världs infektions fonden.

Filling the Gaps to eliminate High Burden Infectious Diseases Among the World's Poor

2021

A report by the World Infection Fund in collaboration with the Swedish International Development Cooperation Agency

In collaboration with Sida

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Anders Björkman, professor Karolinska Institutet
Anna Mia Ekström, professor Karolinska Institutet
Marcus Moll, Sida
Teresa Soop, Sida
Olle Terenius, Associate professor Uppsala Universitet
Susanne von Wächter, the Global Fund
and in particular **Maria-Teresa Bejarano**, Sida, professor Karolinska Institutet.

The World Infection Fund is a nonprofit, independent research foundation that supports research on infectious diseases through funding and knowledge sharing of the impact of these diseases on the societies of the world's poor. Vif is supervised by the Swedish Fundraising Control which ensures that the organisation uses a minimum of 75% of the earnings to the organisation's designated purpose.

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Vif	Världsinfektionsfonden (World Infection Fund)
AIDS	Acquired immunodeficiency syndrome
AMR	Antimicrobial tesistance
ART	Antiretroviral therapy
DALY	Disability-adjusted life year
Global Fund	The Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria
ITN	Insecticide-treated nets
LIC	Low-income country
LMIC	Lower-middle-income country
MDR	Multidrug-resistant
NCD	Noncommunicable disease
NTD	Neglected tropical disease
PMTCT	Prevention of mother-to-child transmission
SDG	Sustainable Development Goal
TB	Tuberculosis
USD	United States dollar
UNAIDS	United Nations Programme on HIV/AIDS

PHOTO **KATIE MOUM**

About the World Infection Fund

Gunilla Källenius, David Samuelson, Claes Ånstrand and Emma Frans—some of the World Infection Fund's board members.

PHOTO **ERIK FLYG**

The World Infection Fund (Vif) was founded in 2005 by prominent researchers with the intention to gather support in order to promote research and development for infectious diseases affecting the world's poor, as well as to contribute to an increased awareness of the impact of these diseases on people in lower-income settings.

Vif has throughout the years made several contributions within the Swedish development for global health. We have funded field work and projects in parts of Africa and Asia. As an opinion-former, Vif has a close dialogue with the Government Offices of Sweden regarding global health, and with international organisations such as the WHO, Médecins Sans Frontières, as well as the Global Fund.

Through advocacy and funding of research, these are some of the diseases that Vif aims to combat:

- African trypanosomiasis
- Chagas disease
- Diarrhoeal diseases
- HIV/AIDS
- Leishmaniasis
- Malaria
- Measles
- Relapsing fever
- Respiratory tract infections
- River blindness
- Schistosomiasis
- Tuberculosis

Background and introduction

The right to health is a fundamental part of our human rights that gives everyone an equal opportunity to enjoy the highest attainable level of health. However, political, social and economic injustices create unequal societies where adverse health outcomes are rife. In our preceding report —»The Burden of Disease Among the World's Poor«—we highlighted that communicable diseases such as acquired immune deficiency syndrome (AIDS), tuberculosis (TB), malaria, and neglected tropical diseases (NTDs), dominate among the leading causes of death and disability-adjusted life year (DALY) loss in low-income countries (LICs).

Reducing disease burden is intrinsically linked to most of the Sustainable Development Goals (SDGs), and is central to SDG 3: *Ensure healthy lives and promote well-being for all at all ages* and its target 3.3: »By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.«

For these diseases, considerable gaps exist in terms of tools to fight them, such as: diagnostics, therapeutics and vaccines; mainly because of the low interest of industry due to lack of financial incentives and return on investments. The persistence of these gaps hampers efforts to attain global targets and perpetuates the continuous spread of infectious diseases. As seen in the ongoing Coronavirus (COVID-19) pandemic, communicable diseases do not respect international borders. While low and middle-income countries are especially vulnerable to the spread of communicable diseases due to low coverage of health services, weaker health systems, and inadequate water and sanitation infrastructure, global public health security is as strong as its weakest link.

In order to meet the Agenda 2030 targets toward ending the epidemics of AIDS, TB, malaria and NTDs, and to improve global health security as a whole, critical gaps in the global response to these diseases must be identified and filled as a matter of priority.

In this report, we highlight gaps in the global response to these epidemic diseases and discuss some cross-cutting approaches to address these gaps. Our goal is that this resource will provide Swedish decision-makers and other relevant stakeholders with a data-informed basis for increased support toward the reduction of the gaps that exist in the fight against communicable diseases that disproportionately affect the poor and marginalized.

Omoh Duze

Medical Doctor and Public Health Specialist at the World Infection Fund

High burden infectious diseases

Globally, about 26% of total all-age DALYs were due to communicable, maternal, neonatal and nutritional causes in 2019. However, in LICs these account for 58% of total all-age DALYs, in high contrast with high-income countries where they contribute only 7% of total all-age DALYs (1). In many LICs there is today a double burden of disease, as the proportion of morbidity and mortality due to non-communicable diseases (NCDs) is on the rise and coexists with an already high burden of communicable diseases. The increasing threat of antimicrobial resistance (AMR) makes both infectious diseases and NCDs harder to treat and increases the risk of disease spread, severe illness and death. Cancer therapies and elective surgery for example are difficult to pursue with no functioning antibiotics. AMR is one of the top 10 global public health threats and requires urgent action in order to achieve the SDGs (2).

TB, malaria, HIV and NTDs are among the leading causes of death and DALY loss due to communicable disease in low and lower-middle-income countries (Fig. 1, page 8). According to the global burden of disease study 2019, in these countries over 128 million DALYs were lost as a result of TB and other respiratory infections alone; over 60 million DALYs lost to malaria and NTDs, and; over 41 million DALYs lost to HIV and other sexually transmitted infections (1). This situation is worsening due to the COVID-19 pandemic.

Human immunodeficiency virus (HIV)

Since the establishment of the Millennium Development Goals, ending the HIV pandemic has been a global health priority. The three zeros, as set by the Joint United Nations Programme on HIV/AIDS (UNAIDS)—»zero new HIV infections, zero AIDS-related deaths and zero discrimination« represent a global consensus on ending AIDS as a public health threat by 2030.

Overarching HIV targets for 2030

- Zero new HIV infections
- Zero AIDS-related deaths
- Zero discrimination

In addition to the above targets, the World Health Organization (WHO) has set an additional goal of eliminating mother-to-child transmission (3). Sadly, 2020 interim targets were missed and progress toward the 2030 HIV targets is lagging (4,5). According to UNAIDS, globally in 2019, an estimated 690,000 AIDS-related deaths occurred and approximately 1.7 million people became newly infected with HIV—more than three times higher than the set target. HIV-related stigma and discrimination are also far from over (5).

