Global Health eLearning Center

Antimicrobial Resistance (Part 1)

What is AMR?

After completing this session, learners will be able to do the following:

- Define antimicrobial resistance and the mechanisms through which it occurs
- Describe the global size and scope of antimicrobial resistance
- Explain how and why antimicrobial resistance spreads and identify key drivers

Background

In 1928, Alexander Fleming made a discovery that would revolutionize the practice of medicine and prove to be one of the greatest public health advances in history. After a piece of mold contaminated his petri dish and produced a substance that killed off the bacteria he was studying, Fleming and others used this finding to develop penicillin, the world's first antibiotic, which could cure common bacterial infections.

In the following years, additional antibiotics were discovered that formed the foundation for treating and preventing many of the deadliest diseases at the time, including tuberculosis (TB) and pneumonia. These new antibiotics were so effective in treating common illnesses that some believed the war against infectious diseases had been won.

Since Fleming's time, similar advances with other antimicrobial agents have helped turn the tide against diseases like HIV and malaria. However, many microbes are able to mutate and evolve over a very short period of time. Some of these mutations make microbes less susceptible to the effects of antimicrobials, a

phenomenon known as antimicrobial resistance. Sure enough, the first cases of bacterial infections resistant to penicillin began appearing only four years after it was put to large-scale use during World War II. Now, antimicrobial resistance (AMR) is present in every corner of the globe and represents an increasingly serious threat to global public health.

Sources: Review on Antimicrobial Resistance 2014; WHO 2015.

Glossary Term:

antibiotic
antimicrobial resistance
antimicrobial agent
microbe

Did You Know?

In a 1945 interview with *The New York Times*, Alexander Fleming, who won a Nobel Prize that year for his discovery of penicillin, warned that misuse of the drug could result in selection for resistant bacteria.

Source: Rosenblatt-Farrell 2009.

What is Antimicrobial Resistance?

According to the World Health Organization (WHO), AMR "occurs when bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness and death" (WHO2020a).

In other words, resistance occurs when an antimicrobial has lost its ability to effectively control or eliminate a microbial infection against which it was once effective. The microbes are then considered resistant and can continue to replicate even when the antimicrobial is present. The microbes, not the human, become antimicrobial resistant. These resistant microbes can then spread among humans, animals, and even within water and soil.

While many people are aware that bacteria can develop resistance to the antibiotics used to treat them (antibiotic resistance), as WHO's definition points out, resistance also occurs in other microbes such as viruses, parasites, and fungi (collectively called antimicrobial resistance).

Sources: Australian Government 2017a; UK Research and Innovation 2021; WHO 2020a.

Glossary Term:

microbe

AMR: A Serious Global Health Threat

The WHO names AMR as one of the top 10 threats to global health.

Need to Preserve Existing Antimicrobials

AMR has existed for as long as antimicrobials themselves; however, global concern has grown as drug resistance outpaces the discovery of new antimicrobial products, which are often time consuming and expensive to research and develop and may not be financially rewarding. Regarding antibiotics, for example, the WHO asserts that, "almost all the new antibiotics that have been brought to market in recent decades

are variations of antibiotic drugs classes that had been discovered by the 1980s" (WHO 2021), and notes that recently approved antibiotics and those in the clinical pipeline are not enough to address the growing global problem of AMR.

Global partners are increasingly paying attention to this challenge. For example, in July 2020, more than 20 biopharmaceutical companies committed to developing innovative antibacterial treatments—aiming to bring 2-4 new treatments to patients by 2030. But the research and development and market challenges still persist.

Because the rate of discovery for new antibiotics and other antimicrobials is so slow, it is paramount that existing antimicrobials are used appropriately and rationally (preserving their effectiveness) alongside efforts to discover completely new—or "novel"—antimicrobials.

Rising Use of Antimicrobials

And now for a global health paradox: Greater access to essential medicines, a major public health achievement, also can mean greater use of antimicrobials and opportunity for drug resistance to emerge and spread, especially if they are used inappropriately. The consumption rate of antibiotics in humans rose 39% from 2000 to 2015 and is projected to increase another 200% by 2030. These increases are attributed mainly to use in low- to middle-income countries. Additionally, animal consumption of antibiotics will increase an estimated 53% between 2013 and 2030.

