatality of untreated cases to the estimate of incidence and subtract it from the estimate of TB deaths for the same years.
- Long-term: apply transmission models such as TIME to capture additional downstream impact of key interventions.

Malaria:

- Short-term: revise the current method (service-based multiplier) to WHO estimate of burden against 2000 counterfactual for assessment of impact of the past investment and use LiST model for forward projection of impact.
- Long-term: replace/strengthen LiST model with transmission models such as OpenMalaria or MalariaTools and apply it in priority countries for impact measurement and program evaluation.

Crosscutting:

- Choice of counterfactual: "no treatment/ no intervention" is agreed as choice of counterfactual for the 3 key interventions (ART, DOTS and LLINs), however, it should be carefully re-visited as part of long-term recommendations.

- Linking cost and impact: where timing and resources allow, modelling of impact should be streamlined with the Secretariat work on measuring and monitoring efficiency and improving allocative efficiency (KPI4).

- Data systems: there is a clear need to strengthen data collection and to build analytical capacity in countries and The Global Fund should play a strategic role in both of these areas.

- Attribution/contribution: the question of how to determine Global Fund contribution to national results was not in the scope of meeting, but a useful brainstorm carried out and the results will be taken into account in due course.

Background

Since its inception The Global Fund has committed US$ 41 billion to low- and middle-income countries to fight the three pandemics. It is crucial to understand the extent to which this support has helped to manage and control these diseases and has contributed to improve the lives of those at risk.

The Global Fund Strategy (2012-2016) sets explicit health goals and targets which reflect the ambitions of The Global Fund to maximise the impact of its investment. The principal impact measures are the number of lives saved and infections averted through Global Fund-supported programmes. Since 2005, The Global Fund has shared its estimates of the number of lives saved, through its support for the provision of antiretroviral therapy (ART) to those infected with HIV, the WHO international standard of care (previously known as DOTS) to treat those with tuberculosis (TB), and long-lasting insecticide-impregnated nets to prevent malaria infections (2). Methods for making these estimates were based on publications in peer-reviewed journals and were agreed with the WHO and UNAIDS (3). In 2011, a meeting with technical partners was convened to advise The Global Fund in setting its strategic goals and targets for the period 2012 to 2016. Methods for estimating the number of lives saved through Global Fund support were reviewed and revised, and a provisional method for setting targets for infections averted was agreed (4).

More recently, a number of methodological and policy limitations of The Global Fund estimate of the number of lives saved were identified, including 1) uncertainty and bias in the key assumptions used in the estimation models; 2) attribution and double-counting of The Global Fund share; and 3) uncounted lives saved from additional services supported by The Global Fund. These additional services include prevention-of-mother-to-child-transmission (PMTCT) services for pregnant women, HIV testing and counselling in the general populations, HIV prevention services for most-at-risk-populations, male circumcision, enrolling HIV co-infected TB patients on ART, treating multi-drug-resistant-TB, indoor residual spraying with insecticides to kill mosquitoes, rapid diagnostic tests (RDTs) for suspected cases of malaria, and artemisinin-based combination therapy (ACT) for confirmed cases of malaria.

To address the limitations of the current methodology and develop a revised methodology to measure the impact of The Global Fund's investment, the Board of The Global Fund asked the Secretariat to update and improve its methods[1]. This was to be done in collaboration with technical partners through an independent, transparent, and authoritative process that would lead to consensus among experts. The improved methods will be used to revisit The Global Fund Strategy targets for 2012 to 2016 and to inform the targets for the next Global Fund Strategy for 2017 to 2021. To this end The Global Fund convened a group of experts (See Addendum) who met in Geneva on the 10th and 11th of July 2014.

As a first step a sub-group of experts was asked to develop recommendations for each of the three diseases. Their recommendations were then circulated to a wider group of experts in two rounds for peer review and feedback. This document describes the consensus reached among the experts on a set of short and long-term recommendations aiming at improving the current Global Fund methodology to assess impact.

Recommendations

HIV

Background

The Global Fund supports a number of interventions to control the spread of HIV and to extend the lives of those already living with HIV. These include:

i. HIV counselling and testing (HCT);
ii. The provision of antiretroviral therapy (ART);
iii. Prevention of mother-to-child-transmission (PMTCT);
iv. Prevention programmes for key populations (KPP), including needle and syringe exchange programmes and opioid substitution therapy for people who inject drugs (PWID)
v. Condom promotion for men-who-have-sex-with-men (MSM),
vi. Pre-exposure prophylaxis (PrEP) and condom promotion for female sex workers (FSW); and
vii. Voluntary medical male circumcision (VMMC).

Measurement of the impact of these individual interventions is needed to understand the impact of the programmes supported by The Global Fund.

Current methods for estimating Global Fund impact related to HIV

The Global Fund reports on the impact of ART based on data provided by UNAIDS on lives saved due to ART (5). UNAIDS supports countries to estimate lives saved due to ART by using the AIDS Impact Module (AIM) within the computer package Spectrum (6). Data are available from 158 countries including those in which Global Fund programmes operate (7). Spectrum provides estimates of the historical and current incidence, and the prevalence of HIV. Allowance is made for the effects of ART in reducing transmission and decreasing mortality. Comparison of cumulative AIDS mortality since the start of the epidemic, from a Spectrum model without ART against one with the reported coverage of ART over time, gives an estimate of the number of lives saved by the provision of ART.

Recommendations

Short term (2014)

- Use Spectrum/AIM to estimate lives saved by ART and infections averted by PMTCT

  The Global Fund should continue to estimate the number of lives saved by ART using the current methodology (Annex 1). The number of infections averted through Global Fund support for the prevention of mother-to-child-transmission (PMTCT) interventions is currently available from national Spectrum estimates and should be added to the current impact measures.

- Add HIV/TB services in lives saved and avoid double-counting of lives saved by TB treatment and ART

  As discussed in the TB section, it was agreed that all lives saved in HIV-positive TB patients should be attributed to HIV treatment and not TB treatment. This will avoid double-counting of HIV and TB deaths in the overall estimates of lives saved by Global Fund programmes.

- Report estimates of uncertainty

  Uncertainty in the estimates of infections averted and lives saved depends on the quality of the data, prior estimates of parameters that define the natural history of HIV, and the structure of the models. The AIM and the Goals modules in Spectrum provide uncertainty estimates for all output data and these should be included when reporting the updated 2012–2016 results for lives saved and infections averted by ART and PMTCT.

Long term (2015-2016)

A more complete assessment of the impact of interventions requires more in-depth understanding of the epidemiology of HIV in each country and the construction of models that take into account past changes in epidemiology and behaviour. Such an approach, undertaken by the countries that contribute the majority of new infections globally, can help to improve the current estimates of impact and expand them to include infections averted and lives saved by HIV programmes beyond ART.

- Implement Goals and AEM in Global Fund focus countries to estimate the impact of other interventions

  Estimating the number of infections averted and lives saved by other interventions that receive Global Fund support, such as HCT, KPP, and VMMC, requires a different type of model than the current Spectrum/AIM model (Annex 1). Such estimates require transmission models that include data on peoples' behaviour and on interventions that have been implemented. An alternative model, which is also available in the Spectrum computer package, is Goals: a transmission model that can be used to estimate the impact of changes in interventions and behaviours on new infections. The AIDS Epidemic Model (AEM) is widely used to assess the impact of programmes beyond ART for concentrated epidemics. With some refinements these models could be used to inform the goals and targets for The Global Fund priority countries, and a few other high investment countries, for the next Global Fund strategy beginning in 2017 (Annex 1). The Global Fund has identified 26 countries (Table 2 in Annex 1) that account for 71% of new HIV infections globally. Targeted interventions in these countries will substantially reduce the scale of the global pandemic. Support for the development of country-specific models using Goals and AEM should be implemented so that they are modelled on the existing global process to develop HIV epidemiological estimates (8). This requires an in-country process in which The Global Fund facilitates the implementation of these tools with support from Technical Partners, modellers and technical specialists.

- Assume that behaviour is constant from the date at which the global scale-up of HIV responses began in 2001 and that ART is not provided

  The choice of a suitable counter-factual is challenging (Annex 1). Many different interventions are in place for both treatment and prevention and in some countries the incidence fell before ART or other interventions were made available to people infected with HIV. The simplest counter-factual for models such as Goals and AEM assumes that, in the absence of treatment and prevention, people's behaviour has not changed. In some but not all countries there has been evidence of significant behaviour change in the absence of widespread interventions; allowing for this may be more realistic, but is extremely difficult to estimate and varies from country to country. Keeping behaviours constant avoids this complexity, but may overestimate the impacts due to control interventions. This should be considered when deciding on the counter-factual prior to engaging in country-specific estimates of impact.