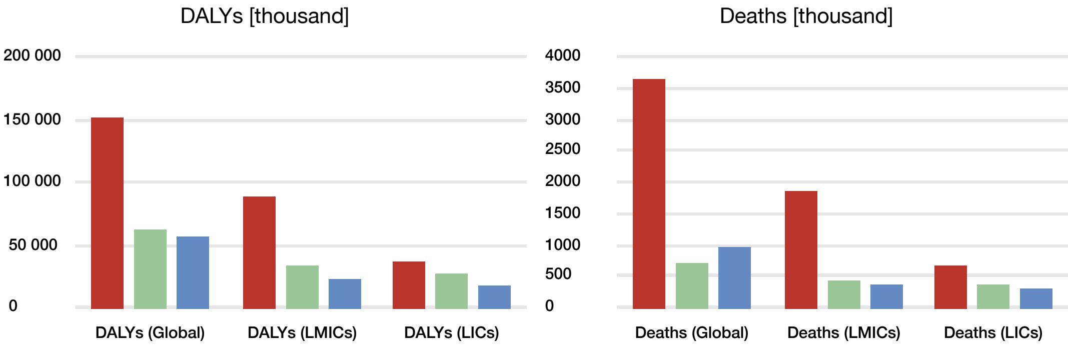
Prevention of HIV drug resistance is critical to achieving the SDG goals. In 12 of 18 countries reporting survey data to the WHO between 2014 and 2018, levels of pre-treatment drug resistance to efavirenz and/or nevirapine among adults initiating first-line antiretroviral therapy (ART) exceeded 10% (6).

Critical gaps in the HIV results chain must be identified and filled in order to set the global response on course to achieving its targets. Funding gaps, in particular, as well as the growing threat of AMR must be addressed in order to ensure that global HIV targets can be met.

Prevention

Sub-Saharan Africa remains the region with the highest burden of HIV, and one where significant prevention gaps for young females exist. Despite being only 24% of the population in sub-Saharan Africa, young women and adolescent girls accounted for 49% of new HIV infections in 2019

FIG. 1 **DALYs and death due to high-burden infectious diseases—Global and in low and lower-middle-income countries**



TB and other respiratory infections · Malaria and NTDs · HIV and other sexually transmitted infections

SOURCE Institute for Health Metrics and Evaluation (IHME), *The Global Burden of Diseases, Injuries, and Risk Factors Study 2019* (GBD 2019) (1)

—about double their share of the population (5). According to UNAIDS, this is driven by demographic and behavioural patterns and underlying drivers of vulnerability, including harmful gender norms and inequalities, poverty, food insecurity, conflict, and violence (7). Key populations can vary significantly across communities within regions, thus, preventive services that are designed and operationalized to respond to the needs of local key populations are crucially needed.

Of the 38 million sexually active adolescent girls aged 15 to 19 years globally, more than half do not use contraceptives. There has also been a global decline in access to HIV prevention services such as condom use and pre-exposure prophylaxis—and targets for these, including voluntary male medical circumcision were way off in 2020 (5,7).

Diagnosis

Significant gaps exist in the testing of HIV exposed infants, adolescents, the least educated and men (5,7,8). Many infants in high burden countries do not access early infant diagnosis, partly due to disintegrated post-partum and HIV care. Also, limited availability of point of care diagnostics for HIV exposed infants means that many infants have to wait for long periods to receive test results and are lost to follow-up in the intervening time (5,9).

Testing rates in adolescent populations are negatively affected by laws requiring parental consent to access HIV care. Third-party authorization requirements remain a significant barrier to uptake of HIV and sexual and reproductive health services among adolescents and young people in many high burden countries. Such policies must be revised such that they are not in violation of sexual and reproductive rights of adolescents.

In the same vein, discriminatory laws and policies against same-sex practices, sex work, transmission and non-disclosure of HIV status, serve as barriers to seeking HIV care which further alienate key populations from the healthcare they so desperately need. Out of 46 countries, 42 criminalize sex work, and 33 out of 46 countries have laws that criminalize HIV transmission and non-disclosure in UNAIDS reporting countries in sub-Saharan Africa (5).

Men are less likely than women to know their HIV status and less likely to access and adhere to HIV treatment, as most programs target women, especially prevention of mother-to-child transmission (PMTCT). In addition, financial, information and geographical access barriers exclude the poor and least educated from accessing diagnostic services.

Treatment

Though PMTCT services have improved globally, gaps in the PMTCT cascade such as treatment coverage among pregnant women living with HIV, interruptions in antiretroviral therapy during pregnancy and breastfeeding, and women acquiring HIV during pregnancy and breastfeeding, continue to expose children to HIV. Forty-two percent of child infections were due to lack of ART during pregnancy, and 18% were due to lack of ART during breastfeeding (5,9).

There is a growing concern around HIV drug resistance among adults and especially among HIV exposed children as this could significantly hamper efforts to attain global HIV targets. The prevalence of pre-treatment drug resistance among HIV positive children under 18 months of age is alarmingly high. Based on surveys conducted in nine countries in sub-Saharan Africa between 2012 and 2018, over half of the infants newly diagnosed with HIV carry a virus that is resistant to efavirenz and/or nevirapine (6). Despite this, these remain commonly used first-line ART in paediatric HIV due to limited paediatric antiretroviral drug formulations and caregiver competency (5,6,9).

There is therefore an urgent need for expanded paediatric treatment options and coverage, as the 2020 targets for reducing new HIV infections among children were missed, and treatment coverage in children remains significantly lower than in adults.

Moreover, treatment coverage globally is twelve percentage points higher among women living with HIV than among men living with HIV, and viral suppression is ten percentage points higher. These missed opportunities for treatment of HIV positive men set back the HIV response significantly as higher viral loads increase chances of transmitting the virus—especially to vulnerable populations such as young adolescent girls. Increased treatment coverage has been shown to be an invaluable aspect of HIV prevention as persons with undetectable viral loads have virtually no chance of transmitting the virus to someone else through sexual contact.

Research and development

To end the HIV pandemic by 2030, innovative technologies and strategies are needed such as sensitive assays and biomarkers coupled with cutting-edge studies of biology, virology, pharmacology, and immunology to advance durable and scalable prevention, treatment and cure in people with HIV (10,11).