Need for Action

Infectious diseases know no borders, and international travel and commerce provide ample opportunity for AMR in one region to quickly escalate to a global crisis. It is critical that every country, regardless of income level, is concerned with and proactively takes steps against AMR. Containment will only occur with concerted, coordinated global action.

With inaction comes the very real risk of reversing the progress made against today's public health challenges such as HIV, TB, malaria, maternal and newborn health, and safe surgery, and a likely resurgence of diseases of the past, including once-easily treated infections like pneumonia.

Sources: Klein et al., 2018; Pew Trust 2020; Review on Antimicrobial Resistance 2016; Theuretzbacher U 2019; Van Boekel 2017; World Bank 2016; WHO 2019a; WHO 2020a; WHO 2020b; WHO 2021; WHO 2021b.

How Does AMR Occur?

Intrinsic and Acquired Methods of Resistance

Some microbes are pre-programmed to be resistant to certain types of antimicrobials. This is known as inherent or intrinsic resistance. For example, gram-negative bacteria have a cell wall covered by an outer membrane that physically blocks some antibiotics from working.

Microbes can also acquire genes that code for resistance, known as acquired resistance, through two ways:

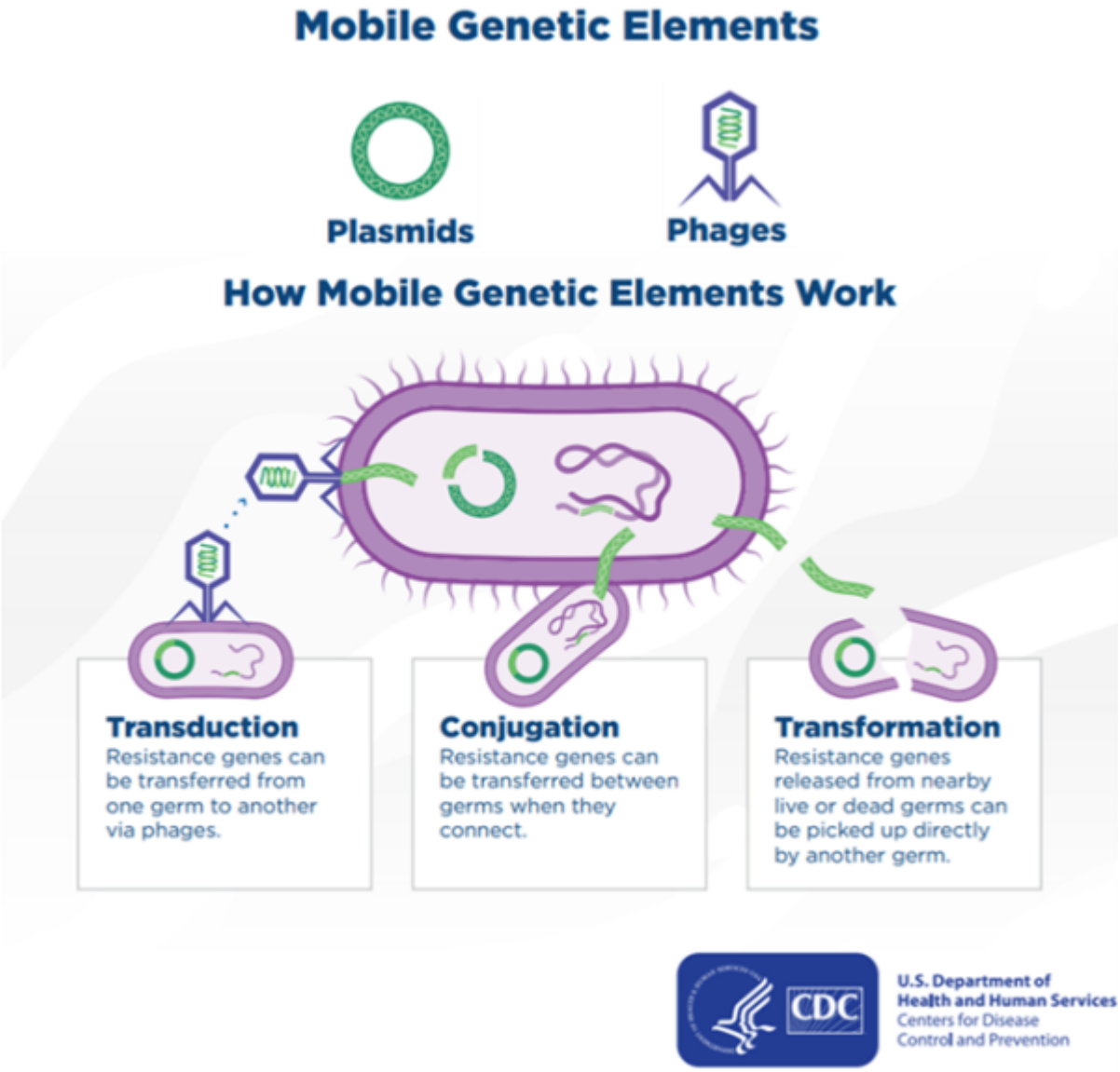
1. gene mutation during replication (vertical transmission)
2. exchange of genes between microbes (horizontal transmission)