TB

Background

The limited availability and quality of data on services other than for 'treatment of all forms of TB', and the difficulty of estimating the impact of other services, led The Global Fund to set targets for the control of TB in terms of the number of lives saved, which takes into account patients with all forms of TB and the number of cases of TB disease averted. In revisiting the targets for 2012–2016 The Global Fund is considering two additional services: the number of TB patients co-infected with HIV and starting anti-retroviral therapy (ART); and the number of TB patients being treated for Multi-Drug Resistant (MDR) TB. The Global Fund has also suggested estimating the additional indirect/downstream impact of their investments such as impact of TB control on the incidence of *Mycobacterium tuberculosis* infection (1).

Current methods for estimating Global Fund impact related to TB

Currently it is assumed that one life is saved for every three cases of TB that are treated, based on the difference in the case fatality ratio of treated and untreated TB (9).

Recommendations

Short term (2014)

- #### Continue to use lives saved by TB treatment as the primary measure of impact

  In the short-term (2014), continue to use lives saved by TB treatment as the primary measure of impact. The approach is simple and easily understood. The method should be modified to address the criticisms raised by McCoy *et al.* (10). Estimates of lives saved will now account for the performance of the national TB control programme, TB in those with HIV, and drug resistant TB, as estimated by the World Health Organisation (WHO) by applying the following method: WHO estimates of TB mortality are compared with a counter-factual of no TB treatment (and no ART in the case of HIV-positive TB cases). To calculate the counter-factual mortality under no treatment, the number of incident cases is multiplied with the relevant case fatality ratio (CFR) (Annex 2).

- #### Report estimates of uncertainty

  Uncertainty in the estimation of the impact on lives saved will be propagated from uncertainty in the CFRs and TB disease incidence estimates as is already being done and reported by WHO (Annex 2).

- #### Assume that there has been no TB treatment and no ART but consider the use of new counter-factuals in the longer term

  In 2014 estimate the impact on lives saved using a counter-factual in which there was no TB treatment or ART for HIV-positive TB cases after the support from The Global Fund began. The counter-factual number of incident cases will then be multiplied by the relevant case fatality ratio (CFR) (Table 3 in Annex 2). Over 2015–2016 evaluate the feasibility of using an alternative TB disease incidence counter-factual to estimate the additional impact on lives saved due to impact on TB disease incidence and the additional indirect/downstream impact of lives saved thanks to TB/HIV care (Annex 2).

Long term (2015-2016 for finalizing models; 2017-2022 for implementation)

- ### Over 2015–2016 collect data and develop and evaluate feasibility of methods to capture the additional indirect/downstream impact of lives saved by providing TB/HIV care, and the impact of TB control on the incidence of infection

  In the longer term (2015–2016) The Global Fund should provide support to WHO, TB MAC, Futures and other experts to improve data quality and develop and evaluate methods that will include the additional impact of Global Fund investments on lives saved due to impact on TB disease incidence, and the additional indirect/downstream impact of lives saved as a result of TB/HIV care. Support WHO, TB MAC, Futures and other experts to develop software that will integrate data validation checklists, burden estimation and projection tools for use at country level such as *TIME-Data*, *TIME-Estimates* and *TIME-Impact* (Annex 2). Support the collection of data from countries through existing mechanisms such as the monitoring and evaluation portion of each grant. Capture the indirect/downstream impact of lives saved by providing TB and HIV care using dynamic transmission models, such as *TIME*, in The Global Fund high impact countries. Validate models in countries with high TB burden and high quality data. After the validation, support country specific application of dynamical models in the higher impact countries and develop approximate methods in countries where data may be lacking. (See draft list of countries and budget in Annex 2)

- ### Ensure data quality and examine the validity of current models

  There is a need to ensure the quality of data used, assess the validity of more complex country mechanistic models, obtain country buy-in and reach a consensus on the best counter-factuals and metrics to use for measuring these impacts within and across diseases. This will necessitate the involvement of a country representatives in the country workshops to discuss the availability and quality of existing data, the collection of new data and the application of models. This will improve the credibility of the process and avoid criticism of the new approach. The Global Fund should commit resources and allow adequate time to collect data and develop methods for estimating the additional impact on lives saved of wider Global Fund investments, indirect and downstream effects, and additional measures such as M. tuberculosis infections averted. This will improve the credibility of the process and avoid criticism of the new approach.

- ### Support methods to improve data collection and further develop dynamic models

  In the longer term (2015–2016) The Global Fund should provide support to WHO, TB MAC, Futures and other experts to collect data, to improve data quality and develop methods for estimating the additional impact on lives saved of wider Global Fund investments, indirect and downstream effects, and additional measures such as *M. tuberculosis* infections averted. Develop and evaluate the feasibility of methods of estimating the impact of TB control on the incidence of *M. tuberculosis* infection using a transmission model, such as *TIME*. Validate the models in countries with a high burden of TB and good data. After the validation, support country specific application of dynamic models in the high impact countries and develop approximate methods in countries where data may be lacking (Annex 2) .

Malaria

Background:

The evidence base for malaria has improved substantially in the last five years and it is now possible to make empirical estimates of the impact of malaria control. In most endemic countries outside Africa, and for a small number within Africa, reporting of uncomplicated cases through National Health Management Information Systems has improved to the point where trends over time for both *Plasmodium falciparum* and *Plasmodium vivax* can now be assessed directly. These data are collated by the WHO Global Malaria Programme on a yearly basis. However, in many high burden countries within Africa, the data are insufficient to make reliable estimates of time-trends (11). In such settings, an alternative is to assess trends in parasite prevalence or trends in estimates of cases of malaria derived from prevalence surveys. The Malaria Atlas Project (MAP) systematically compiles the results of parasitological surveys, including the Malaria Indicator Surveys (MIS), in highly endemic countries in Africa and will use these surveys to produce estimates of *P. falciparum* cases over time (12). Databases on intervention coverage are also available from Demographic and Health Surveys (DHS) (13), Multiple Indicator Cluster Surveys (MICS) (14), and reporting from National Health Management Information Systems. However, the frequency and detail in these datasets vary by country and there are fewer such surveys outside Africa.

Current methods for estimating Global Fund impact related to malaria

The Global Fund estimates of the impact of its malaria funding are currently based on the number of insecticide-treated nets (ITNs) and long-lasting insecticide-treated nets (LLIN) that have been distributed. Assumptions are made about the proportion of children that use nets and the lifespan of treated nets. The lives saved per child protected per year are based on under-5 mortality reported in a Cochrane review of randomised controlled trials of ITNs (15) adjusted for the overall decline in all cause under-5 mortality between 1990 and 2010 in sub-Saharan Africa.

Recommendations

Short term (2014):

- *Use LiST to measure deaths averted and incorporate dynamic models for country use*
  In the short-term revise the current method (service-based multiplier) to WHO estimate of burden against 2000 counterfactual for assessment of impact of the past investment. And use the *LiST* model to estimate cases and deaths averted for forward projection of impact.

- Report estimates of uncertainty
  In countries in which cases and deaths are estimated there is associated uncertainty. The empirical methods for estimation of impact report associated uncertainty which should be propagated through to the estimates reported.

- Use the malaria burden in the year 2000 as counter-factual against which to judge the impact of control. At that time there was little vector control in most high burden countries in Africa and there was growing resistance to the first-line drugs used to treat uncomplicated malaria. In-patient care for severe disease treatment with quinine was effective when delivered appropriately. There have been new developments in in-patient care although their uptake is less well established. Malaria programmes outside Africa did not benefit from the substantial additional resources made available to The Global Fund until after 2004.

Long term (2015-2016):

- *Use the outputs of WHO's malaria burden estimation methods to estimate cases and deaths averted*

  Over time the *LiST* model will be replaced/strengthened by incorporating the findings of dynamic models to measure lives saved/deaths averted as well as program planning (e.g. linking cost to impact for resource optimization) at country level in priority countries, where it can be implemented as part of the *Spectrum*/*OneHealth* suite of programmes. WHO will take lead and work with technical partners with support from donor agencies to implement it (late 2015). For countries where application of dynamic models is not feasible, WHO method for estimation of lives saved and infection averted will be applied. This method is based on WHO estimates of cases and deaths published in the World Malaria Reports (11) for each year between 2000 and latest year (e.g. 2013) applying a counterfactual estimates of cases and deaths in year 2000 adjusting for population growth. Using this approach it is not currently possible to isolate the effect of interventions as opposed to environmental or other changes. However, a process is in place to improve the methodology in which the effects of interventions are explicitly estimated.

- *The malaria burden in the year 2000 represents an appropriate counter-factual against which to judge the impact of control*

  At that time there was little vector control in most high burden countries in Africa and there was growing resistance to the first-line drugs used to treat uncomplicated malaria. Malaria programmes outside Africa did not benefit from the substantial additional resources made available by The Global Fund until after 2004. Counterfactual estimates of cases and deaths averted over time can be made using WHO burden estimates adjusting for population growth. Using this approach it is not currently possible to isolate the effect of interventions as opposed to environmental or other changes. However, a process is in place to improve the methodology in which the effects of interventions are explicitly estimated.