Primary prevention of HIV through the introduction of a vaccine alongside other proven prevention methods still holds the greatest promise for ending the HIV pandemic. Though progress toward a vaccine for HIV has been slow, an efficacious vaccine could decrease global HIV incidence by 44% in the first ten years, and by up to 78% in subsequent years (12). The promise of new and rapid vaccine development technology made available during the COVID-19 pandemic represents new avenues that could speed the development of an HIV vaccine.

Next generation HIV therapies are needed that are less toxic with fewer side effects and complications. Of special importance are pre-exposure prophylaxis candidates and methods of delivery, especially those that improve adherence. The ultimate goal is research toward a cure including development of novel approaches and strategies to study the development of antiretrovirals, viral persistence, latency, reactivation, and eradication.

Other critical research gaps identified by the WHO include interventions to ensure timely linkage between HIV diagnosis, treatment and care; strategies to improve access to and uptake of HIV testing services for infants, children and adolescents—particularly community-based approaches; and psychosocial support strategies and interventions to improve individual and programmatic outcomes (10).

Tuberculosis

TB disproportionately affects the poor, marginalized and immunocompromised. In the face of new challenges, such as COVID-19, the TB response must remain a priority in order to even out entrenched inequities.

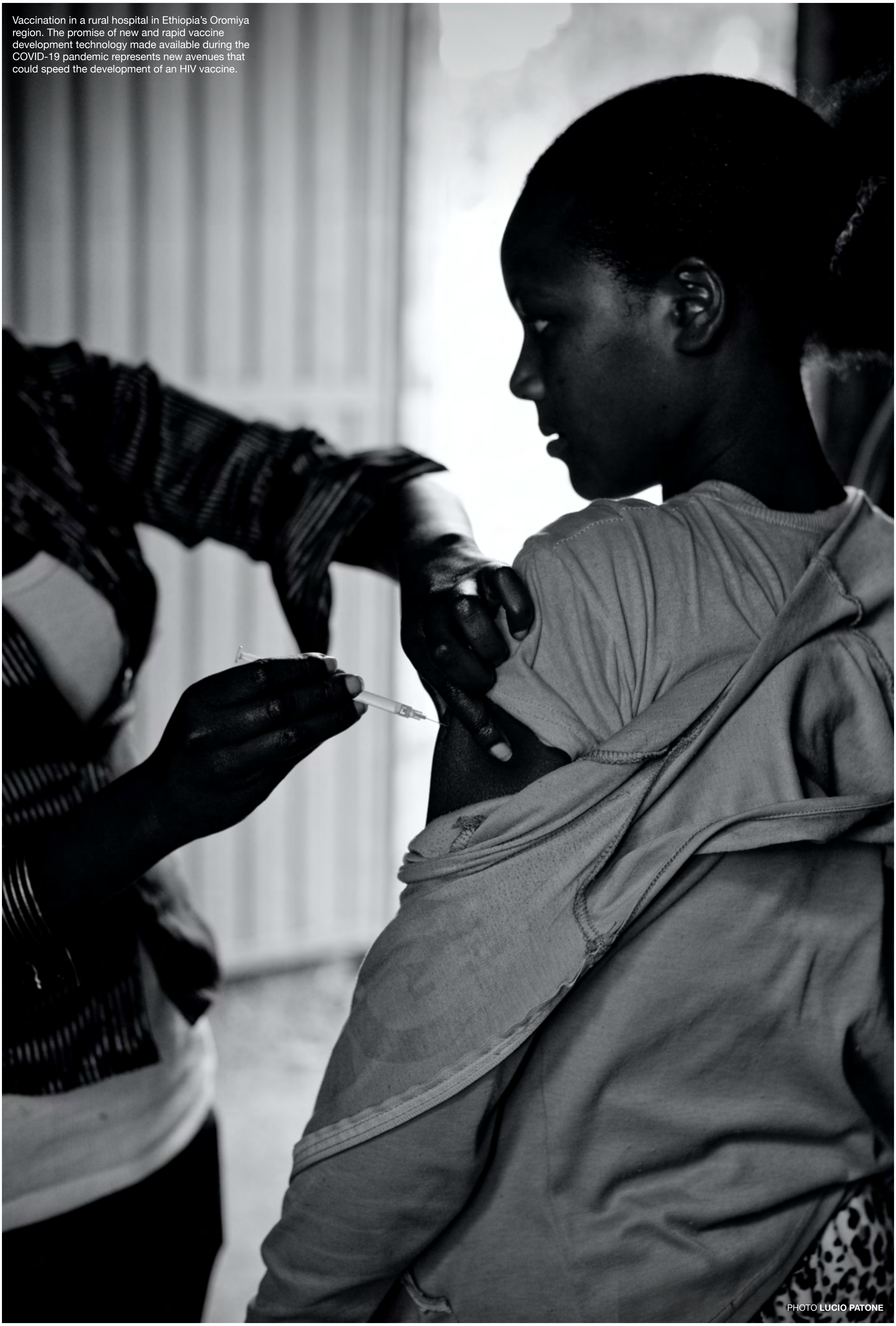
The WHO END TB strategy launched in 2015, aims for a 95% reduction in the number of TB deaths and a 90% reduction in the TB incidence rate by 2035 (compared with levels in 2015). Interim targets for 2020 fell out of track as with many of the global infectious disease targets.

Overarching TB targets for 2030

- A 90% reduction in the number of TB deaths
- An 80% reduction in the TB incidence rate
- No TB patients and their households face catastrophic costs as a result of TB disease

In 2017, the WHO issued a political declaration that included four new global targets, which are:

- Treat 40 million people for TB disease in the 5-year period 2018–2022;
- Reach at least 30 million people with TB preventive treatment for a latent TB infection in the 5-year period 2018–2022;
- Mobilize at least 13 billion USD annually for universal access to TB diagnosis, treatment and care by 2022; and
- Mobilize at least 2 billion USD annually for TB research



Vaccination in a rural hospital in Ethiopia's Oromiya region. The promise of new and rapid vaccine development technology made available during the COVID-19 pandemic represents new avenues that could speed the development of an HIV vaccine.

PHOTO **LUCIO PATONE**

According to the WHO 2020 Global TB report, the global TB incidence rate declined by 9% between the period 2015–2019; this is less than halfway towards the milestone. Globally it is estimated that 1.7 billion people have TB and that in 2019 alone 10 million people acquired TB (out of those new cases 3.4% were drug-resistant TB). Approximately 1.3 million deaths occurred in 2019 (13).

Prevention

Despite the ongoing shift from periodic surveys to continuous surveillance, there are persisting gaps in TB case finding that represent a considerable challenge for the TB response that affect programmatic ability to detect at-risk and new TB cases (13,14). In 2019 the number of new cases reported was only 7.1 million compared to the estimated 10.0 million cases (13).