Genetic mutations are rare spontaneous changes or errors that happen when microbes replicate. Occasionally, these mutations will change the microbe in a way that helps it resist the effect of exposure to an antimicrobial. These new resistant genes are then passed on to the microbe's progeny, a process known as vertical transmission.

Microbes can also acquire resistance through horizontal transmission, in which genetic material is exchanged between microbes. For example, when bacteria come in direct contact with each other, small circular pieces of DNA found in the cytoplasm (plasmids) may be transferred through a process known as conjugation. While this is thought to be the main mechanism of horizontal transmission, bacteria may also

pick up bits of DNA from the external environment (transformation), or through the transfer of DNA from bacteria-specific viruses known as bacteriophages (transduction). The graphic below illustrates how microbes can become resistant through horizontal transmission.

Sources: NIAID 2011; Todar 2011.



Graphic adapted from: CDC. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the U.S. Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. This image is otherwise available on the agency website for no charge.

Glossary Term:
bacteriophage
plasmid
acquired resistance
horizontal transmission
vertical transmission
intrinsic resistance
cytoplasm
conjugation
transformation

transduction

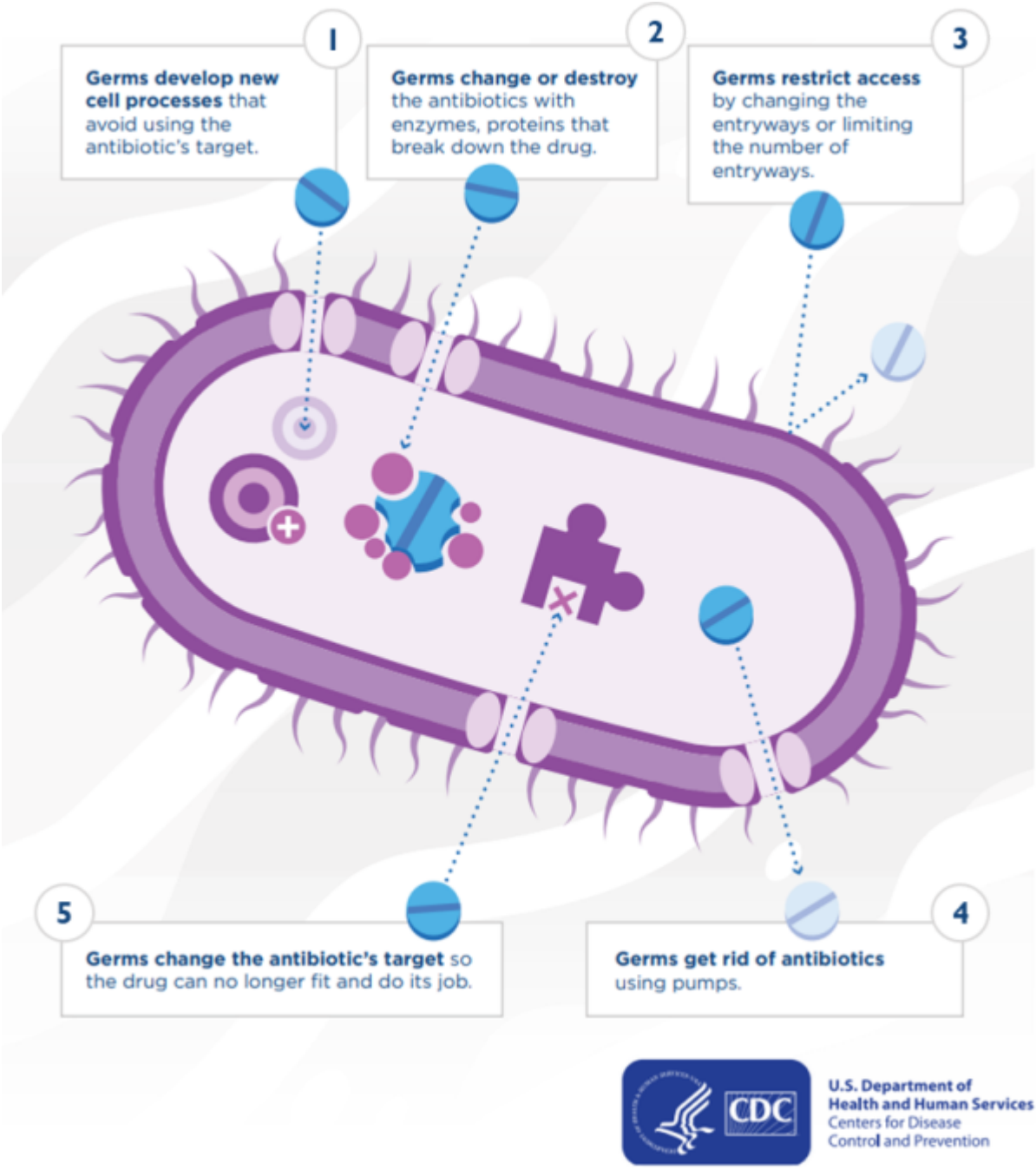
How Does AMR Occur?