  - *Limitations of this approach for estimating deaths averted are:*

    Estimates of malaria specific mortality rates depend mainly on verbal autopsies which are known to be unreliable for malaria in endemic areas. Some of the changes in the burden of malaria since 2000 are likely to be the result of environmental changes, development, urbanisation and changes in rural housing. Further research is needed to allow modification of the counter-factual by estimating the underlying trend in the absence of interventions.

  - *Limitations of this approach for estimating cases averted are:*

    The changing burden of disease episodes does not necessarily reflect underlying changes in infection as many infections are asymptomatic and the same infection may lead to recurrent bouts of disease. An alternative would be to report changes in parasite prevalence but this is not currently recommended as the frequency of prevalence surveys varies and there is substantial spatial heterogeneity in prevalence within countries. There is no standardised definition of a malaria case and hence the incidence of malaria may vary substantially depending on the definition employed by countries.

- *Support the use of dynamic models for country evaluation planning*

  Models are required to estimate the contribution of individual components of a programme to overall impact. These should be encouraged in high priority countries as part of the wider planning, monitoring and evaluation of malaria control programmes. At present *LiST (16)* is used at country level. In the short-term (up to 2015) this will continue to be used to estimate the impact of the contributions of different malaria interventions (ITS, IRS, IPTp) to reductions in malaria. However, it has several limitations, many of which can be addressed by the use of dynamic models that capture variation in transmission intensity and vector behaviours, as well as the indirect impact of interventions on onward transmission.

  Dynamic models have now been used in several settings. Country workshops have been run by WHO-GMP using *MalariaTools* in two key countries in each WHO region, while *OpenMalaria* is being used in others. Further investment will be needed to make these models more accessible and to develop similar tools that include costs, which are needed for planning budgets. The *OneHealth* model (17) for planning country programmes using *LiST* is being adapted to incorporate the results of dynamic models. With modest support from The Global Fund, dynamic models could be integrated into *OneHealth* and used to project the impact of interventions in high priority countries. Consideration could also be given to developing a malaria specific tool, similar to *Spectrum* for HIV. The Global Fund should liaise with WHO's Surveillance, Monitoring and Evaluation Technical Expert Group (SME TEG), along the lines of the UNAIDS modelling reference group, to consider how these models can be developed and integrated into an appropriate tool for country level planning in 2015–2016. Country consultations should be planned alongside this to guide the development of the tool. From 2016 onwards country-level training will need to be planned so that the tools are effectively utilised.

Cross-cutting

- *Improve country data collection and analytical capacity through Global Fund grants M&E investments and special initiave on data quality improvement*

  The Global Fund should encourage countries to include M&E and data quality strenghtning activities in their new or existing Global Fund grants and to seek technical assistance as needed. Existing Global Fund special initiatives to support improved data systems, quality and use should be maintained.

  Clear mapping of the available data and technical capacity in priority countries will be needed to ensure that countries are able to run the models, mobilise resources and develop partnerships with other major funders and common investment plans.

  - *HIV:* Regular surveillance and program monitoring data are limited in many countries and demonstrate important gaps in geographic coverage, reliable sizes of key populations, the number of people reached by interventions and the impact of prevention programmes on behaviour change, incidence and prevalence. Many countries lack the technical capacity and the necessary analytical skills which makes their data analysis weak, their models difficult to implement locally and leads to under-utilisation of the data that are collected. There is an urgent, long-term need to develop analytic capacity in countries, and to recruit and train regional experts.
  - *TB:* Specific recommendations from WHO to assist in strengthening routine surveillance include: i) promote the systematic application of the WHO standards and benchmarks to evaluate the performance of TB surveillance, to identify performance gaps and address them through a costed plan; (ii) conduct systematic epidemiological reviews to inform national strategic plans and concept notes, based on standard terms of reference; (iii) support prevalence surveys in priority countries, particularly in those planning a repeat survey; and (iv) support the implementation of national vital registration systems, or sample vital registration systems as an interim measure.

  - *Malaria:* Support better malaria surveillance to improve the estimation of impact. Empirical estimates of impact provide the most consistent method to monitor the impact of The Global Fund malaria investments. While such estimates have improved through the support of household-based surveys and health information systems, these require continued investment.

- *Apply revised methods to recalibrate and monitor progress towards strategy targets for lives saved and cases/infections averted in The Global Fund 2012–2016 Strategy*

  - *Lives saved*

    Continue to use the Spectrum AIM model for measuring lives saved from ART. Revise the current methods to the methods recommended for short term for TB and malaria (See Part 2 and 3).

  - *Cases/infections averted*

    Continue using the current method for HIV and TB. Replace the current method for malaria with the LiST model. In the current method, the lower bound of target for the total number of cases of incident cases/infections averted between 2012 and 2016 is set by comparing the cumulative number of cases over 2012-2016, if the incidence rate had remained constant at 2010 level compared to the scenario of a linear decline

in incidence rate from 2010 onwards following from the 2005 to 2010 trend. The upper bound of target is calculated by comparing 2010 constant rate with the scenario of declining incidence rate linearly at twice rate of 2005-2010 trend from 2014 to 2016.

- *where timing and resources allow, streamline modelling of impact with the Secretariat work on measuring and monitoring efficiency and improving allocative efficiency (KPI4).*
  Expand the scope of the use of models in order to assess the impact in priority countries, to include cost and cost-effectiveness analysis, to inform resource allocation/optimisation and to maximise impact and inform NSPs.

- *Maintain an advisory group of technical experts*
  The expert advisory group for The Global Fund should be maintained but may need additional support from those with particular expertise in certain areas. Additional experts could be asked to review the models that are currently being used, and those that are under development and to make recommendations for improving the model structure, implementation, uncertainty and sensitivity analyses, and the choice of appropriate counter-factuals. Since models are only as good as the data that drives them, this expert group should be asked to examine the data that are currently available and being used, and to give advice to countries on how to strengthen their monitoring and evaluation processes—epidemiological, economic and social. They could also explore alternative measures of impact and make technical recommendations on the best measures to be used in future.

Measuring Global Fund attribution

The current Global Fund methods for estimation of lives saved are service-based and use the number of HIV-positive people on ART, the number of TB patients on DOTS, and the number of children sleeping under LLINs, to estimate the number of lives saved through support from The Global Fund. The number of services attributed to The Global Fund is estimated by applying a set of criteria to the national results including the financial contribution of The Global Fund (in absolute and/or percentage terms), whether The Global Fund is supporting essential elements of the various progammes such as drug provision and laboratory testing on a national scale and performance of the grant and data quality.

The expert group discussed the current Global Fund method for measuring its contribution without reaching a consensus. One suggestion was to assume that the impact attributed to Global Fund-supported programmes should be calculated in proportion to its share of the total funding, but a number of limitations were identified with this approach. For example, for malaria, outstanding limitations to this approach are: the strong interactions of malaria with pneumonia, diarrhoea, and malnutrition mean that malaria programmes have major impacts on, and are impacted by, the incidence of diseases that are outside the scope of the Fund and this is not captured in this method; and estimating the denominator of funding for malaria control in each country is complex as the funding for commodities alone does not capture the wider health sector support that is central to effective malaria control.

Due to the limitations of the current method for measuring Global Fund contribution or attribution, The Global Fund has set up a process with key stakeholders to review and improve the current method for estimating the contribution/attribution of its impact.

Expanding impact measurement metrics

- *HIV:*

  Continue to measure impact as infections averted and lives saved but include the effects of interventions other than ART on these measures. The current Spectrum/AIM estimates provide measures of the impact of ART for adults and children, as well as infections averted, due to PMTCT. However AIM does not estimate infections averted due to other interventions supported by The Global Fund. In the longer term estimates should be made of the combined impacts of all HIV interventions supported by The Global Fund as well as other impact measures—Quality or Disability Adjusted Life Years (QALYs or DALYs), or children not orphaned, could be considered in the future. While decision makers may find the interpretation of these measures to be less clear than 'lives saved' or 'deaths averted' they can be calculated easily; Spectrum currently estimates the number of QALYs saved while AEM estimates the number of DALYs saved. Lives saved, infections averted or deaths averted should be restricted to the duration of The Global Fund grant. Predicting future deaths and years of life is highly uncertain and should not be part of measuring the impact of The Global Fund. Impact could also be measured in terms of the number of children orphaned under different scenarios.

- TB:

  In the long-term, estimates should include the additional impact on lives saved due to the impact of TB control on transmission, the additional downstream impact of lives saved through the provision of ART to people infected with TB, and additional measures such as *M. tuberculosis* infections averted. This cannot be done in 2014 as there is a need to collect and ensure the quality of the data, assess the validity of more complex country mechanistic models, obtain country buy-in and come to a consensus on the best counter-factuals and metrics to use in measuring these impacts within and across diseases.

