Tuberculosis, HIV, malaria and neglected tropical diseases

Strengthening collaboration to prevent and manage antimicrobial resistance
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### Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviations</td>
<td>iv</td>
</tr>
<tr>
<td>Foreword</td>
<td>v</td>
</tr>
<tr>
<td>Executive summary</td>
<td>1</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>2</td>
</tr>
<tr>
<td>2. Background</td>
<td>3</td>
</tr>
<tr>
<td>2.1 Antimicrobial resistance</td>
<td>3</td>
</tr>
<tr>
<td>2.2 Sustainable Development Goals</td>
<td>3</td>
</tr>
<tr>
<td>2.3 How antimicrobial resistance affects the achievement of the Sustainable Development Goals</td>
<td>3</td>
</tr>
<tr>
<td>2.4 Global Action Plan on Antimicrobial Resistance</td>
<td>4</td>
</tr>
<tr>
<td>2.5 Ad hoc United Nations Interagency Coordination Group on Antimicrobial Resistance</td>
<td>5</td>
</tr>
<tr>
<td>2.6 WHO 13th General Programme of Work (2019–2023)</td>
<td>5</td>
</tr>
<tr>
<td>2.7 TB, HIV, malaria, neglected tropical diseases and antimicrobial resistance</td>
<td>6</td>
</tr>
<tr>
<td>3. Current antimicrobial resistance status: TB, HIV, malaria and relevant neglected tropical diseases</td>
<td>9</td>
</tr>
<tr>
<td>3.1 Factors driving antimicrobial resistance across disease areas</td>
<td>9</td>
</tr>
<tr>
<td>3.2 Tuberculosis</td>
<td>10</td>
</tr>
<tr>
<td>3.3 HIV</td>
<td>12</td>
</tr>
<tr>
<td>3.4 Malaria</td>
<td>13</td>
</tr>
<tr>
<td>3.5 Neglected tropical diseases</td>
<td>14</td>
</tr>
<tr>
<td>4. Preventing antimicrobial resistance related to TB, HIV, malaria and neglected tropical diseases and the WHO response</td>
<td>15</td>
</tr>
<tr>
<td>4.1 Preventing antimicrobial resistance</td>
<td>15</td>
</tr>
<tr>
<td>4.2 Surveillance of antimicrobial resistance</td>
<td>16</td>
</tr>
<tr>
<td>4.3 Laboratory networks</td>
<td>21</td>
</tr>
<tr>
<td>4.4 Communication, awareness-raising, education and training</td>
<td>23</td>
</tr>
<tr>
<td>5. Future directions</td>
<td>25</td>
</tr>
<tr>
<td>5.1 Identify research and development gaps and new tools and approaches</td>
<td>26</td>
</tr>
<tr>
<td>5.2 Clinical and programmatic indicators associated with and predicting the emergence of antimicrobial resistance</td>
<td>28</td>
</tr>
<tr>
<td>5.3 Joint support for countries</td>
<td>30</td>
</tr>
<tr>
<td>5.4 Identifying and optimizing synergy</td>
<td>31</td>
</tr>
<tr>
<td>5.5 Product pipelines</td>
<td>31</td>
</tr>
<tr>
<td>References</td>
<td>32</td>
</tr>
<tr>
<td>WHO antimicrobial resistance resources</td>
<td>34</td>
</tr>
<tr>
<td>Antimicrobial resistance – general</td>
<td>34</td>
</tr>
<tr>
<td>TB</td>
<td>34</td>
</tr>
<tr>
<td>HIV</td>
<td>35</td>
</tr>
<tr>
<td>Malaria</td>
<td>35</td>
</tr>
<tr>
<td>Neglected tropical diseases</td>
<td>36</td>
</tr>
</tbody>
</table>
Abbreviations

ACT  artemisinin-based combination therapy
AIDS acquired immunodeficiency syndrome
AMR  antimicrobial resistance
BBINS Bangladesh, Bhutan, India, Nepal, Sri Lanka
DNDi Drugs for Neglected Diseases initiative
FAO Food and Agriculture Organization of the United Nations
GAP  Global Action Plan on Antimicrobial Resistance
GLASS Global Antimicrobial Resistance Surveillance System
HANMAT Horn of Africa Network for Monitoring Antimalarial Treatment
HIV  human immunodeficiency virus
IACG Interagency Coordination Group on Antimicrobial Resistance
MDR-TB multidrug-resistant tuberculosis
MMV Medicines for Malaria Venture
NTD  neglected tropical disease
OIE  World Organisation for Animal Health
PEPFAR United States President’s Emergency Plan for AIDS Relief
PIAMNET Pakistan, Islamic Republic of Iran and Afghanistan monitoring network
RAVREDRA Red Amazónica para la Vigilancia de la Resistencia a las Drogas Antimaláricas network
RR-TB rifampicin-resistant tuberculosis
TB  tuberculosis
UNEP United Nations Environment Programme
USAID United States Agency for International Development
WHO  World Health Organization
XDR-TB extensively drug-resistant tuberculosis
Foreword

Antimicrobial resistance is one of the greatest health challenges of the 21st century, as recognized in the 2015 World Health Assembly resolution on antimicrobial resistance and the 2016 Political Declaration of the High-level Meeting of the United Nations General Assembly on Antimicrobial Resistance. If antimicrobial resistance is not addressed, it may contribute to millions of deaths per year and cost the world economy USD 1–3 trillion per year after 2030 (1). Drug-resistant TB, HIV, malaria and some neglected tropical diseases will make a substantial contribution to this burden. Antimicrobial resistance threatens to take us back to a time when common infections could not be treated and often led to sustained illness and death. To preserve the health gains of the past century, we will need to take effective and coordinated action.

WHO has recognized the importance of antimicrobial resistance in its 13th General Programme of Work, which requires all programmes at all levels of the Organization to address antimicrobial resistance as a cross-cutting issue. Antimicrobial resistance will impact the achievement of the triple billion targets, especially universal health coverage. The three objectives of universal health coverage including equity, quality and protection from financial risk will not be met without also effectively addressing antimicrobial resistance. Equally, universal health coverage also offers an excellent opportunity for preventing and managing antimicrobial resistance.

WHO is leading the fight to prevent and contain antimicrobial resistance in human health and has been working in close collaboration with the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE) (the FAO/OIE/WHO Tripartite Collaboration on Antimicrobial Resistance) and the United Nations Environment Programme (UNEP). The Tripartite organizations are working together through the Interagency Coordination Group on Antimicrobial Resistance (IACG) and reaffirmed their commitment to strengthen collaboration in a memorandum of understanding signed in May 2018. The IACG will issue a final report to the United Nations Secretary-General in 2019 that re-emphasizes the urgency and the need for a coordinated and stepped-up global response.

The Tripartite and UNEP have developed a One Health approach to managing antimicrobial resistance, as proposed in the Global Action Plan on Antimicrobial Resistance (GAP), launched in 2015. This plan focuses on the importance of strengthening systems for preventing and managing infection, with more appropriate use of antimicrobial agents, as well as strengthening systems for surveillance. One of the core elements of the GAP is to support countries to develop and implement comprehensive, One Health-oriented antimicrobial resistance action plans. As of January 2019, 117 countries have developed national antimicrobial resistance action plans with support from partners. WHO has also developed GLASS, the Global Antimicrobial Surveillance System.

Antimicrobial resistance is also a major challenge for TB, HIV and malaria and has the potential to adversely affect neglected tropical disease programmes. Sustainable Development Goal target 3.3 calls for ending the epidemics of these diseases by 2030. While antimicrobial resistance puts the achievement of many Sustainable Development Goals at risk, Sustainable Development Goal target 3.3 is especially affected, with antimicrobial resistance making treating these diseases more difficult and expensive.

TB, HIV, malaria and neglected tropical disease programmes have been working to address the antimicrobial resistance challenge for many years by focusing on supporting national and global surveillance networks, strengthening laboratory networks, optimizing diagnostic testing and treatment, raising awareness of the dangers of antimicrobial resistance and working with key stakeholders to drive product and service
delivery innovation. These same interventions are core components of strategies to prevent and manage antimicrobial resistance across the human health spectrum. Lessons learned and good practices gained from experience in preventing and managing antimicrobial resistance in these diseases can be adapted and used to strengthen antimicrobial resistance approaches in other settings.