A major factor that undermines the ability to detect new TB cases is the absence of universal health coverage in many high TB burden countries that limits access to diagnostic services and tracing of individuals at risk of developing active TB (15). TB prevention for key populations such as children and people newly enrolled in HIV care is deficient. According to UNAIDS the preventive coverage of TB services in children under five who were household contacts of bacteriologically confirmed pulmonary TB cases and in people living with HIV globally is only about 27%[1] and 49%[2] respectively (16).

Diagnosis

TB diagnostic tools remain inadequate in many high TB burden countries. The gold standard for TB diagnosis is a sputum culture that requires specialized laboratories and trained personnel. However, in many high TB burden countries, sputum microscopy is still the mainstay of TB diagnosis despite its limited sensitivity (17,18). Other available WHO-endorsed molecular-based tests for both rapid diagnosis and detection of drug-resistant TB are also highly specialized and so not performed routinely. Novel rapid and accurate diagnostics that can be used at the point of care and that can predict likelihood to development of active and drug-resistant TB are required to enable more effective diagnosis and treatment of TB (18,19).

Treatment

Between 2000 and 2019, TB treatment alone averted about 60 million deaths in HIV negative people and a combination of ART and TB treatment spared 10 million lives among HIV-positive people (16). A significant challenge in TB treatment is its toxicity and length. This increases patient attrition from treatment programs and contribute to the development of drug-resistant infections. Thus, there is a call for the urgent development of less toxic and shorter course therapies, particularly for the treatment of drug-resistant TB which require regimens with multiple, often toxic drug combinations, given for long durations of time, at up to 32-fold the cost of treating drug-sensitive TB (16,20,21).

Drug-resistant TB continues to be a public health threat. Worldwide in 2019, close to half a million people developed rifampicin-resistant TB, of which 78% had multidrug-resistant (MDR) TB. In 2019, 3.3% of new TB cases and 17.7% of previously treated cases had resistant or MDR TB (13). Of people with MDR TB only about 38% are enrolled in treatment, with a treatment success rate of less than 60% (13). This represents a huge treatment gap with significant potential to set back progress against the spread of TB.

Research and development

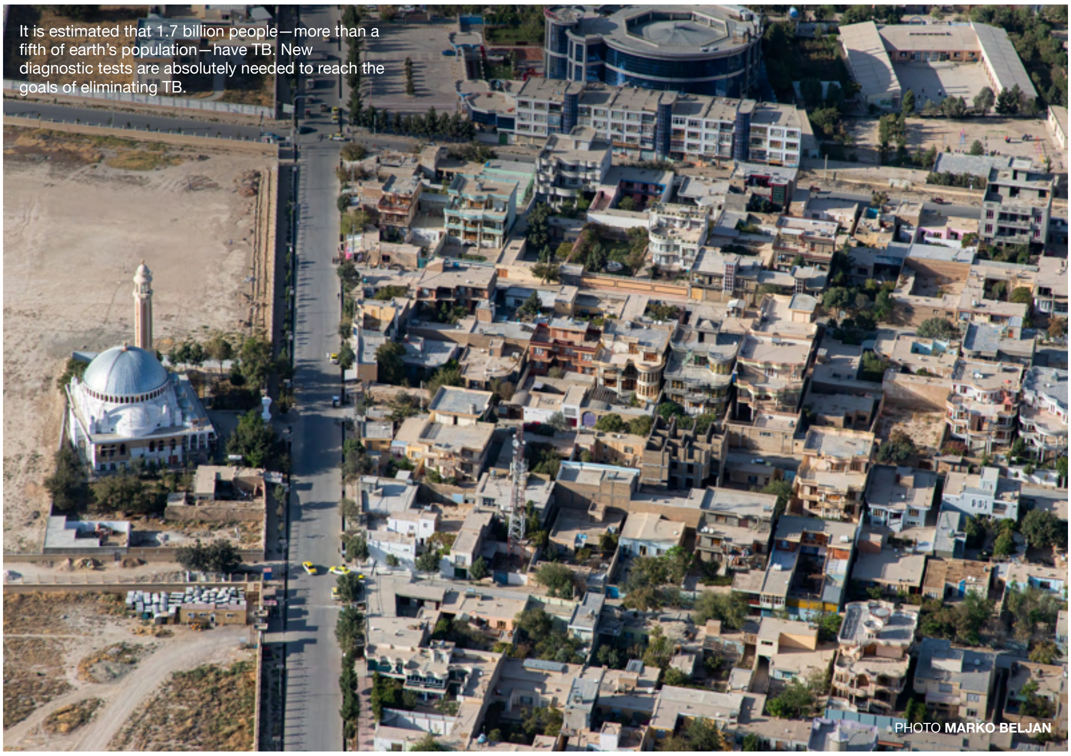
TB elimination by 2030 can only be possible through the development and rapid uptake of new tools, including rapid point of care diagnostics, safe and shorter treatment of latent TB infection and disease, and an efficacious TB vaccine, combined with efficient community-focused health systems and care provision that address the social determinants of TB.

New diagnostic tests are absolutely needed to reach the goals. The WHO has defined the target product profile of the most urgently needed tests for TB. One of the highest priorities is a point of care triage test for systematic screening, to distinguish individuals who need referral for further confirmatory testing (22).

Therapeutic answers to the problem of drug-resistant TB are desperately needed, as inadequate treatment of drug-resistant TB poses a significant global health threat. This includes new drugs, but also development of combination of drugs that allow shorter treatment alternatives. There are currently 22 drugs for both drug-sensitive, resistant and latent TB in various phases of clinical trials which could hold some promise (16).

Till date, the one-hundred-year-old Bacillus

1. Data for 109 countries
2. Data for 66 countries



It is estimated that 1.7 billion people—more than a fifth of earth's population—have TB. New diagnostic tests are absolutely needed to reach the goals of eliminating TB.

PHOTO MARKO BELJAN

Calmette–Guérin (BCG) vaccine is the only vaccine available against TB and the central pillar of TB prevention. Whilst neonatal BCG vaccination is partially efficacious at protecting infants and young children against severe forms of TB, it is poorly protective against pulmonary disease in adolescents and adults, and therefore ineffective at reducing Mycobacterium tuberculosis (Mtb) transmission (23). Vaccine candidates in the pipeline are intended to either replace BCG or to act as booster vaccines after infant BCG vaccination to stop the 35% of the world's population that is already infected with Mtb from developing TB disease.