- Malaria:

  Using 'lives saved' as a measure of impact is problematical because the same children may receive treatment for multiple life-threatening episodes in a short period of time. For malaria this is of less concern—provided the estimate is based on deaths averted. However, in future it will be necessary to consider whether or not to include indirect mortality which may be averted by preventing malaria infection, because malaria has strong synergistic interactions with malnutrition and other paediatric infectious diseases whose treatment may reduce the likelihood of malaria infection and death. Malaria is mainly an acute paediatric disease although, as transmission declines, the proportion of cases in older age groups is increasing. For malaria, disability-adjusted life-years (DALYs) saved are roughly proportional to net life-years saved/malaria deaths averted due to acute nature of disease and the affected age group (mainly in children). Therefore, the choice of metric between these measures to capture impact is less critical than it is for chronic diseases in older people.

Annexes – technical details

Annex 1 – **HIV**

A1.1 Technical details of HIV models

Spectrum (6) is a suite of modules that allows one to determine the impact of different interventions. The *AIDS Impact module* (*AIM*) within *Spectrum* is used to estimate the demographic impact of HIV, including the impact of PMTCT and ART on new infections and AIDS-related deaths. The software projects the HIV epidemic from 1970 until a year defined by the user. Within the module there are separate calculations to estimate the impact on adults and the impact on children.

HIV infections averted among children

Current estimates for infections averted in children are based on the *AIM* module in *Spectrum ((6)*, (18)). The effectiveness of antiretroviral drugs depends on the drug regimen and the $CD4^+$ cell count of the mother. Table 1 shows the probability of transmission by regimen and $CD4^+$ cell count and for the perinatal and breast-feeding period. For the perinatal period the transmission probability is expressed as a rate per pregnancy. For the breastfeeding period the probability is expressed as a rate per month of breastfeeding (19, 20) with the mean duration provided by the country supported by data from Demographic and Health Surveys. Countries enter into the model the number of pregnant women receiving each type of ARV regimen and the number of women, or infants, receiving prophylactic drugs while breastfeeding. Women on lifelong antiretroviral therapy are assumed to remain on therapy for the entire breastfeeding period. Countries can report on whether women stop taking antiretroviral therapy but few have the necessary data. A default value, based on data from Malawi, assumes that women stop taking therapy at a rate of 2.2%/month. The number of infections averted by PMTCT is estimated in the *Spectrum*/*AIM* module (5). Countries update the files annually and submit them to UNAIDS for review and compilation (7).

Table 1. Peripartum and breastfeeding transmission probabilities.

	Perinatal (%)	Breastfeeding (%/month)	
		<350/μL	≥ 350/μL
No prophylaxis			
CD4: 200/μL	37	1.57	•
CD4 200–350/μL	27	1.57	•
CD4 ≥ 350/μL	15		0.51
Incident infections	30	28.0	28
Single dose NVP	12	1.57	0.51
Dual ARV regimen at 26wks	4	1.57	0.51
Option A	2	•	0.2
Option B	2	•	0.2
ART before current pregnancy	0.5	0.16	0.16
ART during current pregnancy	2	0.2	0.2

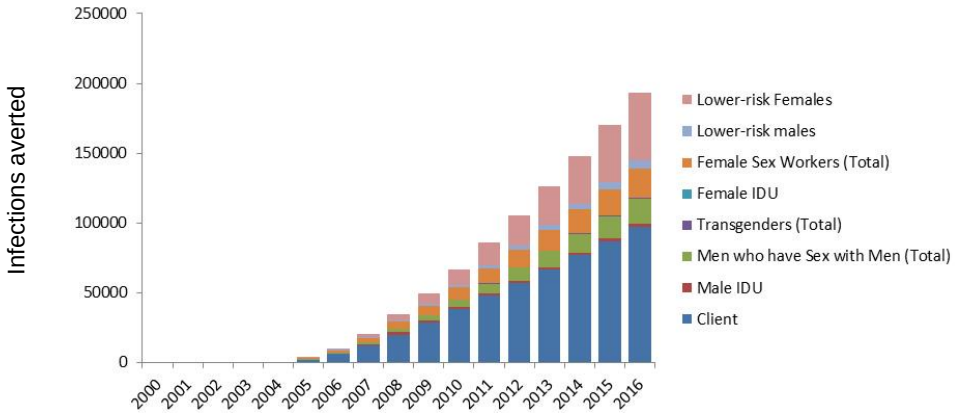

Figure 1. HIV infections averted in Indonesia. Non-Papua baseline scenario. Estimated annual infections averted in different populations since the start of Global Fund support in 2004, based on the national AIDS Epidemic Model (preliminary results).

HIV infections averted among adults

Services not included in the current estimates of HIV infections averted and lives saved can have a large impact. For example, Figure 1 shows preliminary estimates of infections averted in Indonesia, excluding Papua, since the start of Global Fund support, using *AEM*. The Global Fund does not claim credit for all of the impact because the national programme and other major donor programmes were also being scaled-up, simultaneously.

Estimating the number of infections averted and lives saved by other programmes of interest—including HCT, KPP, and VMMC—is challenging for several reasons. The quality and availability of service data varies among countries, with The Global Fund typically supporting a small part of the service delivery in each country.

The effectiveness is variable and poorly characterised. The impact of HCT and KPP varies among populations and places depending on the HIV-associated risk at the time. The impact of ART, PMTCT and VMMC on transmission is better understood but measurement and reporting of effectiveness of other programmes has been weak.

Estimating the impact of prevention programmes requires dynamic models that incorporate the various routes of HIV transmission. This demands data on the frequencies of sexual and injecting risk, the extent of protective behaviour and the size of key populations.

Given good data on the prevention programmes and their effectiveness under trial and field conditions, and a dynamic model that can estimate their impact, it would be possible to explore in detail the impact of the various interventions, independently and in combination, as illustrated schematically in Figure 2.

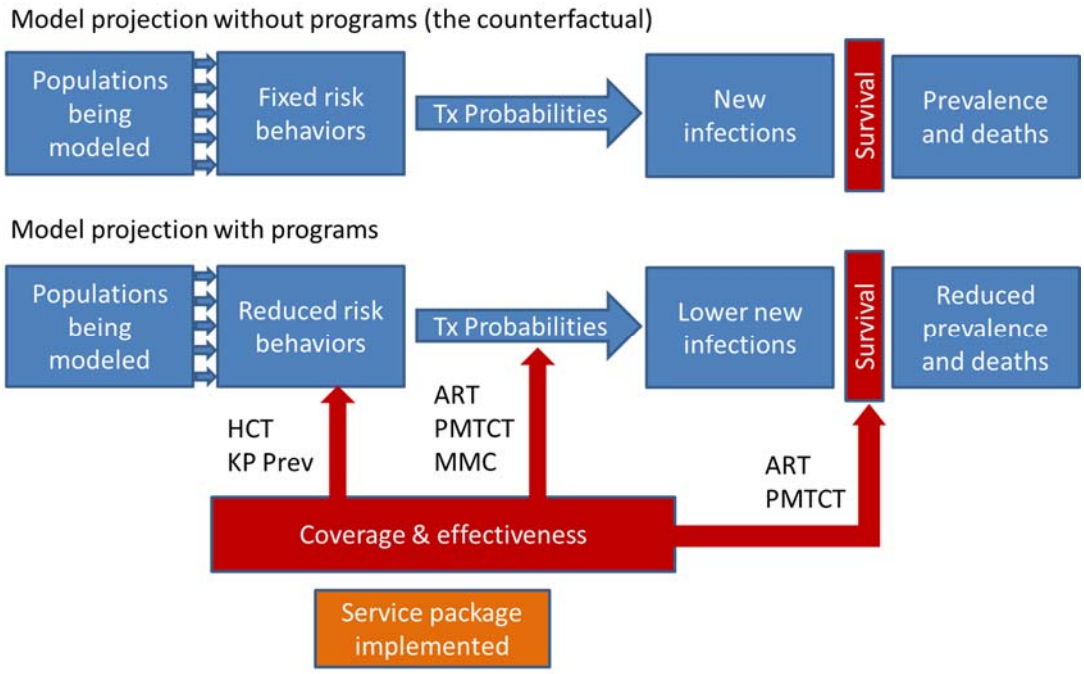

Figure 2. Schematic diagram of the process of estimating service impacts with programme effectiveness defined in terms of behaviour change and transmission reductions.

In the absence of interventions one would fix the risk behaviour for various populations and apply the appropriate transmission probabilities and cofactors to estimate the number of new infections, prevalence and deaths. When the interventions are introduced this will alter risk behaviour, transmission probabilities and survival. Estimating the magnitude of these effects on behaviour and transmission depends on data on programme effectiveness and the coverage achieved for each service. Furthermore, there are many other interventions that may influence people's behaviour, such as Or social marketing, education and information programmes relating to condoms, or which may directly affect transmission, such as the treatment of other sexually transmitted infections, that need to be considered. However, given the limited quality of currently available data on coverage and effectiveness of programmes other than ART and PMTCT, it would be difficult to produce historical estimates of the effects of different interventions by this method.

