TECHNICAL AND ADVOCACY BRIEFING

ANTIMICROBIAL RESISTANCE & HIV, TB AND MALARIA
The second United Nations High Level Meeting on Anti-Microbial Resistance (AMR HLM) will take place in New York in September 2024. This briefing is intended to support HIV, TB, malaria and Global Fund advocates to engage productively in AMR discussions and processes. For more information on the AMR HLM, find a first assessment by ReACT of the state of the negotiations, the modalities document for the HLM and an advocacy guide on TB and AMR put together by Results UK. For context, you can read the political declaration for the first AMR HLM (2016).

IN BRIEF

The burden of anti-microbial resistance (AMR) falls first and foremost on vulnerable populations in low and middle income countries (LMICs). *E. Coli* and *Staphylococcus aureus* are responsible to the most death associated with AMR, but it is also observed across HIV, TB and Malaria:

- **HIV**: ARV resistance is on the rise and requires an acceleration of the roll out of new treatments, and a focus on prevention.
- **TB**: AMR is a major driver of mortality in TB. New tools exist, but lack of funding makes access where they are most needed an enduring challenge.
- **Malaria**: Artemisinin resistance is on the rise, but has not fully blunted the effectiveness of current treatment. There is, however, no effective second-line treatment.

The Global Fund has a dual role to play in the fight against AMR:

- **AMR threatens the population that the Global Fund serves.**
- **The fight against HIV, TB and Malaria is a major contributor to the fight against AMR.**

AMR is often discussed as a technical matter and linked to the need for more investment in R&D. We do need more tools to fight infections, but without an approach that accounts for the socio-economic drivers of AMR, especially barriers to access to quality diagnostic and treatment, the race against resistance cannot be won. AMR is an equity, human rights, and access issue, and strong civil society mobilization and engagement will be crucial to impose this framing. The UN High-level meeting on AMR in September 2024 provides opportunities for civil society to influence global policy and commitments, and HIV, TB and malaria advocates must bring their expertise and voices to the table.
The Rising Threat of Antimicrobial Resistance

Key Facts and Context

AMR and HIV, TB and Malaria

The Role of the Global Fund in Fighting AMR

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THE RISING THREAT OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR), or the rise of pathogens impervious to one or more of our tools to fight them, is a rising threat. Left unchecked, it could erase decades of progress against a wide range of diseases, and cost hundreds of billions of dollars in additional health care costs.

Key Facts and Context

The history of resistance is closely linked to the story of our fight against germs – the first evidence of resistance in E. coli to penicillin were collected in 1940, before even the first human trials of the drug were underway. AMR refers to resistance in all pathogens, whether bacterial, fungal, parasitic, or others; however, discussions on AMR usually focus on resistance in bacteria, or bacterial AMR.

There was an estimated 1.27 million deaths attributable to bacterial AMR in 2019. The bacteria responsible for the most deaths were E. coli and Staphylococcus aureus, and with multi-drug resistant tuberculosis (MDR TB) not far from the top of the list with around 160,000 annual deaths. Though antibiotics resistance is a pressing concern in many high-income countries where antibiotics have been in wide use for over half a century, recent burden estimates find the highest burden in LMICs, despite harder to collect statistics. A wide range of factors drive the spread of AMR. According to the WHO, the factors include:

- Access to clean water, sanitation and hygiene for humans and animals;
- Effectiveness of disease prevention measures in households, healthcare facilities and farms;
- Access to quality vaccine, medicine and diagnostics;
- Medical literacy, including among care workers;
- Legislative and enforcement environment.

These factors relate to the two underlying drivers of AMR: the number of infections, and the quality of treatment. The more common infections are in a population, because of socio-economic factors, marginalization, or barriers to access to prevention and care, the more opportunities pathogens will have to pick up resistance. The poorer the quality of treatment, because of stock-outs, drug prices, misdiagnosis, and treatment interruption, the higher the chance for resistance to develop.
Public campaigns in many countries have focused on inadequate antibiotic use, specifically over-prescription and incorrect use, but these are only part of the equation. Ensuring access to quality diagnostics and treatments and socio-economic support to help people stay on treatment are just as essential, especially in LMICs that carry most of the burden of AMR - and are core elements of the Global Fund’s mandate.