Molecular Mechanisms of Resistance

At a molecular level, the genetic materials discussed in the previous page provide microbes several different ways to resist the effects of antimicrobials:

- The microbe develops new processes that evade the antimicrobial's target (mechanism #1 in the graphic below)
- The microbe chemically modifies or destroys the antimicrobial (mechanism #2 in the graphic below)
- The microbe physically blocks or removes the antimicrobial from the cell (mechanisms #3, and #4 in the graphic below)
- The microbe alters the target site so that it is no longer recognized by the antimicrobial (mechanism #5 in the graphic below)

Source: CDC 2019.



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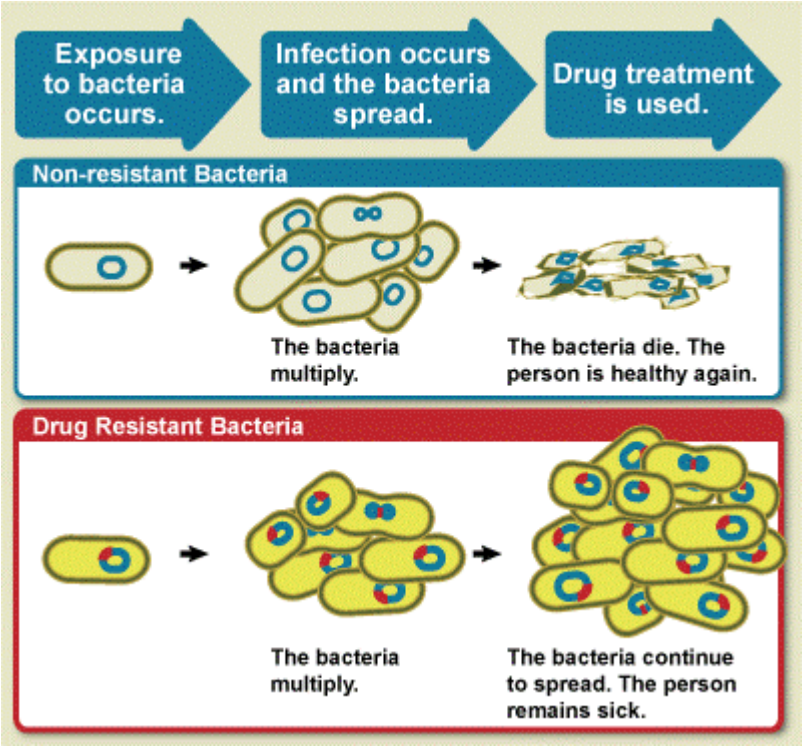
How Does AMR Occur?