Current opportunities exist to strengthen antimicrobial resistance collaboration at the country level by identifying and strengthening programmatic synergies that underpin strategies for preventing and managing antimicrobial resistance. This will require, for example, ensuring that countries develop and implement comprehensive, antimicrobial resistance action plans that include TB, HIV, malaria and neglected tropical diseases where relevant. Achieving this requires a coordinated effort, working in partnership, involving all stakeholders at the global, regional, country and service delivery levels. Preventing and managing antimicrobial resistance will truly require sustained efforts and global collaboration.

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Executive summary

There is global commitment to address antimicrobial resistance through the Global Action Plan on Antimicrobial Resistance. High-impact communicable diseases, including tuberculosis (TB), human immunodeficiency virus (HIV), malaria and neglected tropical diseases (NTDs), should be integrated into and aligned with global antimicrobial resistance efforts.

Antimicrobial resistance puts achievement of Sustainable Development Goal 3 and other Sustainable Development Goals at risk, making effectively treating diseases more difficult and costly and leading to more illness and deaths.

Lessons learned from addressing antimicrobial resistance in TB and the other diseases during the past 20 years provide useful guidance for other antimicrobial resistance programmes in earlier stages of development, including:

- recognizing at an early stage the antimicrobial resistance challenge and advocating and mobilizing global development partners to address it;
- establishing a global antimicrobial resistance surveillance system;
- establishing direct drug resistance testing for individual patients, providing data for population-based surveillance;
- expanding and strengthening national and regional laboratory networks;
- strengthening country capacity for managing antimicrobial resistance;
- reaching out to stakeholders at all levels through a public–private mix, including engaging pharmacies and health-care providers to provide training on testing and treatment protocols; and
- establishing product development partnerships and research consortiums to facilitate the introduction of new pipeline drugs, review new drug formulations and develop improved diagnostic tests to detect antimicrobial resistance.
1. Introduction

The purpose of this report is to provide a brief overview of the status of antimicrobial resistance in high-impact communicable diseases (TB, HIV, malaria and some neglected tropical diseases) and to present some areas in which strengthened efforts will be required in the future and more collaborative programme design may generate efficiency and strengthened systems for addressing antimicrobial resistance more widely. This overview includes a summary of the current antimicrobial resistance situation by disease, current prevention and response efforts in antimicrobial resistance and a future directions section examining opportunities for strengthening collaboration among disease and other antimicrobial resistance programmes.

The report captures key messages in each area and is aimed at technical and funding partners, global and national policy-makers and other relevant stakeholders.
2. Background

2.1 Antimicrobial resistance
Antimicrobial resistance (AMR) occurs when microorganisms such as bacteria, viruses, parasites and fungi develop resistance to antimicrobial agents. Although this is a natural phenomenon, the inappropriate and excessive use of antimicrobial agents can increase the pace and spread of antimicrobial resistance development. Diseases caused by resistant microorganisms are more difficult to treat.

Rising levels of drug resistance are a risk to the success of human immunodeficiency virus (HIV), tuberculosis (TB) and malaria programmes. Microorganisms that are resistant to antimicrobial agents threaten the successful management of infections, safe surgery and cancer treatment. Coinfection with resistant microorganisms poses heightened risks for people with TB and HIV (2).

2.2 Sustainable Development Goals
The United Nations adopted the Sustainable Development Goals (3) in September 2015. These reflect the growing complexity and interdependence of the global development agenda. The Sustainable Development Goals establish 17 global goals that have 169 specific targets, and if they are achieved by 2030 they will help to ensure the sustainability of economic and social development. Sustainable Development Goal 3 focuses on ensuring good health and well-being and covers infectious and noncommunicable diseases. Target 3.3 calls for ending by 2030 the epidemics of AIDS, TB, malaria and neglected tropical diseases and reducing the incidence of hepatitis, waterborne diseases and other communicable diseases. Sustainable Development Goal target 3.8 calls for universal health coverage (4), which is defined as ensuring that all people have access to needed health-care services (including disease prevention, health promotion, treatment, rehabilitation and palliation) of sufficient quality to be effective while also ensuring that the use of these services does not expose the user to financial hardship.

2.3 How antimicrobial resistance affects the achievement of the Sustainable Development Goals
Antimicrobial resistance is a substantial threat to several of the wider development goals, such as economic growth, poverty reduction and sustainable production and consumption (Fig. 1). Progress towards other goals, such as Sustainable Development Goal 6 on water and sanitation and Sustainable Development Goal 17 on working in partnership will make important contributions to addressing antimicrobial resistance. However, the greatest threat will be to Sustainable Development Goal 3, human health. Antimicrobial resistance will make it harder to treat the diseases and lead to increased sickness, more protracted hospital stays and more deaths. The World Bank has estimated that health-care costs could increase by 25% in low-income countries in their worst-case scenario and reduce global gross domestic product (GDP) by 1–4% annually by 2050 (1). The spread of antimicrobial resistance could slow progress towards achieving Sustainable Development Goal 3.3 targets for TB, HIV, malaria and potentially some specific neglected tropical diseases if it is not managed or contained. Antimicrobial resistance will also dramatically increase the costs of providing health-care services. For example, the second- and third-line HIV treatments are 3 and 14 times more expensive, respectively, than first-line treatments (1) and lead to more negative outcomes. Treating extensively drug-resistant TB (XDR-TB) takes up to two years,
and the drugs and treatment required cost nearly six times more than treatments for non-resistant TB (5). Among extensively drug-resistant TB cases starting treatment globally in 2015, only 34% completed it or were cured (versus 82% with drug-sensitive strains), and in 45% the treatment failed or the person died (5). As noted in subsection 3.3 and Fig. 10, the emergence of HIV drug resistance threatens to reduce the gains in morbidity and mortality anticipated by a “treat all” approach and the scale-up of pre-exposure prophylaxis.

2.4 Global Action Plan on Antimicrobial Resistance

The World Health Assembly adopted the Global Action Plan on Antimicrobial Resistance (6) in May 2015, and the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) endorsed it. The Global Action Plan on Antimicrobial Resistance covers antibiotic resistance in most detail but also refers, where appropriate, to existing action plans for viral, parasitic and bacterial diseases, including HIV, malaria and tuberculosis. The Global Action Plan on Antimicrobial Resistance provides the framework for developing multisectoral national
action plans to combat antimicrobial resistance. It sets out the key actions that the various actors involved should take to combat antimicrobial resistance, using an incremental approach over the next 5–10 years. The TB, HIV, malaria and neglected tropical diseases antimicrobial resistance work is aligned with the five objectives of the Global Action Plan:

- to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
- to strengthen the knowledge and evidence base through surveillance and research;
- to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
- to optimize the use of antimicrobial medicines in human and animal health; and
- to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

2.5 Ad hoc United Nations Interagency Coordination Group on Antimicrobial Resistance

The United Nations Secretary-General has established the United Nations Interagency Coordination Group on Antimicrobial Resistance (IACG) (7) to improve coordination between international organizations and to ensure effective global action against this threat to health security. The IACG is co-chaired by the United Nations Deputy Secretary-General and the WHO Director-General and comprises high-level representatives of relevant United Nations agencies, other international organizations and individual experts across different sectors. The IACG’s mandate is to provide practical guidance for approaches needed to ensure sustained, effective global action to address antimicrobial resistance; and to report back to the United Nations Secretary-General in 2019. WHO hosts the IACG Secretariat with contributions from the Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE). WHO is responsible for addressing antimicrobial resistance in relation to human health including TB, HIV, malaria and relevant neglected tropical diseases. The longstanding FAO/OIE/WHO Tripartite Collaboration on Antimicrobial Resistance was further strengthened through the signature of a memorandum of understanding in May 2018. The Tripartite agencies and the United Nations Environment Programme (UNEP) are actively working together to support a global multisectoral response to antimicrobial resistance, including implementing the IACG recommendations working with Member States, civil society and the private sector.