Gaps in operational research hinder the optimal implementation of TB control activities and how these obstacles can be removed. The aim of operational research is to ensure the effective implementation of existing and new tools to diagnose, treat and prevent TB in health care services, and to investigate for the most efficient means to provide optimal TB care globally.

Malaria

According to the World Malaria Report 2020, 229 million cases of malaria occurred globally, 85% of which were shared between 19 countries in sub-Saharan Africa and India. The global incidence rate of malaria has remained at similar levels from 2014 through to 2018 although the WHO Africa region, which accounts for more than half of all malaria cases, recorded a 22% decline in incidence rate during the same period.

Overarching malaria targets for 2030

- Reducing malaria case incidence by at least 90%
- Reducing malaria mortality rates by at least 90%
- Eliminating malaria in at least 35 countries
- Preventing a resurgence of malaria in all countries that are malaria-free

Overall, the malaria mortality reduction rate has slowed since 2016. Out of the 409,000 deaths that were attributed to malaria in 2019, children less than five years accounted for 67% of deaths worldwide, with 94% occurring in the WHO Africa region.

Adaptation by parasites and mosquitos to resist or evade the current interventions is a major threat to achieving the SDGs. Resistance to artemisinin, the gold-standard malaria treatment, has been rising in southeast Asia for a decade and there is evidence that artemisinin-based therapies might start to fail in Rwanda, potentially compromising the continued success of antimalarial chemotherapy in Africa (24,25).

Prevention

Insecticide-treated nets (ITN) coverage has not improved much since 2016 and is far from the target of universal coverage (26). The WHO set a minimum target for universal coverage of ITNs at 80% for both access (ownership) and use. Despite the distribution of over 1.5 billion ITNs since 2008, no country has been able to achieve this target. This calls for a scale-up of repeated mass distribution campaigns; continuous distribution through channels like antenatal care clinics; and improved national ITN policies (27).

Intermittent preventive treatment in pregnancy (IPTp) is one of the very few health interventions with peer-reviewed evidence showing a direct public health impact in reducing malaria-related deaths by significantly reducing neonatal mortality —up to 31% (28). Even in the face of increasing drug resistance, IPTp is still highly efficient and cost-effective. Despite the compelling evidence, IPTp coverage has been inadequate due to conflicting policy guidelines, sulfadoxine/pyrimethamine stock-outs and limited health worker capacity. In 2018, about 18% of women in endemic countries who attended an antenatal care clinic at least once did not receive IPTp (26,29).

Diagnosis

It is estimated that 400 million unnecessary malaria treatments could be averted and 100,000 lives saved annually by using practical, field-appropriate malaria tests (30). An increasing number of patients with febrile symptoms seek care from the private sector (over 40% of the population in endemic countries) and are likely to be treated syndromically, either due to non-existent or expensive rapid diagnostic tests (31). Thus, bridging diagnostic gaps will ensure not only appropriate treatment but also the effective allocation of resources, and will require significant investments in supporting programmes and research.

Treatment

According to the World Malaria Report, a high proportion of febrile children did not receive any medical attention (median: 36%, IQR: 28–45%) due to limited access to health services (26).

Programmatic experience has shown that integrated community case management (iCCM) can be effective in achieving high treatment coverage and delivering high-quality care for sick children even in the most disadvantaged communities. However, despite its promise, there has been poor implementation of iCCM in LICs, including countries with very high disease burden (32). In 2018, 30 countries were implementing iCCM at different levels, with only a few implementing nationally (26). Some of the critical challenges facing adequate scale-up of iCCM include weak policy support and primary health care systems at the community level and inadequate funding (33,34).

Research and development

In order to meet the Global Technical Strategy for Malaria targets, malaria research still needs to cover many scientific areas, from basic molecular sciences to clinical, epidemiological, social sciences and the development of new health products, as well as innovation to ensure that solutions from malaria research can be implemented at scale.

WHO has identified five key challenges that represent threats or barriers to achieving the strategy goals (35):

- Biological adaptation, leading to resistance
- Addressing transmission
- Transforming surveillance
- Achieving universal access
- *Plasmodium vivax* and non-falciparum species

To meet these challenges, the report has prioritized the research needs with relation to vector control, diagnostics, drugs and vaccines.

Vector control Top priorities to reduce transmission of malaria parasites by vector control include development of new insecticides and mosquito repellents, as well as genetic approaches, developing transgenic mosquitoes that renders them inefficient vectors for the disease. Such genetically modified mosquitoes are in the pipeline, but must be approved for use in relation to present regulations with regard to genetically modified organisms.

Diagnostics Continued improvement of diagnostic tools both for point of care as well as for surveillance should take advantage of new molecular technologies to improve both detection of parasitemia and defining parasite characteristics. These diagnostic tools will assist in surveillance of drug resistance and in the understanding of routes of transmission that would enable optimal malaria control strategies, preventing evolution of drug resistance as well prioritizing targeted control interventions. This is especially important in areas moving towards pre- and elimination stages.

Drugs The present chemotherapy against malaria is dependent on artemisinin derivatives but increasing emergence of resistance against these compounds in parts of Southeast Asia constitute a continuous threat to progress made in the global malaria response. This however is not surprising. Resistance has developed and spread against all previous antimalarial treatment in wide scale use.

Vaccines There are a few vaccine candidates in the pipeline. Mosquirix (R) (»RTS,S vaccine«) from Smith Kline and Beacham has emerged as the first licensed malaria vaccine, presently evaluated in a large phase 4 trial in three African countries. Its efficacy in phase 3 trials has been around 50% against clinical disease for the first year after vaccination with some decline the following years. There are however some concerns regarding its safety in young girls and how efficient the vaccine will be when compared with more conventional preventive measures such as LLINs (26,36). The first results of a second vaccine candidate, developed in Oxford, UK, are just about to be published. An early pressrelease quotes a possible efficacy of 77% but without any further details. However, optimized tools are needed to measure incremental improvements and predict potential cost effectiveness of new vaccine candidates (35).

Neglected tropical diseases (NTDs)

The NTD portfolio consists of 20 diseases that impose a devastating human, social and economic burden on 1.7 billion people worldwide—predominantly the poor and marginalized.

NTDs include dengue and chikungunya, rabies, blinding trachoma, Buruli ulcer, endemic treponematoses (yaws), leprosy, Chagas disease, human African trypanosomiasis (sleeping sickness), leishmaniasis, cysticercosis, dracunculiasis (Guinea-worm disease), echinococcosis, food-borne trematode infections, lymphatic filariasis, oncho-cerciasis (river blindness), schistosomiasis (bilharziasis), soil-transmitted helminthiases (intestinal worms), snake bite envenoming, scabies and mycetoma (37).