Selective Pressure

Microbes that acquire resistance genes, either through vertical or horizontal transmission, will survive in the presence of a specific antimicrobial while the ones without the resistance gene will die. This selective pressure will leave resistant microbes behind, and with no competition for growth, they will multiply and spread as the graphic shows. Antimicrobials can actually create a situation where resistant microbes flourish, particularly when incomplete doses are used or when the antimicrobial is poor quality and lacks sufficient potency.



When microbes acquire resistance genes to more than one type of antimicrobial drug, they are referred to as multidrug-resistant organisms.

Source: APUA 2020; NIAID 2011

Glossary Term:

selective pressure

multidrug resistant organisms

How Does AMR Spread?

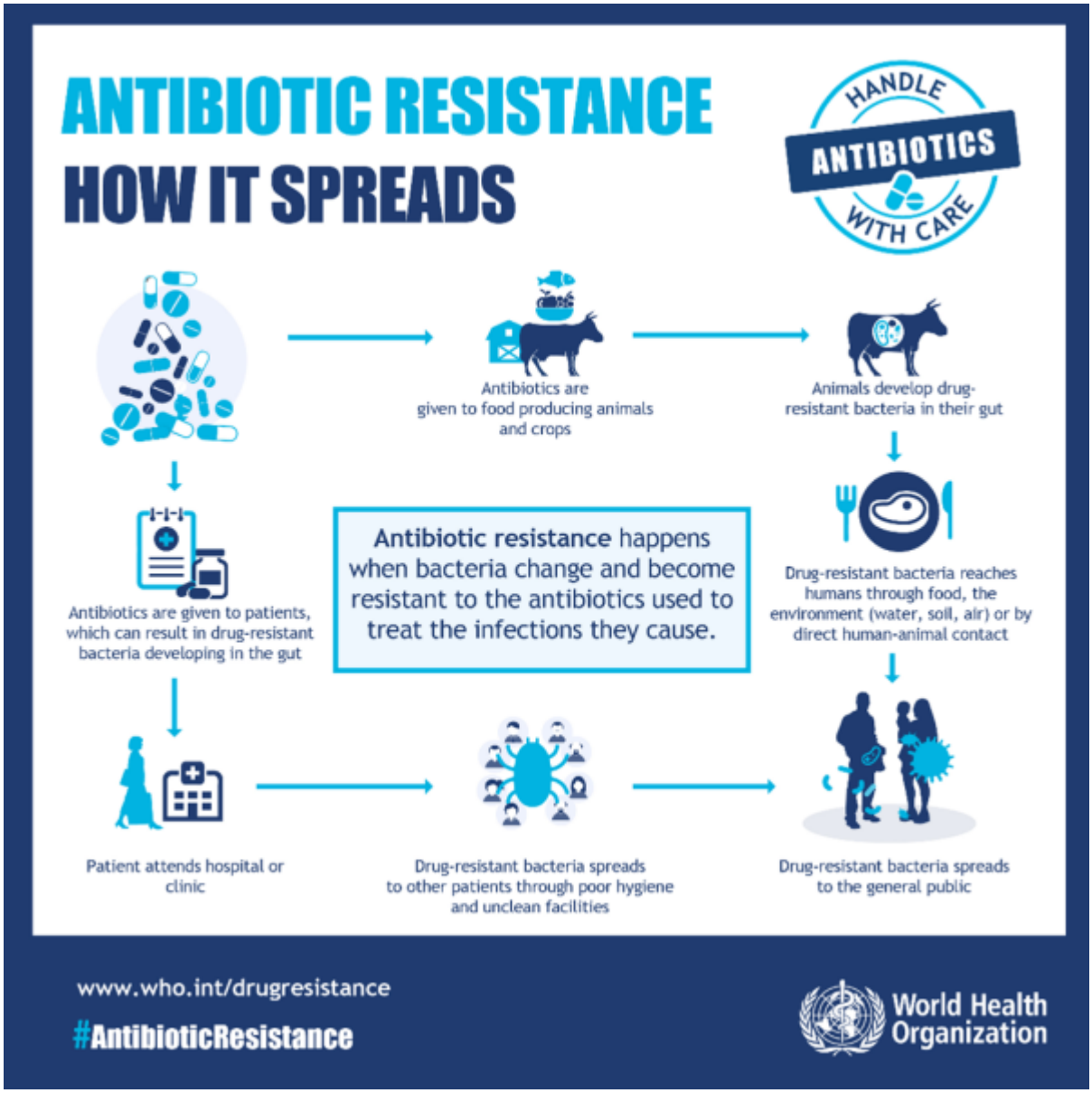
Antimicrobials are used for both human (medical) and animal (agricultural) purposes, both of which can facilitate the spread of AMR.