2.6 WHO 13th General Programme of Work (2019–2023)

The WHO 13th General Programme of Work for 2019–2023 (8) is structured around three interconnected strategic priorities to ensure healthy lives and well-being for all at all ages. The goals are:

- 1 billion people benefiting from universal health coverage;
- 1 billion more people better protected from health emergencies; and
- 1 billion more people enjoying better health and well-being.

Addressing antimicrobial resistance will contribute to all three goals. The 13th General Programme of Work provides the framework for positioning communicable diseases efforts in support of universal health coverage. Both ending the epidemics of high-impact communicable diseases (HIV, TB, malaria and neglected tropical diseases, Fig. 2–5) and preventing and managing antimicrobial resistance are priorities in the 13th General Programme of Work and need to be addressed horizontally across all relevant WHO programmes at all levels of the Organization. The 13th General Programme of Work Impact Framework has specific targets for TB, HIV, malaria and neglected tropical diseases; a target to increase the detection and treatment rates for rifampicin-resistant TB (including multidrug-resistant TB (MDR-TB) or combined resistance to at least rifampicin and isoniazid) to 80% by 2023, and targets to reduce the prevalence of resistant bloodstream infections and
improve the proportion of people with access to antibiotics.

2.7
TB, HIV, malaria, neglected tropical diseases and antimicrobial resistance

Antimicrobial resistance has long posed challenges for managing TB, HIV, malaria and some neglected tropical diseases. Drug-resistant TB is a public health crisis and a health security threat; drug resistance in HIV is a growing challenge and threatens progress to end the epidemic as a public health threat by 2030. In the past, widespread resistance to chloroquine and other drugs led to malaria resurgence and continuing epidemics in many countries and areas. As a consequence of having to address antimicrobial resistance challenges for many years, TB, HIV, malaria and neglected tropical disease programmes have refined their drug resistance management and control strategies to reflect reality on the ground and lessons learned. Unfortunately, strategies for managing and controlling drug resistance related to these diseases have sometimes been implemented separately in the context of each individual disease programme and not under the overall umbrella of antimicrobial resistance. Elements that underpin many of the disease-specific interventions to prevent, detect and manage drug resistance also apply to non-disease-specific antimicrobial resistance management programmes. Better integrating TB, HIV, malaria and neglected tropical disease drug resistance programmes into other antimicrobial resistance efforts would help to strengthen the overall response to antimicrobial resistance and maximize synergy in such areas as surveillance, laboratory strengthening, monitoring and evaluation, procurement and supply chain management, developing human resource capacity and the quality of health services delivered.

FIG. 2
Estimated TB incidence rates by country, 2017

Source: Global tuberculosis report 2018 (5).
FIG. 3
HIV prevalence among people 15–49 years old by country, 2017


FIG. 4
Number of malaria cases by country, 2017

FIG. 5

Number of people requiring treatment and care for neglected tropical diseases by country, 2017

Source: World Health Organization, Department of Control of Neglected Tropical Diseases, 2019.
3. Current antimicrobial resistance status: TB, HIV, malaria and relevant neglected tropical diseases

KEY MESSAGES
- TB drug resistance is a major cause of antimicrobial resistance mortality and morbidity worldwide, and immediate action is required to prevent the further development and spread of resistance.
- Resistance of HIV to efavirenz and nevirapine, the most common first-line drugs, is a current global health threat leading to poor health outcomes such as treatment failure, mortality and increased programme costs and requires urgent action to be taken now to prevent the further development and spread of resistance.
- Malaria drug resistance constitutes a challenge particularly in the Greater Mekong subregion. Drug resistance has developed to artemisinin and some partner drugs used in artemisinin-based combination therapies, making treatment of people with \textit{Plasmodium falciparum} malaria difficult. The risk of importing or developing resistance in the malaria-endemic countries in the rest of the world is a concern, and surveillance of drug efficacy is a high priority.
- Some drug resistance has been identified in neglected tropical diseases caused by bacteria (leprosy and yaws) and a parasite (visceral leishmaniasis). The resistance observed has been at low levels and does not apply to all available treatments. Drug resistance has not yet been observed in helminths that primarily infect humans.
- Antimicrobial resistance is also a phenomenon in other pathogens (such as non-specific bacteria and fungi) that may cause secondary infection in people with TB and HIV. Rising drug resistance levels in bacteria causing common acute infections in humans have been well documented, undermining the ability to treat these infections.

3.1 Factors driving antimicrobial resistance across disease areas

Antimicrobial resistance occurs when drugs (antibiotics, antifungal agents, antiviral agents, antimalarial agents and anthelmintic agents) used to treat infections by microorganisms such as bacteria (TB, leprosy and non-specific bacteria), fungi, viruses (HIV) and parasites (malaria, soil-transmitted helminths and trematodes) kill most of the organisms, but sometimes not all, leaving a small subset of resistant microorganisms that survive. The surviving populations can then multiply, allowing infections to persist in the body, potentially leading to increased morbidity and mortality and increasing the risk of transmitting the resistant organisms to other people. Non-targeted organisms are also affected and can be exposed to antimicrobial residues in the environment from hospitals, pharmaceutical production and agricultural activities. Genes for antimicrobial resistance can be transferred between bacteria in the environment (such as from non-pathogenic species to pathogenic species). Antimicrobial resistance in populations of microorganisms is selected over time based on exposure to specific drugs. The misuse and overuse of antimicrobial
agents accelerate this process (2).

Leading causes of antimicrobial resistance related to these diseases include:

- poor treatment practices, such as treatment interruption because of failure to adhere to prescribed treatment; stock-outs or interrupted access to key drugs; use of monotherapies or substandard medicines; unregulated or informal use of drugs without prescriptions; lack of effective drugs; use of inappropriate drugs to treat illnesses (such as artemisinin-based combination therapy to treat non-malarial febrile illnesses and antibiotics to treat viral infections); and non-optimal use of antibiotics (such as inadequate regimens or effective monotherapy to treat TB);
- failure to identify drug-resistant pathogens, resulting in ineffective treatment and delayed switch to more effective drugs and the potential spread of the resistant pathogens; and
- inadequate disease prevention interventions, including poor infection control practices.

### 3.2 Tuberculosis

The TB bacteria can develop resistance to one, two or more antimicrobial drugs used to cure the disease, leading to rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB). Extensively drug-resistant TB has been reported in 127 countries. MDR-TB is a public health crisis and global health security threat (5).

In 2017, MDR-TB or RR-TB caused 558 000 new cases (3.5% of new cases and 18% of previously treated cases) and 230 000 deaths (Fig. 6). Only 25% of the estimated MDR-TB cases (139 114) were treated, of which 55% that started treatment completed it or were cured (5) (Fig. 6).

Three countries accounted for almost half of the world’s cases of multidrug-resistant or rifampicin-resistant TB: India (24%), China (13%) and the Russian Federation (10%). Globally, 3.5% of new TB cases and 18% of previously treated cases had multidrug-resistant or rifampicin-resistant TB (Fig. 7 and 8). The highest proportions (>50% in previously treated cases) are in countries of the former USSR.

Among cases of multidrug-resistant TB in 2017, an estimated 8.5% had extensively drug-resistant TB (5).

Multidrug-resistant TB is increasing as a proportion of all TB cases in some countries with a high burden of TB, with the burden either increasing faster or decreasing more slowly than the overall TB burden (5).
FIG. 7

Percentage of new TB cases with multidrug-resistant or rifampicin-resistant TB

* Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2002–2018. Source: Global tuberculosis report 2018 (5).

FIG. 8

Percentage of previously treated TB cases with multidrug-resistant or rifampicin-resistant TB

* Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2005–2018. The high percentages of previously treated TB cases with RR-TB in Belize, Guam and Sao Tome and Principe refer to only a small number of notified cases (range: 1–8 notified previously treated TB cases). Source: Global tuberculosis report 2018 (5).
HIV drug resistance is caused by a change (mutation) in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block the replication of the virus. All current antiretroviral drugs are at risk of becoming partly or fully inactive because of the emergence of resistant virus. HIV drug resistance jeopardizes the success of HIV treatment and endangers the attainment of the global targets to end the AIDS epidemic as a public health threat. The emergence of HIV drug resistance threatens the success of the “treat all” approach for HIV because resistance is more likely to lead to illness and potentially death (6).