A1.2 Counter-factuals

A simplified approach to estimate program impact could be as follows: Model the counter-factual by fixing risk behaviour and hence the force of infection at the time when the services of interest are first implemented. Model the actual situation based on the observed historical trends in behaviours, which include the impacts of service provision over time.The difference in outcomes then gives estimates of the impact.

The counter-factual model assumes that behaviour, and therefore the force of infection, is unchanged while the contrasting model is not dependent upon programme effectiveness and coverage estimates because it primarily uses observed epidemiological and behavioural trends over the period of interest. It is important to remember that observed behavioural trends are influenced by the combination of all programmes in place in the country, so it includes the impact of those programmes relative to the

counter-factual. If the future impacts of alternative service packages are to be estimated for planning purposes or 'Concept Note' estimates, this will depend on projections as shown in the lower part of Figure 2, implemented through an in-country process.

A1.3 Updating and Refining Goals and AEM Models

To estimate the total number of infections averted and lives saved requires a model that captures the relationship between changes in behaviour and their impacts on transmission. The *Goals* model, and the *AIDS Epidemic Model* (*AEM*) both have this capacity. Both models have been used in multiple countries. *AEM* has been used primarily in countries with concentrated epidemics. *AEM* will be linked to *Spectrum* in the next six months. In both cases country staff collect and analyse the data needed for the models, prepare and check the inputs and the model structures. Technical advisors work with local experts and stakeholders, and use the results to prepare policy analyses to guide programme choices. Preliminary applications of *Goals* and *AEM* have been made in all The Global Fund's high impact or focus countries (Table 2) but the existing data files should be updated in collaboration with country staff to ensure country buy-in.

Because the data inputs are more demanding and the fitting process is more complex in *Goals* and *AEM* than in *AIM*, a substantial amount of work will be needed to collate and prepare the full range of data inputs, fit them to existing epidemiological patterns, and validate them to ensure they capture the essential features of the national epidemic. The success of this approach will be dependent on having good surveillance data for the epidemiologically important groups in each country and good data on the cost and coverage of treatment and prevention interventions, as well as on behaviours that affect transmission and health outcomes.

The current UNAIDS estimates of lives saved have used *Spectrum/AIM* for the modelling with training provided to local staff supported by UNAIDS. If models to project future trends and estimate impact are to be made, country involvement, training and buy-in will be needed. Local staff should assemble, collate and review the data for validity and participate actively in model development; and national and international experts should vet the country-specific models before using them to estimate impact. A parallel goal should be to develop local capacity and reduce the need for external technical support.

Preliminary *Goals* and *AEM* models have been developed for the countries in Table 2 but not all of them are the result of a comprehensive country consultation. In some countries, including Indonesia, Myanmar and Thailand, *AEM* is already used to prepare the national HIV estimates. The development of *Goals* or *AEM* files for the 26 Global Fund HIV-priority countries will be completed over the period 2015 to 2016, during workshops focussed on models to assess impact, using the most recent data in each country. The set of three one-week workshops will be spaced out over several months, including a final workshop to get buy-in from stakeholders in the country.

Previous workshops for *AEM* have been conducted as a series of three one-week workshops. This approach might serve as a model for this work in each country:

Workshop 1: Focus on data needs and inputs, possible sources, and trend analyses. Followed by 2 to 3 months of in-country work to collate the available information from multiple sources, review it for quality, and prepare estimates of key behavioural and epidemiological trends over time, for input to the model.

Workshop 2: Review trends in the data, build preliminary models and validate them against other sources of data. Identify areas where inputs are weak and more data are needed. Finalise the preliminary models once this additional information is available and review these models with an in-country Technical Working Group of HIV experts and key stakeholders. This group will review the

inputs, outputs and findings to ensure they are consistent with an informed understanding of the local epidemic.

Workshop 3: Finalise the models after technical review, taking into account any recommended changes, extract key programmatic recommendations, and prepare programme scenarios exploring alternative responses. At this point a consensus should also be reached on estimates of infections averted and lives saved, made from the models developed. This concludes with dissemination of the model and may lead to further follow-on work on scenario development to inform investment cases or concept notes.

The exact process to be used and funding sources for the technical support and meeting costs must be negotiated between countries, The Global Fund, UNAIDS and other technical partners. The cost of each set of workshops will be approximately US$25,000 to US$30,000 giving a total cost for 26 countries of US$676 000 to US$780 000. It is critical to provide countries with the time, resources and technical support they need to carry out this process.

Table 2. Application of Goals and AEM by Global Fund priority countries

Countries	*Goals*	*AEM*		*Goals*	*AEM*
High Impact Asia			South Africa	●	
Bangladesh		●	Sudan		●
Cambodia		●	High Impact Africa II		
India		●	Ethiopia	●	
Indonesia		●	Kenya	●	
Myanmar		●	Mozambique	●	
Pakistan		●	Tanzania	●	
Philippines		●	Uganda	●	
Thailand		●	Zambia	●	
Vietnam		●	Zimbabwe	●	
High Impact Africa I			TERG Focus		
Cote d'Ivoire	●		Haiti		●
DRC	●		Malawi	●	
Ghana	●		Rwanda		●
Nigeria	●		Ukraine	●	●

Validated, peer-reviewed models for estimating the number of infections averted and lives saved in each country will depend on the development of local capacity. Countries will then be able to make better use of the data that they already have, identify gaps and develop plans to fill gaps in their data. This will enable national staff to plan their response more strategically and prepare investment cases that will maximise the returns on their investments.

This country process will require technical support and training. UNAIDS and the Futures Institute are training a cadre of consultants who will be able to run workshops on *Goals* and provide on-going support to countries in sub-Saharan Africa. UNAIDS and the East-West Centre in Asia are providing training in that region. The Philippines, Indonesia, Thailand and Myanmar have country teams that are already using these models, with external technical support, to develop investment cases and concept notes.

A1.4 Estimating uncertainty for HIV

The *AIM* and the *Goals* modules in *Spectrum* provide uncertainty estimates for all output data and these should be included when reporting the updated 2012–2016 results for lives saved and infections averted by ART and PMTCT. The *Goals* model provides uncertainties in past estimates by varying key parameters while constraining the model to fit the historical trends; it also provides uncertainties in future projections by allowing the efficacy of interventions to vary while keeping the coverage fixed as specified by the user. The East-West Centre is currently extending *AEM* using Bayesian techniques that will provide estimates of uncertainty in future projections. The UNAIDS Reference Group on Estimates, Modelling and Projections (www.epidem.org) should continue to provide advice on how best to determine uncertainties in the estimates. The UNAIDS Reference Group will consult Global Fund counterparts and its technical advisors in discussions on this issue.

A1.5 Responses to the critisims (10) of the current methods

Critics	Responses
They do not allow for variations in survival on ART within regions	2012 the Spectrum-AIM provides eight regional patterns for survival on ART based on the data from the International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium which tracks large numbers of patients in many regions. Further disaggregation of these data into intra-regional patterns was not seen to be useful by the UNAIDS reference groups given the uncertainty in these data. IeDEA estimates of mortality include the mortality of persons lost to follow-up. While some IeDEA sites might have better than average service delivery, the data from IeDEA represent the best currently available data for survival on ART. Users have the option to enter a custom survival pattern if the data are available.
Survival assumptions are optimistic given the varying quality of service delivery programmes	
There is double-counting of those who receive both ART and TB treatment, which leads to overestimates of the impact of Global Fund support	New method provides separate lives-saved in HIV-negative and HIV-positive TB patients. From now on, all lives saved in HIV-positive TB patients will be counted under HIV only.
The downstream impact of ART on transmission and hence future infections averted and lives saved, is not included, which leads to underestimates of the impact of Global Fund support	The impact of ART on transmission and the impact of other prevention methods will be measured by applying Goals and AEM models in priority countries over 2015–2016 In order to significantly improve current estimates of epidemic trends and the impact of interventions the immediate need is to provide support to enable countries to improve the quality of their routine surveillance and programme monitoring data
The impact of other HIV services supported by The Global Fund is not currently included in the models	

Annex 2 – TB

A2.1 Details of TB Impact Model and Estimates (TIME)

TIME is a new country-level and user-friendly tool for TB-HIV estimates and impact projections embedded in Spectrum and developed by TB Modelling and Analysis Consortium (tb-mac) in collaboration with technical partners (WHO Global TB Program, UNAIDS, Stop TB Partnership). TIME has four modules with the following functionalities (Figure 3):

1 Data review, quality assessment and certification (To be built in 2015)
2 Estimation of current burden and past trends (as WHO methods, to extend in 2015)
3 Projection and epidemiological impact (v1 in Beta, for public release in 2015)
4 Resource needs and cost effectiveness (OneHealth, v1 in Beta, for public release in 2015)

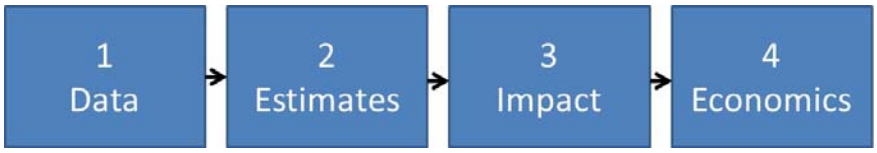

Figure 3. Schematic diagram of *TIME*-Data, *TIME*-Estimates, *TIME*-Impact, and *TIME*-Economics modules

A schematic diagram of the *TIME*-Impact Transmission Model is shown in Figure 4.