In the Agenda 2030, NTDs are mentioned alongside HIV, TB and malaria as global health priorities but have in no way seen a commensurate response. While NTDs have low mortality, they are associated with high morbidity rates. Over a billion people—one-sixth of the world's population—are infected with one or more NTDs, and an additional two billion are at risk (38). Approximately 200,000 deaths and 17 million loss of DALYs can be attributed to NTDs annually (37,39).

Robust NTD targets have been set—both overarching targets and disease-specific targets (37).

Overarching NTD targets for 2030

- 90% fewer people requiring interventions against NTDs
- 75% fewer NTD-related DALYs
- 100 countries having eliminated at least one NTD
- 2 NTDs eradicated (dracunculiasis and yaws)

Cross-cutting targets as relating integrated approaches, multisectoral coordination, universal health coverage, and country ownership have also been articulated (37).

Of the 20 priority NTDs, only four in the current NTD roadmap are targeted for eradication and elimination by 2030. Eight are targeted for elimination as a public health problem, and nine are still only being targeted for control. Critical technical and service delivery gaps exist among 19 of the 20 NTDs (37). NTD interventions are one of the best buys in global public health. The end of NTDs is expected to result in an estimated net benefit to affected individuals of about 25 USD for every USD invested in preventive chemotherapy, and to contribute significantly towards universal health coverage and social protection for the least well-off (37).

The major NTDs which are caused by helminths are soil-transmitted helminthiases, schistosomiasis, lymphatic filariasis and onchocerciasis. These NTDs contribute to 45% of the global burden of NTDs.

Existing gaps within the global NTD response range from understanding disease epidemiology gaps in research which hinder progress towards achieving targets, and gaps in the availability of standardized and affordable point of care diagnostics (37).

Prevention

Despite being some of the most cost-effective

The neglected tropical diseases impose a devastating human, social and economic burden on 1.7 billion people worldwide.

PHOTO **FRIDA AGUILAR**

public health interventions, there are still significant gaps in preventive chemotherapy that include mass drug administration (MDA) for onchocerciasis, lymphatic filariasis, schistosomiasis, food-borne trematodiasis and scabies (37).

Diagnostics

The absence of rapid, user-friendly diagnostics has damaging implication on the effectiveness of surveillance systems for these NTDs. Critical diagnostic gaps exist for onchocerciasis, trypanosomiasis, leprosy and Buruli ulcer (37).

Treatment

The availability of effective treatments for many NTDs is a challenging issue exemplified by the poor quality antivenoms for snakebite envenoming, the toxic and expensive treatments for mycetoma often unavailable in endemic areas and the lack of an easy to administer topical and oral treatments for leishmaniasis (37,40).

Research and development

Till date, there are vaccines available for only dengue and rabies, and BCG used selectively for leprosy. The dengue vaccine is only licensed for people 9–45 years of age and can only be administered in persons with confirmed prior dengue virus infection. Thus, a preventive vaccine for all at-risk populations is needed (37).

Implementation research on how best to deliver preventive chemotherapy is required to help close NTD prevention gaps (37). Moreover, as with many infectious diseases, most medications lack adequate paediatric formulations and thus require further research (41). Research on effective therapeutic approaches in co-endemic locations is also needed to help minimize toxicity in patients with co-morbidities (42,43).

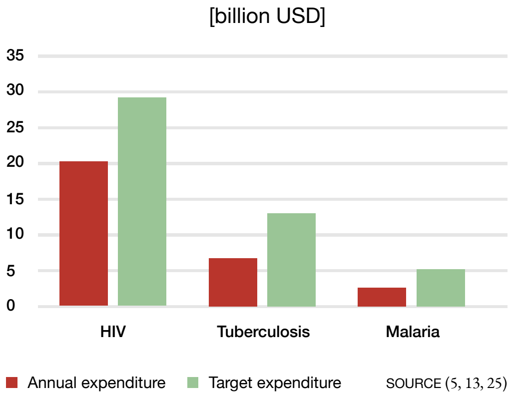
Service delivery gaps such as limited health worker capacity to diagnose clinically and treat various NTDs within the community also exist, as well as gaps in data systems, surveillance and supply chain.

Funding of prevention, diagnosis, treatment and care for HIV, TB, malaria and NTDs

Despite being some of the leading causes of death and disability, the global HIV, TB, malaria and NTD responses continue to face severe funding shortfalls and inadequate diversification of funding streams.

Funding gaps can exist as a shortfall in the amount of money targeted versus what is available, and in the percentage of the whole spent on a specific area versus the percentage that ideally should have been spent (Fig. 2).

FIG. 2 Actual annual expenditure and target annual expenditure



SOURCE (5, 13, 25)

HIV

Between 2017 and 2019, international funding for HIV in low- and middle-income countries has decreased by 7%. As of 2019, almost two-thirds of all financial resources available for the HIV response in low- and middle-income countries were from domestic sources (5). According to the UNAIDS financial estimates as of July 2020, the largest funding deficits for the HIV response were in West and Central Africa (32%) and Asia and the Pacific (26%).

The target set by UN member states to spend at least 25% of resources on effective prevention was not met. The bulk spend goes to testing and ART due to large populations of people infected with HIV in sub-Saharan Africa.

Tuberculosis

According to the Stop TB Partnership's Global Plan to End TB 2018–2022, 10.1 billion USD was required to fight TB in low- and middle-income countries in 2019. Of this, only 6.8 billion USD was available, 87% of which is from domestic funding. In 2019, there was a shortfall of 3.3 billion USD required to respond to TB in LICs and 77% of all international financing for TB came from the Global Fund (13,16).

Malaria

Of the estimated 5 billion USD needed to continue efforts to control and eliminate malaria, only 2.7 billion was available in 2018; a 14% reduction in available funding compared to 2017 (26).

In 2018, 47% of total funding for malaria was invested in LICs and 43% in lower-middle-income countries. International funding has been the primary source of funds in these countries; domestic funding has remained level since 2010—representing about 33% of total funding in 2018 (26).