HIV drug resistance is increasing across all WHO regions, with the yearly increases greatest in eastern and southern Africa (Fig. 9). Pretreatment resistance to the most commonly used first-line drugs (efavirenz and nevirapine) has reached the level of 10%1 or greater among people initiating HIV treatment in many low- and middle-income countries assessed (6).

Women are at great risk of carrying a virus with pretreatment resistance, posing a challenge to eliminating the mother-to-child transmission of HIV and to maternal and child health outcomes; about 50% of children newly diagnosed with HIV are infected with a virus resistant to commonly used first-line drugs (6).

Modelling has predicted that, if resistance to the most common first-line drugs exceeds 10% among people starting HIV therapy in sub-Saharan Africa, in 15 years pretreatment drug resistance could be responsible for cumulatively 16% of deaths from AIDS-related causes (890 000 deaths), 9% of the

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1 WHO guidelines on HIV drug resistance recommend that countries with levels of pretreatment resistance to efavirenz or nevirapine at or above 10% urgently consider using other HIV drugs in first-line regimens.
people acquiring HIV infection (450,000 people) and a programme cost of US$ 6.5 billion in sub-Saharan Africa (Fig. 10). Several low- and middle-income countries are currently transitioning to new regimens in first-line treatment to which resistance is expected to be low (6).

Drug resistance may also be a challenge in some of the opportunistic infections that affect people with HIV, such as TB, cryptococcal meningitis (9), sexually transmitted infections and candidiasis (10).

### 3.4 Malaria

Malaria is caused primarily by the *Plasmodium falciparum* and *P. vivax* parasites. Artemisinin-based combination therapy (ACT) is used to treat *P. falciparum* and chloroquine-resistant strains of *P. vivax*. Chloroquine- or ACTs, complemented with primaquine, are recommended for treating *P. vivax* in areas with chloroquine-susceptible infections (12).

The scale-up of ACTs has been integral to the recent success of global malaria efforts and protecting their efficacy in treating malaria is a global health priority. The efficacy of artemisinin-based combination therapy is threatened by the emergence of both artemisinin and partner drug resistance. Partner drug resistance can arise independently of artemisinin partial resistance. Partner drug resistance with or without artemisinin partial resistance increases the risk of treatment failure, and association of artemisinin resistance will worsen the treatment failure rate (12).

Artemisinin partial resistance is currently limited to five countries of the Greater Mekong subregion: Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam (Fig. 11) and is suspected in Guyana, Papua New Guinea and Rwanda. Artemisinin partial resistance has not been confirmed in Africa; multi-drug resistance is present in Cambodia, the Lao People’s Democratic Republic, Thailand and Viet Nam (12).

*P. vivax* resistance is geographically widespread, but in many countries the parasite is still susceptible to chloroquine, especially when primaquine is taken concurrently. *P. vivax* resistance to

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2 Multidrug-resistant malaria is defined as resistance to more than two antimalarial compounds of different chemical classes. This term usually refers to *P. falciparum* resistance to chloroquine, sulfadoxine-pyrimethamine and a third antimalarial compound.
artemisinin-based combination therapy has not been documented and thus artemisinin-based combination therapy can be used where there is extensive chloroquine resistance (12).

WHO recommends that countries change their first-line treatments for *P. falciparum* and *P. vivax* when treatment failure rates exceed 10% (12).

### 3.5 Neglected tropical diseases

Neglected tropical diseases (13) are a diverse group of 20 different diseases that mostly affect low-income and marginalized populations. For many neglected tropical diseases, the risk of developing resistance to treatment is considered low because of the nature of the diseases (such as parasites with relatively long life cycles) or because no treatments are available to become resistant to (such as dengue, rabies, etc). Some drug resistance has been identified for neglected tropical diseases caused by bacteria – such as leprosy and yaws – and a parasite: visceral leishmaniasis. The resistance observed has been at low levels and does not apply to all available treatments. Drug resistance has not yet been observed for helminths that primarily infect humans.

Antibiotic resistance to at least one of the three antibiotics used to treat leprosy has been detected in 19 countries. Eight per cent of the bacteria were resistant to at least one commonly used antibiotic. Resistance to two different antibiotics was identified in 24 cases. Drug resistance was observed in 12 countries among 5.1% of relapses and 2.0% of new cases. Three countries (Brazil, Colombia and India) reported more than five resistant cases. The numbers of resistant cases are still low, and no bacterial strain has yet shown resistance to all three antibiotics simultaneously (14).

Drug resistance has been reported to some first-line medicines used to treat yaws (15) and visceral leishmaniasis (16).

The strategies for preventing and treating trachoma and yaws call for mass administration of the antibiotic azithromycin to populations at risk (17,18). This intervention can lead to increases in drug resistance related to non-targeted potentially pathogenic bacteria (such as *Streptococcus pneumoniae*). Care is therefore required to plan the mass drug administration to minimize the potential for increasing drug resistance related to non-targeted bacteria (19).

Anthelmintic resistance is not yet a public health problem in human helminthiasis, where mass drug administration is a recommended intervention (schistosomiasis, onchocerciasis, lymphatic filariasis and soil-transmitted helminthiasis), but resistance is problematic in helminths of veterinary importance, indicating that resistance could develop (20).
4. Preventing antimicrobial resistance related to TB, HIV, malaria and neglected tropical diseases and the WHO response

**KEY MESSAGES**

- Achieving universal health coverage and strengthening health systems are key factors for preventing antimicrobial resistance across all diseases and service delivery areas.
- For TB, HIV, malaria and neglected tropical diseases, antimicrobial resistance often can be predicted, prevented, managed and controlled by maintaining focus on it and developing and implementing the right strategies.
- Drug resistance is often a marker of poor-quality treatment service delivery, and identifying and addressing quality gaps is important for preventing resistance.
- Surveillance, laboratory strengthening and expansion of laboratory services, enhanced data collection and use and better communication, awareness-raising, education and training are key components of all strategies for preventing and managing antimicrobial resistance and could be expanded to synergistically address antimicrobial resistance across all disease and service delivery areas.
- Addressing infectious diseases and antimicrobial resistance within the context of universal health coverage in a more integrated way offers opportunities for efficiency and better outcomes.

### 4.1 Preventing antimicrobial resistance

Preventing drug resistance is a critical component of any national communicable disease programme and is achieved by optimizing service delivery and eliminating programmatic gaps in disease prevention, treatment and care. WHO regularly updates its guidelines to optimize service delivery to prevent and treat TB, HIV, malaria and neglected tropical diseases. General disease prevention reduces both the overall disease burden and the transmission of sensitive and resistant pathogens – thus affecting the spread of antimicrobial resistance. WHO also produces specific guidance for managing drug-resistant infections. These include: policy recommendations on the overall public health response required; clinical and programmatic guidance on selecting the most appropriate interventions and treatment regimens, including diagnostic and drug resistance testing; managing programmes and rationally using medicines; and possible recommendations on restricting access to drugs by prescription or using combination therapies. WHO policy and recommendations are informed by programmatic data on access to and use of preventive measures, resistance surveillance and efficacy data and are routinely updated on the prevention, diagnosis and treatment of TB, HIV, malaria and neglected tropical diseases. WHO also produces guidance on other interventions and supporting programmes to better manage antimicrobial resistance in general, such as preventing and controlling infections in clinical settings, water, sanitation and hygiene in clinical settings, procurement and supply chain management, prequalification of drugs and other areas. Table 1 highlights examples of WHO activities to identify, prevent and manage antimicrobial resistance.
Preventing antimicrobial resistance also requires strengthening health systems to provide the needed products and services to people at the time they are required: for example, including critical, quality-assured medicines on lists of essential medicines; ensuring functioning supply chains that deliver the required medicines to health-care facilities; preventing stock-outs and treatment disruption; and ensuring that clinical personnel have the necessary tools (such as treatment algorithms) to enable them to effectively identify and treat a wide range of illnesses with the appropriate drugs. For example, expanded use of malaria rapid diagnostic tests does not always lead to the right treatment outcome. Artemisinin-based combination therapy is sometimes still given to patients with negative tests or antibiotics are provided to treat fever without confirmation that bacteria are the cause (21). This leads to potential misuse and overuse of artemisinin-based combination therapy or antibiotics and increased risk of drug-resistant malaria parasites or non-specific bacteria. For chronic diseases such as HIV, resistance can be prevented by national and clinic-based strategies that support optimal adherence to treatment and retention in care.