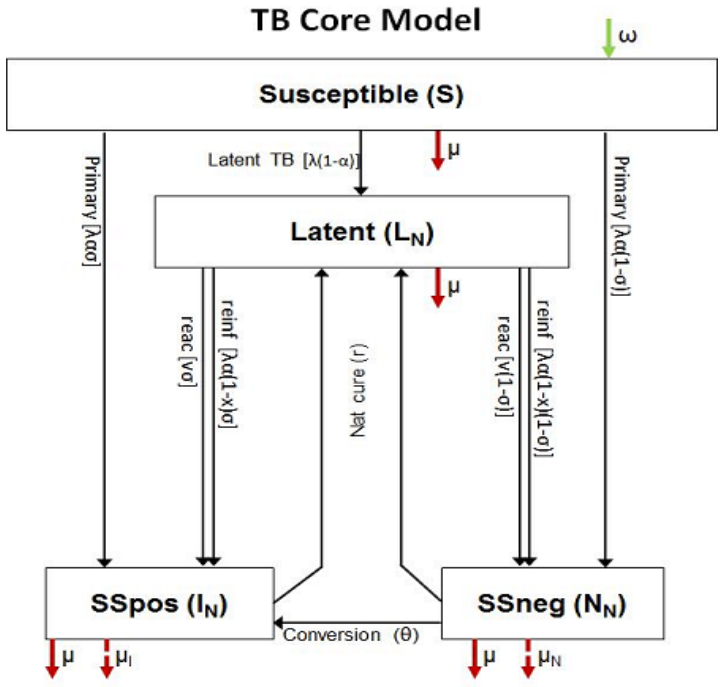

Figure 4. Schematic diagram of the *TIME*-Impact Transmission Model. *TIME* is stratified by DS/DR, HIV/ART status, and age. Black arrows represent transitions between TB states, green arrows represent births, red solid arrows represent background deaths, red dashed represent TB deaths. Adapted from (21)

A2.2 New method proposed for short-term for estimating the impact on lives saved

There was consensus at the meeting in Geneva that lives saved by TB treatment, of all forms of TB, should continue to be the main indicator of the impact on TB in the short-term. The approach is simple and easily understood. It was agreed that the method should be modified to address the criticisms raised by McCoy *et al.* (10) and that the estimates should include uncertainty ranges.

Each year, the World Health Organisation (WHO) publishes estimates of TB incidence and mortality disaggregated by HIV status, in collaboration with the Futures Institute and the TB Modelling and Analysis Consortium (22). Estimates are available for 219 countries over the period 1990–2012. Those estimates of TB mortality should be compared to a counter-factual of no TB treatment (and no ART in the case of HIV-positive TB cases). To calculate the counter-factual mortality under no treatment, the number of incident cases is multiplied with the relevant case fatality ratio (CFR) as summarised in Tables 3 to 5.

Table 3. Summary of case fatality ratios (CFRs) in the absence of treatment. Adopt from (23)

TB cases	CFR (range)	Source
HIV negative not on TB treatment	0.43 (0.28–0.53)	(9) (24, 25)
HIV positive not on ART, not on TB treatment	0.78 (0.65–0.94)	(26)

Table 4. Case fatality ratios (CFRs) in the absence of treatment in HIV negative, not on TB treatment individuals

Point estimate	Smear positive: 70%, Smear negative: 20% agreement between (26) and (9) No confidence interval given in Tiemersma *et al.* (9) Proportion smear positive: 45% (26) Value = (0.7×0.45)+(0.2×0.55) = 0.43
Lower bound	Lower bound of estimate of CFR: smear positive: 55%, smear negative 10% (26) Lower bound of estimated proportion smear positive: 40% (26) Value = (0.55×0.4)+(0.1×0.6) = 0.28
Upper bound	Upper bound of estimate of CFR: smear positive: 75%, smear negative 30% (26) Upper bound of estimated proportion smear positive: 50% (26) Value = (0.75×0.5)+(0.3×0.5) = 0.53
Notes	Assumed a Beta-distribution with shape and scale parameters obtained using the method of moments.

Table 5. Case fatality ratios (CFRs) in the absence of treatment in HIV Positive, not on ART, not on TB treatment individuals

Point estimate	CFR in smear positive: 81%, Smear negative: 76% (26) Proportion smear positive: 35% (26) Value = (0.81×0.35)+(0.76×0.65) = 0.78
Lower bound	Lower bound of estimate of CFR: smear positive: 70%, smear negative 63% (26) Lower bound of estimated proportion smear positive: 30% (26) Value = (0.70×0.3)+(0.63×0.7) = 0.65
Upper bound	Upper bound of estimate of CFR: smear positive: 99%, smear negative 90% (26) Upper bound of estimated proportion smear positive: 40% (26) Value = (0.99×0.4)+(0.9×0.6) = 0.94
Notes	Assumed a uniform distribution

Estimates will be made for TB cases, with and without HIV, for each country and each year. The HIV-positive case fatality ratios (CFR) in Table 3 will be applied to all HIV-positive cases whether or not they are on ART. Lives saved will be estimated as the difference between the counter-factual mortality and the mortality estimated by the WHO (22) (25). Uncertainty in the CFRs and TB disease incidence will be used to calculate the uncertainty in the estimates of lives saved. Country estimates will be aggregated and accumulated over periods of interest to The Global Fund.

This short-term modification will give estimates of lives saved that are sensitive to differences in the performance of the national TB control programme and the burden of HIV-positive and drug resistant TB. It will be assumed that the CFR of untreated drug-resistant TB is the same as for untreated drug-susceptible TB. The method also separates lives-saved among HIV-negative and HIV-positive people to avoid double-counting by assuming that all lives saved in HIV-positive TB-patients are already accounted for by UNAIDS.

The proposed method does not include the impact of TB control or ART on TB disease incidence, or the downstream impact of TB treatment or other services on reducing transmission and therefore on future *M. tuberculosis* infections, TB disease cases and deaths.

In the short-term (2014) The Global Fund should continue to use lives saved by TB treatment as the primary TB impact indicator modified to address the main criticisms. The new method will adjust for differences in the performance of national TB control programme and, the burden of HIV-positive and drug resistant TB as reflected in WHO estimates of TB mortality. Uncertainty estimates will be included. The additional impact on lives saved as a result of wider Global Fund investments, downstream effects, and additional metrics such as *M. tuberculosis* infections averted, will not be included in the short-term (2014).

A2.3 Alternative methods/measures to the proposed method for capturing the impact of lives saved

Capturing the additional impact of lives saved due to the impact of other Global Fund activities on the incidence of TB disease could be achieved by assuming an alternative to the 'no-treatment' counter-factual. The alternative could be to assume that TB disease incidence remains the same as the baseline year. While this is simple it would, like the previous counter-factual, attribute any decline in the incidence of TB disease to health services efforts, and not to wider secular trends such as improved socio-economic status.

Capturing the indirect, downstream impact of lives saved by TB/HIV care could be achieved by using a dynamic transmission model such as the *TIME* TB model which is implemented in the Futures/Spectrum Suite of software (6). The core model structure is illustrated in Figure 3 and Figure 4. The additional impact may be small and would depend on the time horizon. Using a dynamic transmission model may not be possible in all countries but it could be implemented in The Global Fund high impact countries, and the results obtained could be applied to countries with a similar epidemic profile.

The Global Fund and its partners should explore the feasibility of using an alternative TB disease incidence counter-factual, to estimate the additional impact of lives saved due to impact on the incidence of disease of The Global Fund activities other than the treatment of TB cases. The Global Fund and partners should evaluate the feasibility of capturing the additional indirect/downstream impact of lives saved by TB/HIV care, using a dynamic transmission model such as *TIME* for The Global Fund high impact countries, and using the results to derive similar epidemic profiles. This could be coordinated by The Global Fund early in 2015.