NTDs

Funding NTDs are one of the most cost-effective global health interventions. Yet there is a considerable gap between money spent versus target expenditure. NTD funding has been stagnant over the past decade and was almost 10% lower in 2018 than it was in 2009, falling by 34 million USD (-9.1%). Though they affect 1 in 5 people, NTDs attract only 0.6% of development

FIG. 3

Percentage of research expenditure

Research expenditure 2018 (total 3623m USD)

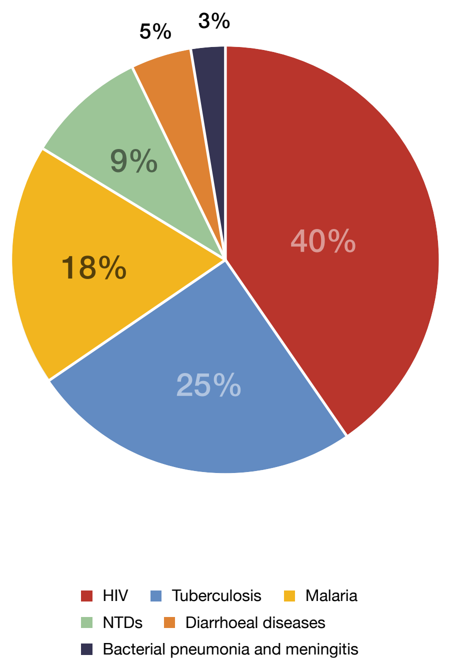
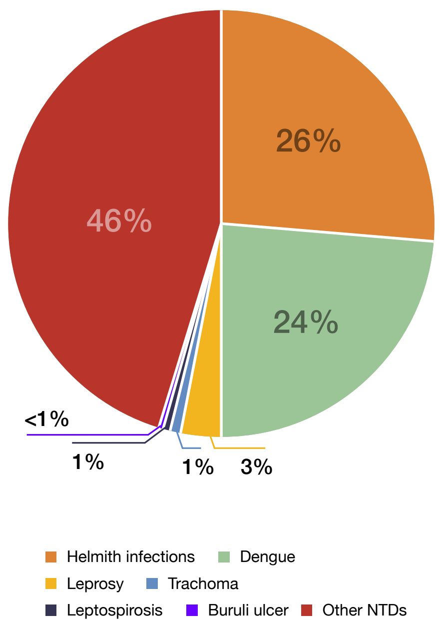


FIG. 4

Distribution of NTD research expenditure

NTD Research Expenditure 2018 (total 340m USD)



SOURCE Saha K, Mozumder S, Rampone D, Serhal S, Truong M, Their MW, et al. *Neglected Disease Research and Development: Uneven Progress* (45)

assistance for health and continue to remain somewhat neglected (45). In the current global health environment, with NTDs not having a »focused« funding mechanism, offsetting this trend seems very unlikely.

Research funding

To end the epidemics and to reach the SDG 3 targets, new tools in diagnostics, prevention, treatment and delivery models are urgently needed. Yet there is a huge funding gap; analysis by the Global Fund estimates that every dollar invested in HIV, TB and malaria results in 19 USD in health gains and economic returns (44).

Of the infectious diseases affecting the world's poor HIV/AIDS research and development receives by far the highest amount of research funding. In 2018 HIV/AIDS, malaria and TB collectively received more than two-thirds (2.8 million USD, 69%) of all global funding, and HIV/AIDS received more than double the amount compared to TB and malaria respectively (Fig. 3).

While funding for HIV/AIDS, TB and malaria research has increased, the research on all three diseases is still vastly underfunded, and funding for NTDs has been essentially flat for the past decade (47). The main research expenditure on NTDs is spent on a few diseases, with the helminth infections and Dengue dominating (Fig. 4). If this trend continues, there is little chance of meaningful progress in developing missing tools—especially drugs and vaccines, with some NTDs attracting only a meagre 2.0 million USD annually (37,46,48). The recent G-finder report on expenditure in 2019—just before the start of the COVID-19 pandemic, does not indicate much progress (46,47).

An example of the discrepancy between funding and actual need is the funding gap for TB. At the United Nations High-Level Meeting on TB in the fall of 2018, delegates endorsed a political declaration that contained a commitment to increase annual global TB research funding to 2 billion USD, which is double to what was spent in 2018. It could also be put in contrast with the amount of spending on COVID-19, reaching over 20 trillion USD in one year (49), resulting in effective diagnostics and vaccines, as well as some treatment options.

Even before the COVID-19 pandemic, the targets set up for infectious diseases were not achieved. While efforts to mitigate the effects of COVID-19 on other disease areas are of utmost importance, so is the COVID-19 response in itself.

PHOTO **ROBIN MUR**

HIV, TB, malaria and NTDs in the shadows of COVID-19

The declaration of COVID-19 as a Public Health Emergency of International Concern at the beginning of 2020, required health systems across the world to reorganize in order to respond effectively to the global crisis and at the same time maintain core functions to limit disruptions in care cascades for other diseases. This re-organization in many cases means fewer resources are available for other disease areas, of which HIV, TB, malaria and NTDs are not exempted.

Even before the COVID-19 pandemic, the targets set up for infectious diseases were not achieved. The Global Fund estimated in 2019 that since 2016 we are off track to fulfil the targets to eliminate the HIV, TB and malaria epidemics (Fig. 5).

Disruptions have occurred in almost all HIV, TB and malaria programmes across 106 countries, according to a recent Global Fund survey (50). Alarming figures such as a 59% decline in TB referrals, 41% decline in HIV testing, and a 31% decline in malaria diagnoses between April to September 2020, compared to the same six-month period in 2019 were noted (51). In addition to these, disruptions in essential services such as antenatal care and routine immunization campaigns for several childhood diseases have also occurred.

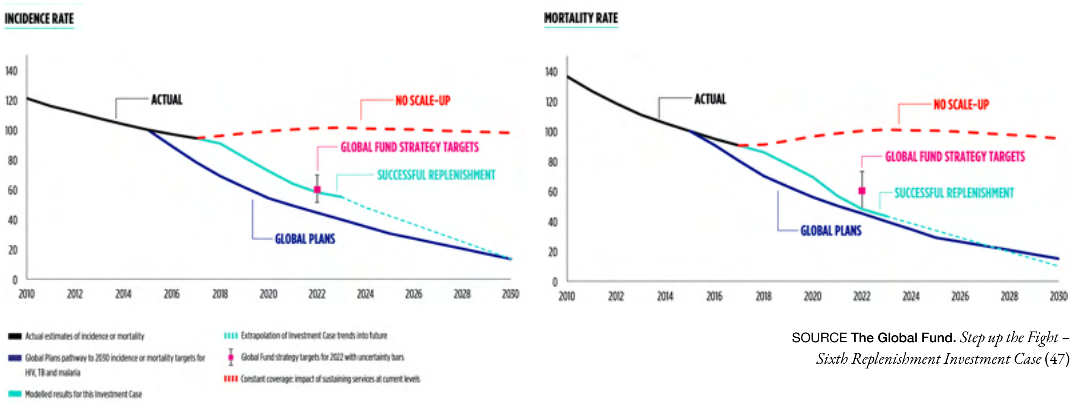
Mitigating the effect of COVID-19 on the response to these high burden infectious diseases is crucial in ensuring that decades of progress against HIV, TB, malaria and NTDs is not reversed, as the knock-on effects of COVID-19 could potentially double annual death tolls of malaria, HIV and TB (50).