A final consideration is the acknowledgment that AMR is an especially potent threat in healthcare settings, where the wide use of antimicrobial leads to the development of resistant strains of common pathogens, especially bacteria – for some context see this NCBI article. This means that patients with infections requiring long-lasting hospital stays or frequent visits (such as HIV and tuberculosis) are put at greater risk of contracting infections from resistant strains. It also increases the risk associated with surgeries, no-matter how routine, and degrades the quality of care for all patients.

**AMR and HIV, TB and malaria**

Resistance across the three diseases threatens the efficacy of available treatment and jeopardizes our progress and the lives of millions. Prevention and reducing the incidence of the three diseases, especially TB, will reduce the use of antibiotics, and hence the development of AMR, dramatically.

HIV is a rapidly mutating virus, which has from the start of the epidemic posed considerable challenges to the development of effective treatment, and favorizes the emergence of ARV resistance. It plays out at the individual and community scale, especially in contexts with lower access to HIV testing, including viral load testing. The virus can acquire resistance to treatment during the course of infection, so people living with HIV can have to change treatment regimen regularly, which is rarely available in low-resource settings.

The development of resistance is made more likely by treatment interruption, poor adherence or lack of access to correct treatment and adequate doses, both common challenges for key and vulnerable populations and children living with HIV. The existence of resistant strains in a community leads to resistance among new infections, as these are passed on. The WHO notes in its 2021 HIV drug resistance report that across surveys done in 30 countries, resistance to NVP- and EFV-based regimens was above 10% in 21 countries. It reached 24% among treatment-initiators who reported previous ARV use (i.e. who had gone through treatment interruption), against 7% among ARV-naive initiators. Though resistance to dolutegravir (DTG)-based regimens (recommended first-line treatment since 2019) was extremely rare in 2021, a 2024 report found it to be on the rise, though levels are still very low.

Drug resistance in HIV already leads to treatment failure, though rarely for people using DTG-based regimens, and the WHO recommends the acceleration of the transition to DTG-based regimens as first line ARVs in countries where it is not yet the case, as well as close and regular monitoring of resistance among people living with HIV and treatment initiators. AMR has an outsize impact on people living with HIV, as bacterial infections are their second-leading cause of hospitalization, and often from infections prone to drug resistance such as TB.

Long treatment regimens, old drugs, and inadequate diagnostics, coupled with poor follow up for people on treatment have been the perfect storm for the development of drug resistant TB. Resistance in TB is classified as Drug Resistant TB (DR TB), Multi-Drug Resistant TB (MDR TB) and Extensively Drug Resistant TB (XDR TB), each indicating resistance to additional types of antibiotics.
In 2022, the WHO estimates in its [Global TB Report](https://www.who.int) that 3.3% of new TB cases were either DR or MDR TB, with that share reaching 17% among people who had been previously treated. In some countries this is much higher, reaching up to 54% in the European region. Drug resistance is a major driver of the TB burden with more than 400 000 new cases in 2022, however, only 2 in 5 accessed diagnosis and treatment. A treatment that is longer and more toxic, and with poor treatment outcomes.

The spread of resistance in TB is closely linked to misdiagnosis and treatment interruption, both of which are being addressed thanks to the roll-out of new tools: rapid molecular testing for more accurate diagnostic, and shorter and less toxic bedaquiline-based regiments (see the [1/4/6x24 campaign](https://www.tagglobal.org) led by TAG). However, challenges remain with high costs preventing scale-up, and due to lack of adequate medical and socio-economic follow-up, resistance to Bedaquiline is already documented in some countries.