In agriculture, animals are often given antibiotics for treatment or to promote quicker growth. The resistant bacteria they carry can be passed to humans through food or direct contact or through crops contaminated with affected manure.

Humans can also develop resistant microbes through a natural adaptive process when they are treated with antimicrobials and also in health care facilities where unclean hands or contaminated objects can spread resistant microbes to patients who then spread them to the community.

Resistant microbes from animals and people can also end up in the environment—particularly water.

The figure below shows how antibiotic resistance can spread between animals, humans, and the environment.



Source: ECDCWHO 2015b

Drivers of AMR

Any use of antimicrobials—even appropriate use—contributes to the development of resistance. However, **unnecessary and inappropriate use of antimicrobials exacerbates AMR development and spread.**

Improper use in humans

Globally, more than half of medicines are prescribed, dispensed, or sold inappropriately. Overuse and misuse of antimicrobials is a huge global problem. For example, antimicrobials are often unnecessarily used to treat acute viral conditions, such as the common cold or flu. Complex and interacting deficiencies across all levels of the health system, including legislation and regulation, supply chain management, quality assurance, prescribing and dispensing practices, and patient behavior contribute to inappropriate use. *These areas, as well as strategies to combat AMR, are explored in depth in Antimicrobial Resistance, Part 2.*

Improper use in animals

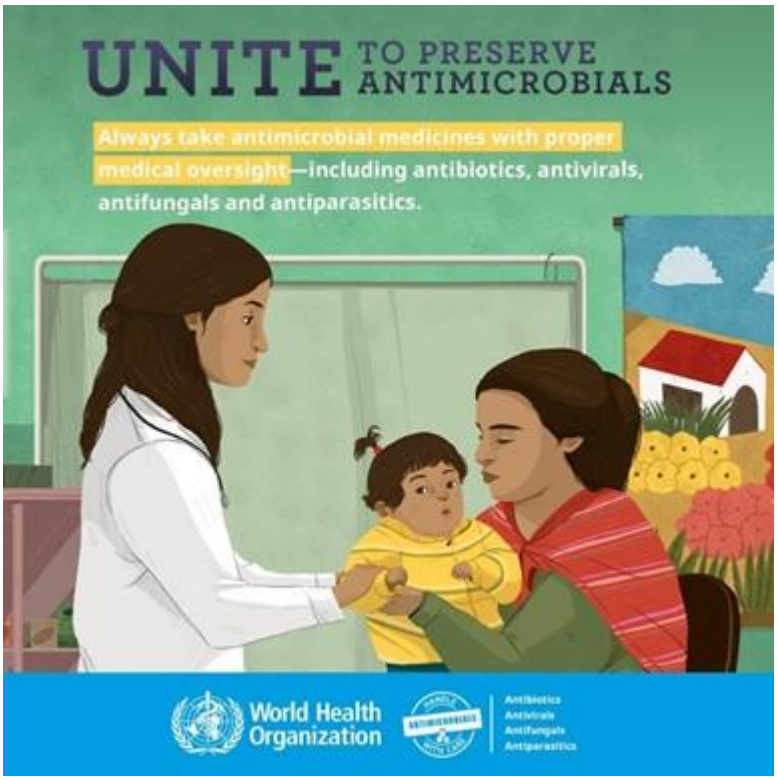
Antimicrobial products are used extensively for agricultural purposes, including for the treatment and prevention of illnesses and for increased growth promotion. In fact, in some countries, up to 80% of the total consumption of antibiotics that are medically important for humans is in the animal sector.

Accumulation in the environment

Excessive and inappropriate use of antimicrobials in both humans and animals also means that these compounds are accumulating in the environment—for example, through wastewater, sewage, and runoff. Hospital effluents and discharged wastes from antimicrobial manufacturing plants can also contaminate the rivers and soils with these compounds. The impact of such accumulation on the emergence of antibiotic resistance should not be understated. Most water quality legislation does not include provisions to monitor the concentrations of antimicrobial-resistant microbes in sewage or treatment plants.

