Annex 3
Methodology for impact modeling

The modeling for this Investment Case aims to quantify the *minimum* funding necessary to generate health impacts and epidemiological trajectories over the Global Fund's implementation period 2027-2029 that are consistent with the long-term targets (2030) described in the global plans for HIV, TB and malaria. The required funding is made up of different funding sources, including the Global Fund Replenishment amount, domestic funding, and non-Global Fund international funding to Global Fund-eligible countries.

The modeling groups undertaking these analyses and the models used are those that were responsible for the modeling of the respective disease global plans.[1] The three disease models are population-scale dynamic transmission models, providing country-level projections that are then aggregated to the Global Fund portfolio. The models for HIV/AIDS and malaria have, over several years, been reviewed and developed in collaboration with international modeling consortia. The model for TB is a new release of the well-established TIME model, the development of which has been guided by the TB Modelling and Analysis Consortium (TB MAC) and experts and academics linked to TB MAC, including the Stop TB Partnership. The scope and application of the models is described in Section 1.

The model projections were generated in three steps. First, the disease transmission models are calibrated with the aim to recreate historic trajectories in each country for each disease up to the year of most recent data that is consistent with latest official estimates published by WHO and UNAIDS. The official estimates are informed by epidemiological data, program data and modeling assumptions.[2] Second, the models were used to project impact up to 2026 based on assumptions about the programs' configurations, as set out in the Global Fund Performance Frameworks. Third, the models made projections over the 2027-2029 Replenishment period, based on assumptions around available funding and the level of service coverage that could be achieved with that funding (Section 3).

[1] UNAIDS, "Global AIDS Strategy 2021-2026" (Geneva, 2021), https://www.unaids.org/en/Global-AIDS-Strategy-2021-2026; Stop TB Partnership, "Global Plan to End TB 2023-2030" (Geneva, 2022), https://www.stoptb.org/what-we-do/advocate-endtb/global-plan-end-tb; World Health Organization, "Global Technical Strategy for Malaria 2016-2030, 2021 Update" (Geneva, 2021), https://www.who.int/publications/i/item/9789240031357; See Annex 8 for further details of technical partners and strategies.

[2] See accounts provided in the Global Tuberculosis Report 2024, World Malaria Report 2024, and UNAIDS Global AIDS Update 2024.

Section 1: Description and application of models

HIV: Impact modeling was performed by Avenir Health using the Goals model,[3] which was set up for 95 countries. Costs included in the Global AIDS Strategy estimates, in addition to the direct cost of interventions (including community mobilization, testing, enabling environment and program support), are accounted for by applying a proportional mark-up to the intervention costs, following UNAIDS methods.

TB: Impact modeling was performed by Avenir Health applying a new version of the TIME model. The earlier version of the same model was used in supplementary modeling work for the Global Plan to End TB, 2023-2030 and has since been developed further to fully replicate the main results of the Global Plan to End TB, 2023-2030.[4] The new model was applied in 29 Global Fund-eligible countries with the greatest TB burden. Unit cost estimates for diagnostics, drugs and other supplies were obtained from four sources (Value TB study database, WHO Global TB Program's CHOICE Health service delivery costs, the Global Health Costing Consortium, and the Global Drug Facility product catalogue) following a methodology developed by a Stop TB Partnership-led technical working group convened to inform the resource needs estimates for the TB Global Plan (2022). Program support costs were obtained from expenditure reports that countries submit each year to WHO.

Malaria: Impact modeling was performed using the *malariasimulation* malaria transmission model developed at Imperial College London,[5] which contributed to the development of the WHO Global Technical Strategy for Malaria. It represents 51 Global Fund-eligible countries that have stable Plasmodium falciparum transmission and includes geographic specificity to the first administrative level. Those countries with unstable transmission or that were in prevention of reintroduction stages were not modeled.

For each disease area, therefore, models are produced for a subset of countries in the Global Fund portfolio that account for the vast majority of the burden of disease in

[3] "Modeling the Epidemiological Impact of the UNAIDS 2025 Targets to End AIDS as a Public Health Threat by 2030". John Stover et al. *PLOS Medicine* 18, no. 10 (October 18, 2021): e1003831, doi:10.1371/journal.pmed.1003831.

[4] The main results of the global plan 2023-2030 were developed with the TB Impact Model and Estimates (TIME). The model structure of TIME is detailed in the publication: TIME Impact – a New User-Friendly Tuberculosis (TB) Model to Inform TB Policy Decisions, Hoeben et al, BMC Medicine 2016 14:56. The new global and portfolio-level model, which builds on and aligns with TIME modeling structures, was used in validation work. It was also used in supplementary modeling work, such as modeling vaccine impact, which the current version of TIME cannot do.