4.2 Surveillance of antimicrobial resistance

Surveillance involves collecting, analysing and interpreting epidemiological data on antimicrobial resistance. Data can be collected from surveys that cover selected populations or at the individual level from routine data provided by health facilities and laboratories. Surveillance is critically important for monitoring trends and developing evidence-informed policies and interventions to prevent and manage antimicrobial resistance.

In the past decades, WHO has helped to establish global, regional and country-level surveillance systems to monitor drug resistance and therapeutic efficacy trends in TB, HIV, malaria and neglected tropical diseases (Boxes 1–4). Overall, WHO supports drug resistance and therapeutic efficacy surveillance activities in nearly all affected countries: 160 countries for multidrug-resistant TB, 69 countries for HIV drug resistance and 64 countries for malaria, representing most of the world’s population and most of the burden of high-impact communicable diseases. Drug resistance status and trends for these diseases are routinely published in disease-specific reports and in peer-reviewed publications.

To support the second strategic objective of the Global Action Plan on Antimicrobial Resistance to strengthen the knowledge and evidence base through surveillance and research, WHO launched the Global Antimicrobial Resistance Surveillance System (GLASS) in October 2015 and started country enrolment in March 2016. GLASS fosters the development of national antimicrobial resistance surveillance systems and provides a standardized approach to collecting, analysing and sharing antimicrobial resistance data for bacteria causing common acute infections. To date, 72 countries participate in GLASS (22).

As a core function of disease-specific programmes, WHO surveillance activities include:

- developing standardized methods and tools for antimicrobial resistance surveillance, data collection and analysis;
- routinely collecting, quality assuring, analysing and disseminating surveillance data on drug resistance and therapeutic efficacy and resistance trends at the global, regional and national levels;
- using surveillance data to inform WHO guidelines and national treatment policies;
- providing guidance on appropriate programme indicators associated with and predictive of resistance to be included in health information systems;
- providing a framework for early detection and reporting of emerging antimicrobial resistance;
- building global data repositories, country databases and portals to support countries in storing, quality assuring and disseminating their data in a timely fashion; and
- providing technical support to countries in designing and conducting drug resistance and therapeutic efficacy studies and surveys and in collecting, quality assuring, analysing, interpreting and disseminating their data.
### TABLE 1

**Pathogen resistance, resistance monitoring and WHO activities**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Status of resistance</th>
<th>Literature review</th>
<th>Nationally and regionally representative surveys</th>
<th>Collection and use of routine drug resistance data</th>
<th>Therapeutic efficacy studies at sentinel sites (parasite clearance)</th>
<th>Culture</th>
<th>Molecular methods (gene probes, sequencing)</th>
<th>Global monitoring and reporting</th>
<th>Standardized protocols and tools for drug resistance surveillance, data collection, analysis and interpretation</th>
<th>Global database</th>
<th>Global laboratory networks with WHO designation</th>
<th>Technical assistance for countries to implement drug resistance surveys and studies</th>
<th>Early warning indicators for drug resistance emergence</th>
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<tbody>
<tr>
<td>HIV</td>
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<td>Mycobacterium tuberculosis (TB)</td>
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<td>Mycobacterium leprae or lepromatosis (leprosy)</td>
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<td>Treponema pallidum (yaws)</td>
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<td>Leishmania donovani (visceral leishmaniasis)</td>
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<tr>
<td>Helminths (soil-transmitted helminthiasis)</td>
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<td>Helminths (schistosomes)</td>
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</table>

- **Green** = no documented resistance; **orange** = drug resistance documented but not widespread or remains regionally confined; **red** = drug resistance as current global health threat.
- Interventions require mass drug administration with the same antibiotic azithromycin; mass use has led to drug resistance in yaws bacteria and other pathogenic bacteria but not trachoma bacteria.
- Anthelminthic drug resistance has been observed in helminths that infect domestic animals but not yet in strains that primarily infect humans.
- Under development.
BOX 1

Surveillance of resistance to TB

Established in 1994, the global surveillance system for TB drug resistance remains the oldest and largest initiative on antimicrobial resistance surveillance in the world (Fig. 12). TB Surveillance data are being collected either (1) through continuous surveillance systems based on routine testing of everyone with TB in countries with extensive laboratory capacity or (2) through periodic surveys, which are discrete studies measuring drug resistance among a selected sample of people who are representative of an entire population of people with TB in countries with insufficient laboratory capacity for routine drug susceptibility testing of everyone with TB.

Standardized methods allow comparability of data within countries over time and between countries. Surveillance data on TB drug resistance are collected annually through a web-based data collection tool that gathers notification data on everyone with TB worldwide. On average, 15 country surveys are conducted every year. New molecular technologies, including whole-genome sequencing technologies, have recently been incorporated into drug resistance surveys. Since 1994, data on drug resistance have been systematically collected and analysed from 165 countries (82% of the 194 WHO Member States), which collectively represent more than 97% of the world’s population and TB cases (23,24).
**Surveillance of HIV drug resistance**

The emergence and transmission of some level of HIV drug resistance is inevitable, even when appropriate regimens are prescribed and adherence to treatment is optimal. To address this challenge, WHO developed a global strategy for the surveillance and monitoring of HIV drug resistance in 2004 and updated it in 2015. The strategy includes four key activities: (1) annual monitoring of quality-of-care indicators of HIV drug resistance at all antiretroviral therapy clinics in a country; (2) surveillance of pretreatment HIV drug resistance among adults initiating first-line antiretroviral therapy; (3) surveillance of acquired HIV drug resistance in adults and children receiving treatment; and (4) surveillance of HIV drug resistance among children younger than 18 months newly diagnosed with HIV.

Survey data were generated from sentinel clinics from 2004 to 2014, but since 2014, nationally representative HIV drug resistance methods have been recommended. The data generated from the HIV drug resistance surveys are representative of the entire population of individuals with HIV initiating HIV treatment or receiving HIV treatment, respectively.

Since 2004, data from 271 surveys in 69 countries have been collected using standardized epidemiological and laboratory methods, allowing comparability of data within countries over time and across countries (Fig. 13).

The survey results have been used to inform policies and treatment guidelines at the national and global levels.

Quality assurance and dissemination of HIV drug resistance data are core activities of WHO. Surveillance data for HIV drug resistance are entered and safely stored in the WHO global HIV drug resistance database, which has three main purposes: (1) supporting countries and genotyping laboratories in the quality assurance of epidemiological and sequence data for the purpose of generating high-quality country reports; (2) providing standardized resistance interpretations by linking to the most recent algorithm for interpreting HIV drug resistance; and (3) providing countries with a long-term secure repository for their HIV drug resistance data (25,26).

A global network of WHO-designated laboratories for HIV drug resistance supports the global effort by producing reliable and quality-assured genotypic data.
**Surveillance of antimalarial drug efficacy**

WHO set up surveillance of antimalarial drug efficacy in 1996 with the development of a standard protocol to monitor antimalarial efficacy through therapeutic efficacy studies in collaboration with the United States Centers for Disease Control and Prevention. The protocol was first implemented in areas with high malaria transmission rates, mainly in Africa. Later the standard protocol was updated twice to include countries with low to moderate malaria transmission rates. WHO has developed a series of tools (including in vitro tests, molecular analysis and measuring drug concentrations) to better define and detect drug resistance among treatment failures. The use of these standardized procedures facilitates the comparison of results within and across regions over time. WHO organizes training at the regional and country levels on drug efficacy monitoring and continually supports regional networks on drug efficacy (27).