Sources: CIDRAP 2019; Review on Antimicrobial Resistance 2014; WHO 2011; WHO 2017a.

Session Summary



To recap, this session defined antimicrobial resistance (AMR) and briefly described its global scope. The session also explained and provided graphics for the molecular mechanisms through which AMR occurs. Finally, it identified the human, animal, and environmental drivers of AMR and how these drivers cause AMR to spread.

The next session discusses the threat AMR poses in more detail.

The Impact of AMR on Specific Diseases of Public Health Importance

As discussed in the previous section, the infectious disease burden, greatest in low- and middle-income countries, is significantly complicated by increasing antimicrobial resistance. And while bacterial resistance to antibiotics is of chief concern, strains of resistant parasites, viruses, and fungi also represent clear public health threats.

In the past, conditions such as pneumonia, diarrhea, malaria, sexually transmitted infections (STIs), and others were readily managed with available therapies. But as resistance to common medications increases, such conditions are becoming more difficult and costly to treat.

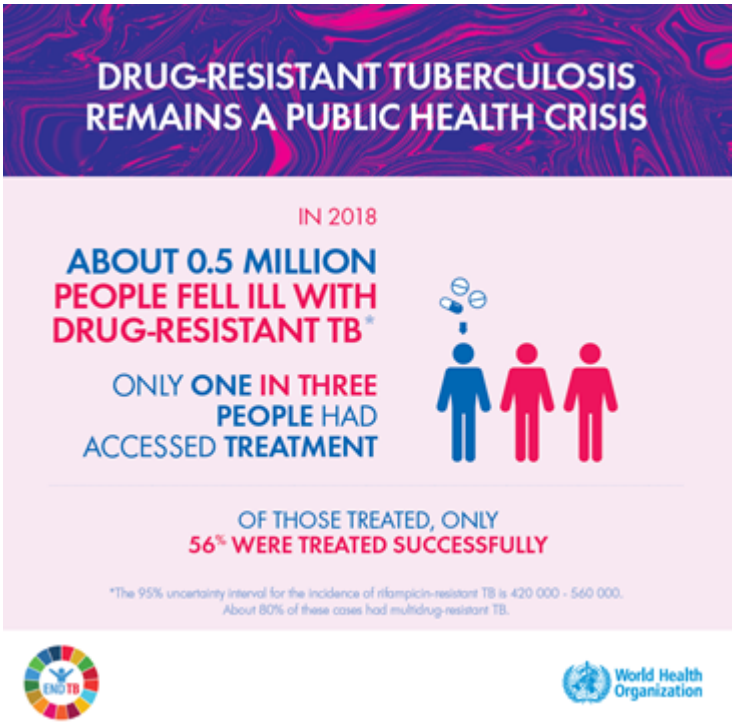
Tuberculosis, malaria, and hospital-acquired infections (also known as nosocomial infections), which can be difficult to treat even with effective first-line agents, have become huge burdens on health systems as resistance has increased.

After completing this session, learners will be able briefly describe how resistance is affecting the control of the following diseases of major public health importance:

- Bacteria: TB, pneumonia, gonorrhea, methicillin-resistant *Staphylococcus aureus* (MRSA) and others
- Parasites: malaria
- Viruses: HIV
- Fungi: *Candida*

Glossary Term:
nosocomial infections

Bacterium: Tuberculosis



Overall global incidence of tuberculosis (TB) is holding steady at an estimated 10 million people per year, but TB still claims the lives of approximately 1.5 million people each year. The 2020 milestones of decreasing incidence by 20% and the number of deaths by 35% are still far away.

In an attempt to slow the development of resistance, patients are treated with multiple drugs over the course of generally six months. The long duration of treatment, plus medication side effects and other factors, make it difficult for patients to adhere to a full course of treatment. WHO's End TB strategy recommends counseling and social support for treatment adherence, through directly observed treatment when necessary.

The Burden of Multidrug Resistance

An estimated 3.5% of new TB cases and 18% of previously treated cases have been found to have multidrug-resistant TB (MDR-TB). Thirty countries are classified as having a high MDR-TB burden; the countries with the highest incidence rates of MDR-TB are located in the former Soviet Union.