[5] Jamie T. Griffin et al., "Potential for Reduction of Burden and Local Elimination of Malaria by Reducing Plasmodium Falciparum Malaria Transmission: A Mathematical Modelling Study," *The Lancet Infectious Diseases* 16, no. 4 (April 1, 2016): 465–72, doi:10.1016/S1473-3099(15)00423-5; Michael T. White et al., "Modelling the Impact of Vector Control Interventions on Anopheles Gambiae Population Dynamics," *Parasites & Vectors* 4, no. 1 (July 28, 2011): 153, doi:10.1186/1756-3305-4-153; Jamie T. Griffin, Neil M. Ferguson, and Azra C. Ghani, "Estimates of the Changing Age-Burden of Plasmodium Falciparum Malaria Disease in Sub-Saharan Africa," *Nature Communications* 5 (2014): 3136, doi:10.1038/ncomms4136; Jamie T. Griffin et al., "Gradual Acquisition of Immunity to Severe Malaria with Increasing Exposure," *Proceedings. Biological Sciences* 282, no. 1801 (February 22, 2015): 20142657, doi:10.1098/rspb.2014.2657; Griffin et al., "Potential for Reduction of Burden and Local Elimination of Malaria by Reducing Plasmodium Falciparum Malaria Transmission."

Global Fund-eligible countries (99% for HIV, 90% for TB, 99% for malaria of the estimated burden of the three diseases).[6] Extrapolations are made to the full portfolio by assuming that the trajectory of the "unmodeled" countries is the same as in "modeled" countries.

Section 2: Projecting impact up to the beginning of the Replenishment period (2024-2026)

The projections for the period from the start of 2024 to the end of 2026 are constructed assuming that country programs over that period fully achieve the targets agreed in the Global Fund Performance Frameworks. The Global Fund Performance Framework contains country-specific indicators and targets the programs need to achieve, which are submitted by grant implementers when applying for Global Fund funding.

In some cases, the Performance Framework does not include national targets for all indicators or all years for a given country. In these cases, targets were taken from a similar modeling exercise, the Global Fund 2021-2028 Strategy impact target setting exercise, which used the same disease transmission models to project programmatic targets that would be consistent with the funding projected to be available for the 2024-2026 period.

Section 3: Projecting service delivery and impact over the Replenishment period (2027-2029)

To estimate the epidemiological impact over the period 2027-2029, assumptions for available funding were handled as described below, with available funding made up of different funding sources: the Global Fund Replenishment amount, domestic funding, and non-Global Fund international funding to Global Fund-eligible countries. First, available resources were allocated between countries and across intervention elements (and also across sub-national units for malaria). Second, the impact on the epidemic was projected as a result of the configuration of interventions, as outlined above. The starting point for these projections is the epidemic status and intervention configurations achieved at the end of 2026 (see Section 2).

[6] Sum of new HIV infections and AIDS-related deaths, sum of new TB cases and TB deaths (excluding HIV+), sum of malaria cases and malaria deaths in modeled countries in 2023 compared to the Global Fund-eligible countries for which estimation of burden was available from WHO and UNAIDS.

Stage 1: Determining the allocation of resources between countries, sub-national units and across intervention elements

For each country and disease, the models are used to find the program configuration that would allow for the greatest impact. That "impact" is defined as achieving the lowest number for deaths and new infections (for HIV) or cases (for malaria and TB) [7] given a cap on the total cost of the program. The program configuration in the model can vary in the extent to which different services are scaled up, nationally or in particular regions, but prioritizes maintaining existing levels of treatment coverage. This is repeated for a wide range of values for the cap.

Two types of program funding are projected for each disease for the Replenishment period (see Annex 2: Methodology for projection of available resources for HIV, TB and malaria): (i) non-Global Fund resources (comprising domestic and external sources other than the Global Fund); (ii) funds from a successful Global Fund Replenishment.

The Global Fund budget that would become available for use in each disease area consists of the Replenishment amount (excluding the overhead cost) split between the three diseases, in accordance with the Global Fund's global disease split formula.[8] Then, for each disease, the share of funds available to each country is determined to be the amount that maximizes the overall impact across the Global Fund portfolio of countries.[9] The same applies to non-Global Fund external funding amounts within each disease that have not been earmarked to specific countries (see Annex 2: Methodology for projection of available resources).

Stage 2: Projecting impact and service delivery over 2027-2029 and later

The models are used to project the impact on the epidemic that would result from the program configurations that are specified by the approach outlined above. Projected impact after the Replenishment period (from the start of 2030 to the end of 2030 for HIV/AIDS and malaria and to the end of 2035 for TB) assume that this program configuration achieved by the start of 2030 is maintained for all interventions, except for a TB vaccine, which is assumed to increase to coverages outlined in the TB Global Plan by 2035. Intervals for the projections represent the uncertainty that arises as a result of the uncertainty in the overall disease burden, intervention effectiveness, and costs of the proposed interventions.

[7] Equal weighting is given to the proportionate reduction in total deaths and infections/cases in the period 2027-2030, relative to the respective value achieved in the global plans, under the assumption that the program can be continued in the years following the Replenishment.