Although accounting for a significant proportion of AMR-related deaths, drug resistant TB is largely overlooked in the broader AMR agenda, hence it is important that that we continue to document and share the heavy burden it lays on individuals and communities.

In **malaria**, there are two main stories of resistance, with only one falling within the scope of AMR. Both the vectors of malaria, mosquitoes, and its causal agent, the plasmodium, are developing resistance to the tools we use to fight them. Mosquitoes are increasingly resistant to insecticides, forcing investment in more expensive Dual AI Net to maintain effectiveness. But mosquitoes fall outside of the realm of antimicrobial resistance (they are not microbes), and in the context of AMR resistance plasmodium is the key focus.

The cornerstone of modern malaria regiments is artemisinin, via artemisinin-based combination therapies (ACTs). [Partial resistance to artemisinin was first detected in South-East Asia over 20 years ago](https://www.who.int), and has grown in the region while overall malaria cases were falling. A [2019 WHO assessment](https://www.who.int) found that treatment failure rates remained low globally, with some local exceptions. One important consideration is that the definition of treatment failure in malaria is a delay in the clearing of parasite, and the need to extend treatment from two to three or four days. In other words, even if it is a major public health challenge, it is different from the situation of other types of resistance where certain types of antimicrobial become almost fully ineffective.

There has been widespread fear of the impact of the spread of resistance to Africa, where over 95% of malaria cases are found, and partial resistance and growing rates of treatment failure have been observed on the continent. Yet the [WHO estimates](https://www.who.int) that the resistance rates in Africa have remained low, under 10% of cases, and the impact on overall burden is still limited. The situation of resistance in malaria is hard to gauge; on the one hand stopping the spread of artemisinin resistance is essential, as there is as of now no alternative treatment available; on the other hand, the tools we have at our disposal have remained effective, in part thanks to close monitoring and early intervention. In addition, malaria treatment is secondary to prevention across most malaria programs, hence the impact of insecticide resistance is the most immediate concern.
The Global Fund is the largest single funder of global health. Through sheer scale, its policies and investments impact national, regional and global disease trends. It is essential to highlight the role of the Global Fund in fighting AMR and ensure that key measures are taken in its programs to contribute to the fight.

The Global Fund’s relationship to AMR goes two ways. Success in curbing AMR is essential to successfully end the three epidemics and save lives among vulnerable populations:

- AMR is a major risk for people living with HIV, who are reliant on antimicrobials to fight infections.
- Hospital Acquired Infections (HAIs) are a particular threat to PLHIV and people ongoing TB treatment as they are in regular contact with healthcare settings; they were also a major driver of mortality during COVID-19.
- AMR is a possible source of disease X (though less likely than a viral spillover), controlling its spread is a key component of pandemic preparedness, one of the Global Fund cross-cutting strategic objective.
- TB is a major cause of AMR deaths (7th), and drug resistance in TB is a major challenge towards elimination and tends to increase as a share of national burden as countries get closer to elimination.

The Global Fund will be a key partner in the fight against AMR, which should be reflected in the upcoming AMR HLM. Here are some of the key levers the Global Fund can and does use to support the fight against resistance, from the 2023 Global Fund Results report:

1. Investment in disease prevention: Preventing infection and further transmission is the best way to stop the spread of AMR, since reducing disease prevalence means less use of antimicrobials.

   - The Global Fund has invested over $850 million in HIV prevention over the 2021-2023 period and has been instrumental over the past 20 years in lowering the rate of new HIV infection by 61%.
   - It has invested in scaling up new tools such as oral PrEP and the dapivirine vaginal ring, as well as human rights and socio-economic initiatives to broaden access to comprehensive HIV prevention beyond condoms.
   - It has been a key partner in the roll out of the malaria vaccines, and is likely to play a similar role for the roll out of future TB, and perhaps eventually HIV, vaccines.
   - In 2022 the Global Fund pushed for a surge in TB-preventive therapy, reaching 1.5 million people who had been in contact with the disease, or a four-fold increase from 2021.
   - In malaria preventive measures are the cornerstone of the Global Fund response, with key results including a more than fifteen-fold increase in children receiving seasonal preventive chemotherapy.
Better diagnostics: Accurate and timely diagnostics is essential to access to adequate treatment and reduction in the burden of AMR; this is especially challenging with regard to TB where misdiagnosis is a major driver of resistance.