WHO set up a global database in response to the challenges posed by the emergence of resistance to antimalarial drugs. The contents of the database are extracted from published and unpublished therapeutic efficacy studies and surveys of molecular markers on antimalarial drug resistance conducted by partners at the country level. The database is the source for WHO’s online Malaria Threats Map, the *World malaria report* and update reports on antimalarial drug efficacy and drug resistance.

WHO has provided support in creating subregional networks for monitoring antimalarial resistance. The Mekong network, the Red Amazónica para la Vigilancia de la Resistencia a las Drogas Antimaláricas (RAVREDRA) network, the Pacific network, the BBINS (Bangladesh, Bhutan, India, ...
Nepal, Sri Lanka) network, the Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT) and PIAMNET (Pakistan, Islamic Republic of Iran and Afghanistan monitoring network) have successfully increased drug efficacy surveillance in the regions and generated the data needed for updating national treatment policies. Through these networks, WHO has offered training for implementing protocols, microscopy, analysing and validating data and preparing reports and publications, which in turn improved the quality of the data.

BOX 4

Therapeutic efficacy testing for selected neglected tropical diseases

Threats of growing drug resistance related to some neglected tropical diseases has led WHO to call for monitoring drug efficacy and resistance at selected sentinel sites. The WHO Strategic and Technical Advisory Group on Neglected Tropical Diseases has created a subgroup to support the monitoring of drug resistance in neglected tropical diseases. WHO has developed standard protocols for monitoring the efficacy of the anthelminthic drugs used in preventive chemotherapy. Research is currently ongoing to develop appropriate combinations of anthelmintics to prevent or respond to the emergence of resistance. Countries have been encouraged to use the WHO-recommended protocols to monitor the local situation. The Working Group on Monitoring Neglected Tropical Diseases Drug Efficacy is working to establish a network of laboratories with experience evaluating anthelminthic drug efficacy and to develop more sensitive methods to measure anthelminthic efficacy.

4.3 Laboratory networks

For TB, HIV, malaria and neglected tropical diseases, drug resistance cannot yet be directly detected at the point of care. Samples (sputum, blood and faeces) are collected from patients and analysed in laboratories. In some cases, organisms are cultured and tested for resistance, or molecular methods (gene probes or sequencing) are used to detect resistance genes. For malaria and some neglected tropical diseases (soil-transmitted helminths and trematodes), therapeutic efficacy tests are used to screen for treatment failure, which may be related to drug resistance. Support to strengthen and expand laboratory services is often needed to detect drug resistance (Box 5).

WHO’s role has been to support the development and expansion of national, regional or specialized reference laboratories that monitor TB and HIV drug resistance (Fig. 14 and 15). WHO activities include:

- developing standardized drug resistance testing protocols, assay validation, standard operating procedures, tools and quality standards for internal and external quality assurance;
- undertaking quality assurance of resistance data and therapeutic efficacy testing data to ensure accurate and reliable laboratory results and to facilitate the comparison of data over time and across countries;
- designating specialized, regional and national reference laboratories that support resistance testing for surveillance and diagnostic purposes from countries with limited or no testing capacity;
- identifying opportunities for efficiently integrating drug resistance and therapeutic efficacy monitoring into broader national antimicrobial resistance and laboratory strengthening strategies and plans, including using shared health systems and laboratory platforms; and
- training laboratory workers, facilitating South–South collaboration across laboratories and strengthening laboratory capacity to detect and report on drug resistance at the country and regional levels.
**FIG. 14**

WHO TB Supranational Reference Laboratory Network


**FIG. 15**

HIV Drug Resistance Laboratory Network as of July 2018

Laboratory networks for TB, HIV and neglected tropical diseases

WHO established a global TB drug resistance surveillance programme in 1994, supported by a network of global TB supranational reference laboratories. As of December 2018, 155 countries participated in the TB drug resistance surveillance programme, covering more than 95% of the world’s population and TB cases. The network of supranational reference laboratories includes 36 laboratories overseeing the drug resistance surveillance programme through more than 100 national TB reference laboratories (24).

A global HIV drug resistance laboratory network was established in 2005 to support HIV drug resistance surveillance activities. As of July 2018, WHO had designated 30 laboratories in five of WHO’s six regions (Africa, the Americas, Europe, South-East Asia and the Western Pacific) to conduct HIV drug resistance testing for public health surveillance (26).

The first steps to establish a global neglected tropical disease drug resistance laboratory network were taken in February 2019: the Working Group on Monitoring Neglected Tropical Diseases Drug Efficacy met to define the terms of reference of the networks and the characteristics, capacity and geographical distribution of the laboratories that will be part of the network.

4.4 Communication, awareness-raising, education and training

The first strategic objective of the Global Action Plan on Antimicrobial Resistance is to improve awareness and understanding of antimicrobial resistance through effective communication, education and training. As highlighted in Section 3, antimicrobial resistance threatens sustainable development and is a major risk to ending the HIV, TB and malaria epidemics. It is therefore critically important to maintain the issue of drug resistance on the global and national development agendas.

WHO is working to improve awareness and understanding of drug resistance in countries, with different audiences, as part of long-standing programmes in TB, HIV, malaria and neglected tropical diseases. Ongoing activities include:

- convening Member States, civil society, researchers, implementing partners, donors, developers of drugs and diagnostics and other stakeholders to increase awareness and understanding around the status and impact of resistance;

- engaging and convening experts (through strategic and technical advisory groups, technical expert groups, global working groups etc.) to ensure timely and appropriate responses to elevated levels of resistance when they arise;

- compiling, interpreting and disseminating information and data on drug resistance to countries and development partners and supporting the strengthening of their situation analyses;

- using data generated by surveillance to inform policy and recommendations;

- providing regular updates about drug resistance trends to Member States through meetings of WHO Governing Bodies and urging countries to take action;

- using international days mandated by the World Health Assembly (such as World Tuberculosis Day, World Malaria Day, World AIDS Day and World Antibiotic Awareness Week) to raise awareness about the challenge of drug resistance;

- supporting knowledge transfer, training and capacity development of WHO regional and country offices as well as national disease programmes on prevention and clinical and programmatic management of drug-resistant TB, HIV, malaria and neglected tropical diseases;
- engaging manufacturers of diagnostics, drugs and medical devices in dialogue to ensure that key medicines are affordable and that drugs that contribute to antimicrobial resistance are taken off the market (such as malaria monotherapies);
- involving civil society and engaging communities in improving literacy on resistance and treatment adherence;
- engaging all relevant health-care providers in disease treatment, care and control through public–private mix approaches; and
- supporting countries in developing and implementing comprehensive national action plans to address antimicrobial resistance that include TB, HIV, malaria and neglected tropical diseases where relevant.
5. Future directions

KEY MESSAGES

- Addressing antimicrobial resistance is part of the agendas of universal health coverage, patient safety and the quality of health-care services.
- Innovation and research in treatment and diagnostics will play key roles in reducing the development and spread of drug resistance related to TB, HIV, malaria and neglected tropical diseases and its risk to health.
- Product development partnerships have demonstrated effectiveness in identifying and facilitating the development of new pipeline drugs for TB, malaria and neglected tropical diseases as drug resistance to current therapies spreads.
- Sets of clinical and programmatic quality-of-care indicators that predict and are associated with developing drug resistance have been identified and monitored for HIV. Similar approaches might be explored to predict the emergence of resistance related to other diseases or at health-care delivery points, enabling early action to prevent and minimize the spread of antimicrobial resistance.
- Antimicrobial resistance related to bacteria, TB, HIV, malaria and neglected tropical diseases is a critical issue and needs to be kept high on the global, regional and national health development agendas.
- WHO has a key role to play in compiling and disseminating information on levels of resistance and trends as well as innovative practices to prevent, manage and control the development and spread of antimicrobial resistance related to TB, HIV, malaria, bacteria, fungi and neglected tropical diseases.
- WHO, working collaboratively with other development partners, will provide joint support to countries in developing, implementing and tracking progress against comprehensive, evidence-informed national antimicrobial resistance action plans that include TB, HIV, malaria and neglected tropical diseases where relevant.
- WHO will work with countries to identify and maximize synergy across programmes or service delivery areas and platforms to address TB, HIV, malaria and neglected tropical diseases antimicrobial resistance.
5.1 Identify research and development gaps and new tools and approaches

New products, technologies and service delivery approaches will be needed to address antimicrobial resistance related to TB, HIV, malaria, neglected tropical diseases and across the whole spectrum of antimicrobial resistance. Research and development will play an important role in preventing and managing antimicrobial resistance.