According to the WHO, an estimated 38 billion USD is required to ensure global and equitable access to COVID-19 tests, treatments and vaccines. However, despite over 10 billion USD in contributions thus far, an additional 22 billion USD is required (52,53).

While efforts to mitigate the effects of COVID-19 on other disease areas are of utmost importance, so is the COVID-19 response in itself. Till date, an estimated 20.5 trillion USD has been invested, with over 100 vaccine candidates under

FIG. 5 **Combined trajectory of incidence and mortality**

Estimated trajectory of incidence and mortality of HIV/AIDS, TB and malaria depending on funding, according to the Global Fund in a 2019 report, i.e. before COVID-19. Lines are first normalized to 100 in 2015 for each disease, and then combined with equal weighting across the three diseases, separately for incidence and mortality rates.



SOURCE **The Global Fund.** *Step up the Fight – Sixth Replenishment Investment Case* (47)

Over 100 COVID-19 vaccine candidates under are under development. However, gaps still exist, including quick and reliable diagnostics and effective treatments. There are also disparities in access to testing services between poorer and richer countries.

PHOTO **FADIL FAUZI**

development and over 2,500 COVID-19 clinical trials registered globally. However, gaps still exist within the COVID-19 response, including quick and reliable diagnostics and effective treatments. There are also disparities in access to testing services between poorer and richer countries. For instance, countries like Nigeria and Ivory Coast have performed less than 20 tests per thousand people compared with countries like Australia and Denmark that have more than 100 tests per thousand people (54).

The sheer financial investment and the speed and scale of the global COVID-19 response show how much can be done in record time when priorities are aligned with political will. However, as health systems across the world respond to the COVID-19 pandemic, chronically underfunded and weak health systems in several low and middle-income countries are much less adequately positioned to respond effectively.

As with the HIV, TB, malaria, and NTDs, disease-specific approaches and investments in new tools alone will not suffice. While these are essential, simultaneous investments in health system strengthening and ensuring universal access to health services for those most at risk are pivotal in ensuring that lives and livelihoods are preserved and decades of progress is not lost.

Cross-cutting approaches to filling the gaps: universal health coverage and health systems strengthening

While health systems operate at national levels, COVID-19 has illustrated the need for a functional global health system. Pandemics do not respect international borders; thus, global health security is as strong as its weakest link. Inadvertently, gaps in disease response in one part of the world will affect other parts of the world. Also addressing gaps around health systems enablers such as water, sanitation and hygiene infrastructure and increased attention to climate change and pollution mitigation are necessary components of the global infectious disease response. As these actions will have far-reaching implications in reducing the spread of vector-borne diseases and other infectious diseases.

Strengthening health systems across its building blocks—service delivery, health workforce, data and information systems, research and development, leadership and governance, and financing—as a tool to simultaneously address emerging public health threats and infectious disease burden cannot be overemphasized. For instance, according to »Money and Microbes«, a report from the International Vaccines Task Force, investments in health workforce geared at improving local research capacity in low- and middle-income countries have been recommended as a crucial element of pandemic preparedness and a component of the global health security agenda (55). Strengthening health research capacity will also serve to improve healthcare in general by reducing mortality and morbidity due to disease and help in the drive towards universal health care and achievement of the SDGs.

Achieving universal health coverage plays a significant role in enhancing global health security. For example, higher immunization coverage diminishes the likelihood of disease outbreaks; and universal access to essential health services facilitates early alert in the event of an outbreak, potentially minimizing its effect. Likewise, access to population-wide health data allows for better healthcare planning and resource allocation, which in turn allows for better identification and focus on key populations.

Despite the cross-cutting benefits of health systems strengthening and the establishment of universal health coverage frameworks, the percentage of total development assistance for health allocated to health systems strengthening is down from 21% (1.6 billion USD) in 1990 to 14% (5.6 billion USD) in 2019 (56). As advanced economies contract due to the effects of the COVID-19 pandemic, there is a risk that official development assistance will plummet. During the current crisis, only a strong political commitment to global solidarity would safeguard and possibly increase development assistance.

Critical gaps still exist in the global response to the infectious diseases, for example poor access to HIV prevention services for young girls in sub-Saharan Africa.

PHOTO **ANNIE SPRATT**

Conclusions

Interim targets across HIV, TB, malaria and NTDs are off track, and critical gaps still exist in the global response to these diseases. Prevention gaps such as poor access to HIV prevention services for young girls in sub-Saharan Africa; diagnostic gaps such as the absence of rapid, user-friendly diagnostics for NTDs; treatment gaps such as the need for less toxic and shorter course treatments against drug-sensitive and resistant TB; and research gaps such as the absence of research and evaluation of resistant infections to available treatments and interventions continue to hamper the global response against these diseases.

Expanding access to effective diagnostics and treatment for these diseases is a crucial step that must be taken toward attaining 2030 targets. Bespoke preventative services targeted at key populations are some of the most cost-effective interventions against HIV and several other infectious diseases and must also be scaled up. Likewise, vaccine development, though expensive, has a good return on investment and should remain a research priority for these high burden infectious diseases.

Incorporating intersectional gender analyses and gender-sensitive approaches to the delivery of healthcare, such that it caters to nuances in how men, women and non-binary identities seek and access—or fail to access care must be anticipated and accommodated if indeed universal access to healthcare remains the goal. It is also crucial that programmes work with, for and by key populations to progressively eliminate barriers to health access.

The full impact of the COVID-19 pandemic across these diseases is still being evaluated but could have devastating impacts on each of them, potentially reversing decades of progress. Not only does COVID-19 require tremendous resources itself, in a shrinking global fiscal space, this means far fewer resources are available to continue responding to existing threats. Thus, it is vital that the COVID-19 response is delivered in a way that safeguards and reinforces existing health priorities.

To avoid a panic-neglect cycle, continuous investments in health systems strengthening are required alongside investments in pandemic preparedness, disease-specific interventions and local health research capacity development. While health systems strengthening efforts must be country-specific, they will have transnational implications with cross-cutting and longer-range benefits, and is an excellent way to address old and new threats simultaneously. Thus, health security efforts for prevention, alert, and response to disease outbreaks such as COVID-19 need to be pursued in parallel with health system strengthening, as part of a mutually reinforcing approach to developing resilient health systems globally.

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