- The Global Fund plays a pivotal role in the roll-out of molecular testing for TB via market-shaping intervention to lower the price of systems and cartridges.
- Across its malaria and TB programs the Global Fund has also invested in service integration, allowing for people to get tested for a range of diseases at TB and malaria clinic, both reducing stigma and strengthening the health system overall.

Widening access to better treatment: poor quality treatment (including expired and counterfeit drugs) and treatment interruption (promoted by long course of toxic antibiotics, stigma, and stockouts) are two key drivers of resistance across the three diseases.

- The Global Fund is the largest external source of financing for treatment of drug-resistant TB in LMIC, with 483,000 people treated in 2018-2022, and it provides stipend for transport and food to people on treatment for drug resistant TB, enabling treatment adherence and completion.
- A core pillar of the Global Fund’s intervention has been widening access to quality treatment. In 2022, it adopted a NextGen Market Shaping Framework, streamlining its approach to partnership with drug manufacturers and aiming to promote local manufacturing and increase country resilience.

Health system and pandemic preparedness: Resilient and Sustainable Systems for Health (RSSH) and Pandemic Preparedness and Response (PPR) have been integrated as cross cutting objective under the Global Fund 2023-28 strategy. The Global Fund has invested over a $1 billion in the 2021-23 period in laboratory strengthening and surveillance, and nearly half a billion in digital health and information system, essential elements of the effective monitoring of AMR.

- The Global Fund through its partnerships and competitive tenders reduced the cost of first-line, dolutegravir-based treatment by 25% for LMICs, helping expand access.
- The Global Fund invests $400 million per year in logistics and supply chain management, to increase the reliability of drug procurement. The prevention of stock-outs, like the ones that hit many Indian states in 2023, is key to preventing treatment interruption and loss to follow-up.
- The Global Fund has promoted the roll-out of new bedaquiline-based regimens that are shorter and less toxic, now adopted as standard by 92 countries where the Global Fund invests.

AMR is increasingly being seen as an equity, human rights, and access issue. Strong civil society mobilization and engagement must influence the commitments in the AMR HLM in September 2024, and hold governments and other stakeholders accountable to fund and implement their resolutions.
TB and AMR: the benefits of dual-use investments

Strengthening health systems, including laboratory networks, promotion of universal health coverage, strong community systems, infection control, and research- and equal distribution, of drugs, diagnostics and vaccine are all part of the TB response. This will contribute significantly to prevent and control AMR, as well as play an important part in pandemic preparedness. This was demonstrated during Covid-19 as TB diagnostics (GeneXpert), and TB health staff and community volunteers, were key factors in national responses.

AMR is more than a matter of more investment in R&D. Without an approach that accounts for the socio-economic drivers of AMR, especially barriers to access to quality diagnostic and treatment, the race against resistance cannot be won.

Some basic science and context:
WHO AMR factsheet
Discovery of penicillin and resistance: Penicillin’s Discovery and Antibiotic Resistance: Lessons for the Future?
The authoritative source for a robust estimate of global AMR burden from The Lancet: Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis
How to think about AMR burden estimates
ReACT piece on gene transfer: Transfer of antibiotic resistance
Fighting AMR in the Healthcare Environment: Microbiome-Based Sanitation Approaches and Monitoring Tools, NCBI 2019

On resistance in HIV and TB:
WHO HIV drug resistance report 2021 & Brief HIV drug resistance report 2024
WHO Global TB report, (see p. 28 for discussion of resistance)