WHO has a clear leadership role to play in identifying prevention and management gaps in antimicrobial resistance related to TB, HIV, malaria and neglected tropical diseases, which can include the need for new products and approaches to service delivery. WHO’s role includes:

- monitoring antimicrobial resistance prevalence and trends to assess needs and gaps;
- identifying and setting global, regional and national research agendas and priorities for antimicrobial resistance;
- convening institutions and expert networks to address antimicrobial resistance gaps, including collaborative efforts to identify antimicrobial resistance management needs in the animal health and agricultural sectors (such as through the FAO/OIE/WHO Tripartite Collaboration on Antimicrobial Resistance and UNEP) and how this affects human health;
- compiling and disseminating good practices in preventing and managing antimicrobial resistance to facilitate changes in approaches to service delivery to address gaps in service quality and effectiveness;
- supporting countries in conducting implementation research across a variety of settings and populations to improve approaches to service delivery (such as improving treatment adherence, preventing drug stock-outs, identifying drug resistance and optimizing treatment protocols in the face of increasing resistance) or address other factors that lead to the emergence and spread of antimicrobial resistance;
- assessing the burden of disease caused by antimicrobial resistance; and
- advocating for increased research and development investment to strengthen product pipelines that address aspects of antimicrobial resistance.

To prevent and manage drug resistance related to TB, HIV, malaria and neglected tropical diseases, WHO can:

- identify and advocate for the development of better and more affordable tools, such as vaccines, effective drugs with shorter or simplified treatment protocols, point-of-use diagnostic tests, gene sequencing and molecular methods for surveillance of drug resistance;
- recommend models of service delivery that improve the quality and follow-up of key interventions that influence antimicrobial resistance, such as treatment adherence, diagnostic testing and appropriate response, algorithms to ensure effective treatment and infection control to minimize disease transmission in hospital settings;
- collaborate to further address antimicrobial resistance in the animal husbandry and agricultural sectors;
- engage with product development partnerships, the private sector and other partners to advocate for developing new drug candidates (Box 6) or diagnostics and other products (Box 7); and
- support countries in rapidly adopting innovative practices or new products to prevent or manage antimicrobial resistance for maximum impact.
**BOX 6**

**Product development partnerships to identify and develop new candidate drugs**

The Medicines for Malaria Venture (MMV) and Drugs for Neglected Diseases initiative (DNDi) are product development partnerships that have identified and developed an innovative model to develop new pipeline drugs to treat malaria and neglected diseases. These partnerships provide a systematic way for partners to work together to identify and develop new medicines and/or better formulations to increase the pipeline of available drugs to treat malaria and neglected tropical diseases. These partnerships facilitate the development of drugs that pharmaceutical companies may be reluctant to pursue by themselves because of economic considerations.

Since it was created in 1999, MMV has built an extensive network of over 400 pharmaceutical, academic and endemic-country partners in more than 55 countries and has developed and brought forward 10 new medicines to treat malaria (28). Increasing the pipeline of available malaria drugs will help to mitigate the impact if current resistance to artemisinin-based combination therapy becomes widespread. The product development partnership model has also been used to address drug resistance related to other diseases.

The Global Antibiotic Research and Development Partnership was established in May 2016 as a joint initiative by WHO and the DNDi. This not-for-profit research and development initiative addresses global public health needs by developing and delivering new or improved antibiotic treatments while endeavouring to ensure sustainable access. It also harnesses WHO’s mandate to drive the global response to antimicrobial resistance and set health priorities and DNDi’s expertise in maximizing partnerships to build a pipeline for neglected diseases and deliver not-for-profit, needs-driven research and development. Various partners and donors are contributing to this collaborative effort.

In 2010, the WHO Department of Control of Neglected Tropical Diseases established the Working Group on Monitoring Neglected Tropical Diseases Drug Efficacy to promote the testing of new anthelminthic drugs or combinations of existing drugs. The group identified several potential drug candidates. Three WHO collaborating centres are participating in this working group.

**BOX 7**

**Role of development partners in the response to antimicrobial resistance**

In recent years, the work to respond to antimicrobial resistance has benefited from investment by technical agencies, donor initiatives and the private sector.

Unitaid, the United States Agency for International Development (USAID) and the Bill & Melinda Gates Foundation have supported trials and other studies of new medicines and novel regimens for multidrug-resistant TB (such as the EndTB project coordinated by Partners in Health, Médecins Sans Frontières and Interactive Research and Development in Pakistan; the Global Alliance for TB Drug Development; and the STREAM trial of a shorter nine-month multidrug-resistant TB regimen). The initiatives of manufacturers of diagnostics (such as HAIN for line probe assay and CEPHEID for GeneXpert) and medications (such as bedaquiline by Janssen and delamanid by Otsuka) have also been critical to improve multidrug-resistant TB care.

Unitaid has made critical contributions to support national TB laboratory networks to consolidate their work and implement new diagnostics for drug-resistant TB (EXPAND-TB project) and improve access to new TB medicines.
For HIV, the Bill & Melinda Gates Foundation has supported the establishment of the WHO Global Strategy for the Surveillance and Monitoring of HIV Drug Resistance and the Global Action Plan on HIV Drug Resistance; the Global Fund to Fight AIDS, Tuberculosis and Malaria and the United States President’s Emergency Plan for AIDS Relief (PEPFAR) have supported countries in implementing national HIV drug resistance surveys and in strengthening laboratory capacity for HIV drug resistance testing. The United States Centers for Disease Control and Prevention has provided technical assistance to PEPFAR-supported countries in activities related to surveillance of HIV drug resistance. The United States National Institutes of Health provide in-kind support to the quality assurance of the global HIV drug resistance laboratory network. Over the years, some specialized WHO-designated HIV drug resistance laboratories (such as the University of British Columbia (Vancouver, Canada), Public Health Agency of Canada (Winnipeg, Canada), Center for Research in Infectious Diseases (CIENI, Mexico City, Mexico), United States Centers for Disease Control and Prevention/Global Action Plan on Antimicrobial Resistance (Atlanta, USA) have provided HIV drug resistance testing free of charge to support HIV drug resistance surveillance in several low- and middle-income countries with limited financial and technical capacity. Other partners, including the Public Health Agency of Canada, have contributed to different aspects of HIV drug resistance monitoring and surveillance efforts. HIVResNet, a large network of institutions and experts, has provided strategic guidance to WHO over the years and contributed to the global efforts to monitor, respond to and prevent HIV drug resistance. Unitaid is funding clinical trials for emerging antiretroviral medicines and supports treatment monitoring to facilitate treatment optimization, including for children.

Partners have also played a key role in the work to develop new malaria treatments, in supporting the surveillance of the efficacy of existing antimalarial drugs, and in the efforts to contain resistance and eliminate malaria in the Greater Mekong Subregion. The Bill & Melinda Gates Foundation, the Australian Department of Foreign Affairs and Trade, the United Kingdom Department for International Development, the Global Fund to Fight AIDS, Tuberculosis and Malaria and USAID provide essential support to the surveillance of efficacy. The Global Fund to Fight AIDS, Tuberculosis and Malaria is the main funder of the work to eliminate *P. falciparum* malaria in the Greater Mekong subregion and thereby minimize the risk of future spread of drug-resistant parasites from this area. Unitaid is also funding malaria projects to improve diagnostics and prevention for pregnant women.

The Bill & Melinda Gates Foundation and USAID have provided financial support for neglected tropical diseases, identifying alternative anthelminthics and establishing a network of laboratories while technical support was provided by three collaborating centres in Basel, Switzerland, Ghent, Belgium and Negrar, Italy and by McGill University, the University of Texas, the University of London and Universidad de Valencia.