A2.4 Advantages and disadvantages of the existing Global Fund method for capturing the impact on TB disease cases/M. tuberculosis infections averted, and alternatives

Summary of advantages and disadvantages

The current method used by The Global Fund includes the impact of Global Fund investments only on cases of TB disease, not on infections with *M. tuberculosis* averted. Assuming a fixed incidence after a specific year, currently taken as 2010, for the counter-factual captures the direct and indirect impact of TB and HIV treatment and other healthcare services in TB disease cases averted. However, it also includes the impact of secular trends that should not be attributed to health services efforts but which are difficult to remove. The method also does not capture the impact of *M. tuberculosis* infections averted, which could be quite large, and should fall roughly as quickly as the prevalence of TB disease, assuming a fixed number of new infections for each prevalent case. For example, assuming 70–90 million new *M. tuberculosis* infections per year, if TB disease prevalence could be reduced by 25% over 5 years, then the cumulative *M. tuberculosis* infection incidence would be expected to fall by 43–56 million infections (assuming that the number of infections per disease case is unchanged, a linear decline in TB disease prevalence and a flat TB disease incidence counter-factual). For the 2017–2022 targets, The Global Fund should consider revising the current methods to capture the impact on *M. tuberculosis* infections averted.

Alternative methods and measures to estimate TB disease cases and M. tuberculosis infections averted

In order to estimate the impact of control on the incidence of infection one could assume that for each untreated, prevalent case there are, say, five new infections; but recent work has shown that the size of this number is not well known and is likely to vary among countries (27) and over time. An alternative approach would be to use a dynamic transmission model, such as *TIME*, that would explicitly make a similar assumption, but would have the benefit of having to simultaneously fit the model to the estimated burden of TB disease prevalence and TB disease incidence, with appropriate constraints.

The Global Fund should support the evaluation of the feasibility and utility of estimating the impact of control on the incidence of *M. tuberculosis* infections averted, using a transmission model such as *TIME*, in The Global Fund's high impact countries and make comparisons with simpler approaches. This should start with countries with high quality TB surveillance systems generating data with high coverage, complemented with measurements of mortality and/or prevalence.

A2.5 Provisional list of countries and budget

List of Countries

The draft list of countries will be the WHO 22 high TB burden countries (2): Afghanistan, Bangladesh, Brazil, Cambodia, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russia Federation, South Africa, Thailand, Uganda, UR Tanzania, Viet Nam, Zimbabwe. The methods would first be applied to countries with high TB burden and high quality data, such as Brazil and China.

Table 6. Work to be done with estimated costs. Note that current costs cover only the Futures institute. Funds may also be needed to cover WHO and TB MAC time

Categories	Description	Cost USD
Labour		
Model building and analysis	30 days of building and analysis. 8 days of project meetings. 20 days of travel for country workshops. One or two TB modellers.	33,292
Software	15 days for *TIME*-Data, 5 days for GF-scenario generator software, 10 days for *TIME*-Estimates. One programmer.	9,240
Software Management	5 days of software management. One Manager.	4,030
Travel		
Travel for project meetings	1 trip to Geneva for project steering meetings. 1 trip to Geneva pilot workshop. 4 days per trip.	7,320
Country visits	5 trips to facilitate country workshops. 4 days per trip.	78,420
Overhead for direct costs (travel)		
G&A	General and administrative for direct costs	12,861
Total		145,163

Model development and workshops

Time span

1 January 2015–31 March 2016

Purpose

Develop *TIME*-data capture interface, Global Fund-live-saved tools within time, facilitate country workshops

Input

The formulation and final results will be based on recommendations from a reference group.
Data information platform (design using existing validation method) from WHO TB
Specifications for *TIME* interface from TB Mac and Global Fund reference group

Deliverables

TIME-Data—a new data capture and validation interface within *TIME*
A mechanism to communicate country data changes/issues to WHO TB in order for WHO to make database updates

A scenario generator to produce Global Fund estimates of lives-saved
Enhancements to *TIME-Estimates*, using vital registration data to estimate TB mortality
Two project steering meetings, two day meetings and two days travel for each meeting
Five, two-day group country workshops and two days travel for each workshop

A2.6 Responses to the critisims (10) of the current methods

McCoy *et al.* (10) raised following criticisms of the current methods of estimation:

- The assumed TB case fatality rates in untreated patients were unduly pessimistic;
- The case fatality rate is fixed and does not allow for variations among countries or the effect of HIV;
- The choice of 'no-treatment counter-factual' is unduly pessimistic because patients untreated in the formal health sector might seek treatment from other providers;
- There is double counting of lives saved by ART and TB treatment in HIV-infected TB cases;
- The uncertainty in the current measures of impact needs to be provided and documented;
- The focus on impact of TB treatment only, excluding other services, such as infection control.

Responses:

The new (2014) method for estimating lives saved in the short-term improves on the current method which assumes that one life is saved for every three people that are successfully treated for TB, by making the following changes. It will:

- Allow for variation among countries in the performance of the national TB control programmes, the burden of HIV-positive TB, and the burden of drug resistant TB;
- Capture the direct impact of TB and HIV treatment on lives saved, including lives saved from not-notified TB treatments in countries where WHO derives mortality trends from vital or sample registration data;
- Provide and document uncertainty in the estimates;
- Separate lives-saved in HIV-negative from HIV-positive individuals. Attribute all lives saved in HIV-positive individuals to treatment with HIV.

There are, nevertheless, limitations in the proposed method but these will be captured in the methods that will be developed and validated over 2015–2016 for implementation 2017–2022.

The current limitations are:

- It does not change the 'no-treatment' counter-factual. There was little consensus at the Geneva meeting on the most appropriate counter-factual with some meeting attendees preferring to use pre-DOTS outcomes and others 'no treatment'. Those in favour of a 'no treatment' counter-factual argued that poor treatment may be worse than no treatment, by increasing transmission and generating drug resistance. The issue of consistency with other diseases was also raised. Despite the lack of consensus on the counter-factual at the meeting, the proposed method to calculate lives saved in the short-term (recommendation 1) uses a no treatment counter-factual, and the meeting agreed that this measure should be used in 2014.
- It does not capture the additional impact on lives saved of other Global Fund activities that reduce *M. tuberculosis* infection transmission or progression from latent to active disease including infection control, treatment of latent *M. tuberculosis* infection and ART.
- The estimated number of lives saved will be greater in the coming years if the decline in incidence does not accelerate, because then more patients will be put on treatment compared with a scenario where the decline in incidence accelerates.
- It does not capture the additional indirect downstream impact of TB/HIV care on lives saved by reducing the risk of *M. tuberculosis* infection through reducing the number of *M. tuberculosis* infections and therefore averting future TB disease cases.

A2.7 Revised estimates of impact

Provisional estimates of lives saved are given in in Table 7 using a counter-factual of no treatment, so that the number of lives saved is equal to the case-fatality ratio in untreated patients multiplied by the incidence of TB disease minus TB deaths. As expected, the new estimates are greater than the previous estimates. In 2013, we now estimate that 2.85 million lives were saved globally; based on the old method, we would have estimated approximately 2 million lives saved globally. The difference is mostly due to people who were treated but not recorded as such. The new method provides estimates of uncertainty and allows for differences in TB control among countries. However, it can only be applied retrospectively if suitable projections for incidence and mortality are made. Because more lives will be saved if incidence does not decline under the counter-factual, and if more cases are put on treatment over time, it will be important to state clearly the assumptions underlying the estimates.

In the Table 7 and 8, the counter-factual assumes that there was no TB treatment so the number of lives saved is equal to the CFR in untreated patients multiplied by the incidence of TB disease minus TB deaths. Estimates accounting for updates in case reporting over the month of July and for country feedback on country profiles and numbers by country will be available soon.

Table 7. Estimated number of lives saved in millions by TB treatment in the world (2000–2013).

Year	HIV-negative	HIV-positive	Total
2000	1.93 (0.909-2.98)	0.341 (0.174-0.477)	2.27 (1.24-3.34)
2001	1.96 (0.941-3.02)	0.38 (0.199-0.528)	2.34 (1.31-3.41)
2002	1.99 (0.969-3.04)	0.418 (0.224-0.575)	2.41 (1.37-3.48)
2003	2.02 (1.01-3.08)	0.452 (0.249-0.616)	2.48 (1.44-3.55)
2004	2.07 (1.05-3.12)	0.482 (0.273-0.652)	2.55 (1.51-3.62)
2005	2.11 (1.1-3.16)	0.504 (0.292-0.676)	2.62 (1.59-3.68)
2006	2.16 (1.15-3.21)	0.523 (0.311-0.696)	2.69 (1.66-3.75)
2007	2.2 (1.19-3.25)	0.540 (0.33-0.712)	2.74 (1.71-3.8)
2008	2.23 (1.23-3.27)	0.555 (0.347-0.725)	2.78 (1.76-3.84)
2009	2.25 (1.26-3.28)	0.570 (0.362-0.739)	2.82 (1.81-3.87)
2010	2.27 (1.28-3.29)	0.578 (0.372-0.749)	2.85 (1.84-3.89)
2011	2.28 (1.3-3.3)	0.576 (0.374-0.742)	2.86 (1.86-3.89)
2012	2.30 (1.32-3.32)	0.559 (0.364-0.722)	2.86 (1.86-3.9)
2013	2.30 (1.32-3.33)	0.546 (0.354-0.709)	2.85 (1.85-3.89)

Table 8. Cumulative number of lives saved by TB treatment by region (2000–2013).