[8] Allocation Methodology GC8. The Global Fund. https://archive.theglobalfund.org/media/15310/archive_bm52-08b-allocation-methodology-gc8_report_en.pdf.

[9] Using the same approach to defining maximal impact as done for each country.

The impact on the program scale-up in terms of lives saved over 2027-2029 is computed by comparing the modeled trajectories of deaths under the Replenishment scenario to a counterfactual scenario, which is defined as follows:

- For HIV/AIDS, there is an assumption of no antiretroviral therapy (ART) from the beginning of 2024 onwards. All other interventions and risk behavior are assumed to remain at the same level as the beginning of 2023.
- For TB, there is an assumption of no prevention or treatment for TB from the beginning of 2024, applying the case fatality rate of untreated cases to the estimate of incidence.
- For malaria, the counterfactual scenario is constructed by applying the 2000 mortality rates to the projected population at risk from the beginning of 2024, i.e., returning to the levels they were at without intervention.

The impact in terms of infections (for HIV) or cases averted (for TB and malaria) is estimated by comparing model-based trajectories of infections or cases based on the Replenishment scenario compared to a counterfactual scenario, as follows:

- For HIV/AIDS and TB the counterfactual assumes service coverage of disease programs are maintained at 2023 service levels.
- For malaria, the counterfactual scenario is constructed by applying the 2023 incidence rate to the projected population at risk.

The choice of counterfactuals reflects the recommendations of a Global Fund health impact experts meeting held in July 2014 and is aligned with the counterfactual used in other Global Fund exercises.

The models make epidemiological projections at the country level for countries that are in the Global Fund portfolio. Funding for the programs, which are driving this epidemiological impact, comes from various sources (see Annex 2: Methodology for projection of available resources). As a result, the impact that is ascribed to the set of countries in the Global Fund portfolio has been *contributed* to by the Global Fund. No estimate of what fraction of that impact could be *attributed* to the Global Fund is offered because the overall impact is a result of the entirety of a country's response. It would not be meaningful, for instance, to try to estimate the impact of diagnostics alone (which one funder might cover), or the impact of health care workers alone (which another funder might cover), as the value of such components is only realized in combination with one another, and with other factors, such as treatment availability, prevention programs, etc.

The assumptions that are made in the disease models regarding how interventions develop during the Replenishment period, including new interventions becoming available, are the same as those made in the respective disease global plans:

- For HIV/AIDS, the model incorporates improvements in the proportion of patients being tested and being virally suppressed through new approaches (e.g., community-based testing, adherence support groups, etc.), improvements in diagnostics (e.g., self-tests, point-of-care viral load testing, and early infant diagnosis, etc.) and availability of new treatments.
- For TB, several programmatic changes are incorporated into algorithms that implement screening, diagnosis and first- and second-line treatment (including multidrug-resistant TB (MDR-TB) according to prevailing guidelines for both adults and children. In addition, the TB global plan calls for more active screening for TB, including screening for subclinical TB, using X-rays for screening and rapid molecular tests (GeneXpert and other molecular WHO-recommended rapid diagnostic tests) for diagnosis. It further calls for universal access to the latest short, safe and effective treatment regimens, routine drug susceptibility testing with GeneXpert to inform correct treatment approaches and patient support (including psychosocial and nutritional support) as a routine part of care. According to the global plan, prevention, based on the latest preventive treatment regimens, should be provided to all eligible contacts, ART patients and other persons at high risk of TB infection. Further, it was agreed with partners that for the purpose of this Investment Case, the rollout of a vaccine is assumed, starting in 2029.
- For malaria, it is assumed that there is a rollout of a vaccine consistent with projections that Gavi, the Vaccine Alliance (Gavi) has formulated as part of their Investment Opportunity 2026-2030. To achieve high target usage rates, we assumed that net mass distribution frequency could increase from every 3 years to every 2 years; and that next generation indoor residual spraying, rectal artesunate, and next generation long-lasting insecticidal nets are all introduced. The model incorporates the increasing risk of insecticide resistance, but otherwise assumes that changing epidemiological circumstances do not have a material impact on the cost or effectiveness of the program. The potential impact of the emergence and spread of artemisinin and partner drug resistance in sub-Saharan Africa is not modeled.

The Global Fund commissioned the Vice President of Avenir Health,[10] a senior analyst at Avenir Health[11] and research fellow from Imperial College London[12] to perform the modeling work. There are the same individuals who conducted modeling work for the three global plans.

[10] "Avenir Health," accessed January 23, 2025, https://www.avenirhealth.org/our-team.php.

[11] "Avenir Health," accessed January 23, 2025, https://www.avenirhealth.org/our-team.php.

[12] Peter Winskill, Advanced Research Fellow, School of Public Health – Faculty of Medicine, Imperial College London. https://profiles.imperial.ac.uk/p.winskill.