5.2 Clinical and programmatic indicators associated with and predicting the emergence of antimicrobial resistance

Evidence from HIV programmes has shown that it is possible to identify and monitor a set of programmatic quality-of-care indicators that provide an early warning for the emergence of drug resistance in certain populations or settings (see Box 8 and Table 2). Monitoring this set of indicators can help to predict where resistance may emerge, enabling corrective actions to be taken to prevent the emergence and subsequent spread of drug resistance (29). For several diseases (such as TB, HIV and leprosy) drug resistance is more likely to arise among people who have been previously treated and stopped treatment or experienced treatment failure. This should prompt the use of a different drug combination for subsequent treatment.
regimens in accordance with WHO treatment guidelines. For neglected tropical diseases, the emergence of parasite resistance to some anthelminthics used to treat infections in livestock signals that human pathogenic helminth strains also need to be monitored for resistance, especially given the scale of the mass drug administration approaches used to treat these parasites in humans.

Future work across disease areas might help to identify common sets of service delivery and/or quality-of-care indicators that can be routinely monitored to prevent the emergence and spread of drug resistance.

**BOX 8**

**Quality-of-care indicators associated with and predicting the emergence of HIV drug resistance**

Monitoring a subset of quality of care indicators – also known as early warning indicators of HIV drug resistance – is a key component of the WHO public health strategy to prevent HIV drug resistance in countries scaling up antiretroviral therapy. These quality-of-care indicators specifically assess factors at individual antiretroviral therapy clinics associated with and predicting the emergence of HIV drug resistance. Monitoring these quality-of-care indicators is designed to provide countries with actionable information to improve clinical and programmatic performance to prevent HIV drug resistance from emerging.

Many factors are associated with the emergence of HIV drug resistance. They include viral factors (such as subtype, replication capacity and pre-existing polymorphisms); drug-related factors (such as drug potency, pharmacokinetics, drug–drug interactions, drug tolerability and genetic barriers to selecting resistance) and programme factors (such as patient adherence, drug stock-outs and supply continuity and retention in treatment). Although viral and drug-related factors are often beyond the control of public health or programme action, monitoring the clinical or programmatic factors associated with HIV drug resistance can alert antiretroviral therapy programmes to situations that may favour the emergence of HIV drug resistance or failure to suppress viral load at the population level.

This set of quality-of-care indicators monitors factors related to patient care (appropriate prescribing and viral load suppression at 12 months); patient behaviour (adherence); and clinic-level and programme management (follow-up, retention on antiretroviral therapy, procurement and supply management of antiretroviral drugs and appropriately switching regimen among people with failure to suppress viral load).

Early warning indicators use internationally agreed standardized definitions and accompanying targets. Annual monitoring of early warning indicators enables the degrees of improvement or decline over time to be measured, both within and between clinics (28).
Joint support for countries

The Global Action Plan on Antimicrobial Resistance outlines a framework for action on antimicrobial resistance with supporting countries to develop, implement and monitor antimicrobial resistance national action plans as a priority. The One Health concept requires a perspective that covers antimicrobial resistance across all key components, including human health, animal health and agriculture because preventing and managing antimicrobial resistance requires activities across all relevant sectors. As of January 2019, 117 countries had national action plans, but the extent to which TB, HIV, malaria and neglected tropical disease programmes are involved varies. WHO and other development partners need to collaborate better and make more effort in providing joint support to countries to develop comprehensive national action plans that include interventions to address TB, HIV, malaria and neglected tropical diseases where relevant. Countries need coordinated support in collecting and using data on antimicrobial resistance (national and subnational) for evidence-informed decision-making. Technical support should also target drug regulatory authorities to ensure that new effective medicines and other relevant products (such as diagnostic tests that detect drug resistance) are added to national lists of essential medicines and that treatment policies are changed as soon as possible if antimicrobial resistance is reducing the effectiveness of existing treatment protocols.

### Table 2

<table>
<thead>
<tr>
<th>WHO-recommended early warning indicators of HIV drug resistance</th>
<th>Target (green: good performance; amber: fair performance; red: poor performance)</th>
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</table>
| Retention on antiretroviral therapy at 12 months (ART.5, antiretroviral therapy retention) | Green: >85%  
Amber: 75–85%  
Red: <75% |
| % of patients retained on antiretroviral therapy 12 months after initiating antiretroviral therapy | Green: >85%  
Amber: 75–85%  
Red: <75% |
| On-time pill pick-up (ART.7, antiretroviral therapy adherence proxy) | Green: >90%  
Amber: 80–90%  
Red: <80% |
| % of people who pick up antiretroviral therapy no more than two days late at the first drug pick-up after a defined baseline pick-up | Green: >90%  
Amber: 80–90%  
Red: <80% |
| Pharmacy stock-out (not collectable through the HIV patient monitoring system) | Green: 0%  
Red: >0% |
| % of months with any days of stock-out of any routinely dispensed antiretroviral drug | Green: 0%  
Red: >0% |
| Viral load suppression (VLS.1, viral load suppression at 12 months) | Green: ≥90%  
Amber: 80–<90%  
Red: <80% |
| % of people with viral load <1000 copies/mL 12 months after initiating antiretroviral therapy | Green: ≥90%  
Amber: 80–<90%  
Red: <80% |
| Viral load completion (VLS.2, viral load testing coverage) | Green: ≥70%  
Red: <70% |
| % of people with a 12-month viral load test result available | Green: ≥70%  
Red: <70% |

* Stock-out refers to lack of availability of first-line antiretroviral drugs.
* The denominator for the viral load suppression indicator is the number of people alive and receiving antiretroviral therapy 12 months after initiating treatment who have a viral load test result available.
* The denominator for the viral load completion indicator is the number of people alive and receiving antiretroviral therapy 12 months after initiating treatment, who are therefore, consistent with the policy, expected to have a viral load test result available in the primary medical record. For all early warning indicators, a grey classification is applied in situations where a sampled antiretroviral therapy clinic is unable to report on a specific indicator because more than 30% of the data are missing.

Source: Consolidated guidelines on person-centred HIV patient monitoring and case surveillance (28).
5.4 Identifying and optimizing synergy

As countries move to strengthen their primary health care systems and towards achieving universal health coverage in the context of reduced reliance on external funding resources, they will need to look for opportunities to increase the efficiency of health services and reach more people with essential services. For antimicrobial resistance, this might mean using diagnostic platforms that can detect drug-resistant strains of pathogens for several diseases and strengthening and expanding the services offered by laboratories to detect drug resistance. Synergy can also be found by training health-care providers to prevent and manage antimicrobial resistance across multiple diseases and at various service delivery points, provide better treatment by using adapted treatment algorithms and undertake infection control and prevention interventions. Strengthening procurement and supply chain management systems to reduce drug stock-outs is also an important intervention for preventing antimicrobial resistance related to TB and HIV and to other diseases as well. Ensuring that health-care facilities have clean water and functioning sanitation facilities and that wastewater is adequately treated before being discharged into the environment from health-care facilities and drug manufacturing facilities can strongly reduce antimicrobial resistance.

5.5 Product pipelines

Collaboration is required to identify new drug candidates. New drugs take a long time to develop, are expensive and must go through at least three phases of clinical trials before they can be approved for widespread use among humans. Pharmaceutical companies are often unwilling to invest the time and money required to bring new drugs to market unless they have a high probability of achieving adequate returns on investment. This is often a challenge for such diseases as TB, HIV, malaria and neglected tropical diseases, which have their greatest impact in low- and middle-income countries. As highlighted in Box 6, product development partnerships and other research consortia can facilitate and fund work to identify new pipeline drugs.

Further research is also needed to develop formulations for children, shorter duration treatments, treatments with reduced side-effects, more effective combinations of existing drugs, lower cost treatments, medicines with greater stability and long-acting formulations.

Point-of-care diagnostic tests that directly measure drug resistance are not currently available. Research and funding are also needed to develop new technologies and products and common diagnostic platforms that can detect drug resistance across multiple diseases.
References


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Antimicrobial resistance – general

WHO antimicrobial resistance website
http://www.who.int/topics/antimicrobial_resistance/en

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Global Antimicrobial Resistance Surveillance System: Manual for Early Implementation

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