Region	HIV-negative	HIV-positive	Total
AFR	3.98 (3.16–4.81)	5.10 (4.56–5.63)	9.08 (8.1–10.1)
AMR	1.39 (1.26–1.52)	0.25 (0.23–0.27)	1.64 (1.52–1.77)
EMR	2.56 (2.13–3.00)	0.031 (0.028–0.034)	2.59 (2.16–3.03)
EUR	2.06 (1.84–2.28)	0.137 (0.127–0.147)	2.2 (1.97–2.42)
SEA	11.40 (9.81–13.00)	1.06 (0.951–1.17)	12.5 (10.9–14.1)
WPR	8.75 (7.91–9.60)	0.134 (0.123–0.146)	8.89 (8.05–9.73)
Global	30.10 (26.20–33.90)	7.03 (6.34–7.71)	37.1 (33.2–41)

Annex 3 – Malaria

A3.1 Available models

For predicting future impact, the Lives Saved Tool (*LiST*) is a static model that makes projections of malaria deaths in children under 5 years of age under a range of scenarios for the scale-up of multiple interventions, including ITNs, intermittent preventive therapy in pregnancy (IPTp) and case management. Effect sizes are based on meta-analyses of impact from clinical trials adjusted in proportion to data on coverage. For ITNs, *LiST* uses the same basic information as The Global Fund, but it takes into account variation in malaria mortality rates across different settings (whereas The Global Fund's existing model assumes a fixed reduction in mortality in all settings). *LiST*-based estimates of the contributions of different malaria interventions (ITS, IRS, IPTp) to reductions in malaria mortality for 2002–2008 and 2000–2010 have been published (3, 4). WHO's Global Malaria Programme (GMP) has adapted the *LiST* model to include the effect of ITNs on malaria cases. Validation exercises suggest that *LiST* gives a reasonable estimate of the average effect of ITNs in many settings.

Dynamic models to estimate the impact of interventions for malaria have been developed but have not been widely used by The Global Fund. *OpenMalaria (28)* is designed to simulate the impact of control on transmission as well as on malaria incidence and mortality for a set of currently recommended malaria interventions, and has been used in Global Fund planning workshops in Mozambique and Bangladesh. *Malaria Tools (29)* similarly simulates the impact of multiple interventions on transmission and case incidence. It has been used to plan scenarios for malaria elimination and is currently used by GMP in country planning workshops. A malaria elimination model has been developed for Cambodia and is being used to evaluate the potential for elimination in that region (5). A range of other mathematical models that may inform country programmes in the future are currently under development. Outputs from dynamic models are increasingly being used by a range of stakeholders, including for burden estimation (2), in the evaluation of the potential public health impact (6), cost-effectiveness of new interventions (7) and to inform product development.

A3.2 Responses to the critisims (10) of the current methods

The following criticisms have been made regarding current estimates (10):

- The impact of LLINs is known to vary among settings depending on the intensity of transmission. The risk of infection is lower in places with crepuscular outdoor-biting malaria vectors, or where malaria is predominantly *Plasmodium vivax* rather than *P. falciparum*.
- The assumption of linearity in the relationship between the coverage of LLIN and health impacts is too simplistic: at high levels of use, the health effects of LLINs saturate, while at low transmission levels there are important additional effects which reduce transmission.
- Substantial components of national malaria control programme investments relate to interventions other than LLINs, including case management, intermittent preventive treatment, indoor residual spraying, various test-and-treat strategies, and surveillance-response systems.
- Both curative and preventive malaria interventions induce dynamic effects on transmission and immunity that persist for longer than the time courses of field trials. These effects include age- and time-shifting of morbidity and mortality over longer time-scales than those of field trials.
- As malaria transmission is reduced, the burden of disease shifts to older people and the impact of interventions is no longer restricted to the under-5 age group.

Responses:

- By using empirical estimates of cases and deaths averted, this assumption is no longer implicit and a variation in impact between countries with similar intervention coverage levels, but different vectors, is to be expected.
- By using empirical estimates of cases and deaths averted, this assumption is no longer implicit and the variation in impact between countries and at different stages in the pathway to elimination is to be expected.
- By using empirical estimates of cases and deaths averted, the impact of all interventions is captured. A remaining limitation is that non-intervention trends will be attributed as intervention impact.
- By using empirical estimates of cases and deaths averted, dynamic impacts will be captured.

While deaths averted are likely to remain focused on the under-5 age group, given the relative paucity of data amongst older ages the estimates of cases averted will capture all age-groups and age-stratified indicators can be reported, if the data are sufficiently disaggregated.

Addendum: Experts participated in the meeting or invited for peer review

Report author teams*/core group†:

HIV: Mary Mahy*†, Tim Brown*†, Txema Garcia*†, Timothy Hallett†, Nalinee Sangrujee†
TB: Richard White*†, Philippe Glaziou*†, Martien Borgdorff†, Ibrahim Abubakar†
Malaria: Richard Cibulskis*†, Tom Smith*†, Steven Kern*†, Azra Ghani*†, Bruno Moonen†

Participated* and/or invited for peer review†:

#	Name	Affiliation
1	Abdisalan Mohamed Noor†	RBM MERG
2	Ade Fakoya†	Global Fund
3	Alka Aggarwal Singh†	Global Fund
4	Andrew Kennedy†	Global Fund
5	Annette Reinisch*†	Global Fund
6	Azra Ghani†	Imperial College
7	Bertha Simwaka*†	Global Fund
8	Brian Williams*†	SACEMA
9	Bruno Moonen*†	Bill & Melinda Gates Foundation
10	Carol D'Souza*†	Global Fund
11	Christopher Murray†	IHME
12	Cynthia Mwase*†	Global Fund
13	David McCoy*†	Queen Mary University London
14	David Schellenberg†	SME TEG
15	David Wilson†	World Bank
16	Don de Savigny†	Global Fund TERG
17	Eliud Wandwalo*†	Global Fund
18	Estifanos Shargie*†	Global Fund
19	Frédéric Goyet†	Global Fund
20	Hannah Grant†	Global Fund
21	Ibrahim Abubakar*†	WHO impact reference group
22	Jaap Broekmans†	WHO impact reference group
23	Jason Lane*†	DIFID
24	Jinkou Zhao*†	Global Fund
25	John Stover†	Future Institute
26	Justin Cohen†	Clinton Health Access Initiative
27	Katherine Rockwell*†	RBM/UNSEO
28	Lucica Ditiu†	Stop TB Partnership
29	Maria-Iuliana Danu†	-
30	Mark Dybul†	Global Fund
31	Mark Grabowsky†	RBM/UNSEO
32	Martien Borgdorff*†	CDC
33	Mary Mahy*†	UNAIDS
34	Mehran Hosseini*†	Global Fund
35	Melanie Renshaw*†	RBM/UNSEO
36	Michael Borowitz†	Global Fund

37	Michael Johnson†	Global Fund
38	Misun Choi†	USAID
39	Nalinee Sangrujee*†	PEPFAR
40	Nathalie Zorzi†	Global Fund
41	Neff Walker†	Johns Hopkins School of Public Health
42	Nicolas Bidault*†	Global Fund
43	Nicole Hassoun*†	SUNY Binghamton University
44	Obinna Onyekwena*†	Global Fund
45	Olivier Briet*†	Swiss Tropical Institute
46	Osamu Kunii*†	Global Fund
47	Parijat Baijal†	Global Fund
48	Peter Gething†	Oxford University
49	Philippe Glaziou*†	WHO/TB
50	Richard Cibulskis*†	WHO/malaria
51	Richard White*†	London School of Public Health/TB-MAC
52	Rick Steketee†	PATH
53	Robin Thompson†	UNITAID
54	Ryuichi Komatsu*†	Global Fund
55	Sai Pothapregada*†	Global Fund
56	Sandra Kuzmanovska†	Global Fund
57	Scott Filler*†	Global Fund
58	Silvia Ferazzi†	RBM
59	Steven Kern*†	Bill & Melinda Gates Foundation
60	Suman Jain*†	Global Fund
61	Suvanand Sahu*†	Stop TB Partnership
62	Thomas Eisele†	Tulane University
63	Tim Brown*†	East-West Centre
64	Timothy Hallett*†	Imperial College
65	Tom Smith*†	Swiss Tropical Institute
66	Txema Calleja*†	WHO/HIV
67	Viviana Mangiaterra†	Global Fund
68	Zhang Shufang*†	Global Fund

Project coordinators and quality/consistency checks: Brian Williams, Nicolas Bidault, Johannes Hunger and Mehran Hosseini

Admin/logistic support: Jutta Hornig and Joan Cameron

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