Consequences

Treatment of MDR-TB can last up to 20 months, can cost up to 250 times more than treatment of susceptible TB, has more side effects, and yields lower cure rates. About one in three patients with MDR-TB access treatment, and of those who do, about 56% are cured.

Worryingly, cases of extensively drug-resistant TB (XDR-TB) have also occurred. XDR-TB has been reported in 128 countries and territories. An estimated 6% of people with MDR-TB had XDR-TB in 2019. The treatment success rate is only 34%. In some cases, these strains of TB are virtually untreatable.

Sources: KFF 2020; WHO 2015b; WHO 2018a; WHO 2018b; WHO 2019b WHO 2020e.

Glossary Term:
incidence rate
Extensively Drug-resistant Tuberculosis (XDR TB)
Multidrug-resistant tuberculosis (MDR TB)
tuberculosis

Did You Know?

In recent years, two drugs, bedaquiline and delamanid emerged as effective new treatments for MDR-TB. At the end of 2020, 109 countries reported having introduced bedaquiline in an effort to improve the effectiveness of MDR-TB treatment regimens. In 2019, the TB Alliance announced the approval of pretomanid for use in combination with other drugs for stubborn cases of MDR-TB as well as XDR-TB.

Sources: TB Alliance 2019; WHO 2020c.

Case Study: Thandiwe's Fight against TB

Thinking her coughing was due to the flu, Thandiwe, who lives in Ethiopia, went to the doctor who prescribed antibiotics and cough syrup. When they were ineffective, a sputum test revealed TB. She started on treatment but after a couple of months, she started developing some bad side effects, including extreme weakness and yellowing around the whites of her eyes. Additional tests showed she had MDR-TB, and once again, her treatment changed.

After three months, her TB symptoms were gone, and she felt like she was on the road to recovery. Through counseling from the medical staff, whom she praised highly, she learned that TB is curable, and she is hopeful for the future.

“I also made some friends among other TB patients; we always share and eat food together, and this has helped me emotionally.”

Source: Adapted from WHO’s *Personal Stories from TB Survivors - My Journey Fighting TB.*

Highlights

Other personal stories of TB patients can be found on WHO and US Centers of Disease Control and Prevention (including Spanish-language versions) websites.

Bacterium: Pneumonia

Pneumonia can be caused by multiple types of pathogens, including bacteria, viruses, and fungi. In children, the most common cause of pneumonia is the bacterium *Streptococcus pneumoniae* (*S. pneumoniae*).

Prevailing Resistance

The CDC has classified drug-resistant *S. pneumoniae* as a serious threat that requires prompt and sustained action.

For many years, pneumonia was cured inexpensively with penicillin. However, resistant strains were identified only four years after penicillin's introduction. WHO data from 22 countries showed that resistance to penicillin ranged from zero to 51%. Penicillin-resistant strains are also more likely to be resistant to other antibiotics. Between 20 and 40% of the isolates are resistant to macrolide antibiotics, around 22% to clindamycin, and about 35% to trimethoprim-sulfamethoxazole.

Consequences

S. pneumoniae is the leading cause of death from pneumonia worldwide. It claimed the lives of an estimated 808,694 children under five years of age in 2017. It also causes a huge burden of disease in adults. In the US alone, pneumococcal pneumonia in adults leads to an estimated 150,000 hospitalizations each year.

Sources: CDC 2019; Review on Antimicrobial Resistance 2016; WHO 2018c; WHO 2019c. Cherazard 2017.

Glossary Term:

pneumococcal conjugate vaccine

pneumonia

Did You Know?

Since the pneumococcal conjugate vaccine has been in wide use, resistant strains of *S. pneumoniae* have sharply fallen; for example, since the vaccine was introduced in the US in 2000, the rates of antibiotic-resistant invasive pneumococcal infections caused by vaccine strains decreased by 97% among children younger than 5 years old and by more than 60% among adults. Universal coverage of the vaccine could potentially avert over 11 million days of antibiotic use per year in children under 5, equivalent to a 47% reduction in the amount of antibiotics used to treat *S. pneumoniae*.

Sources: CDC 2020; Review on Antimicrobial Resistance 2016.

Bacterium: Gonorrhea

Data from 2016 estimated that 87 million people were infected with gonorrhea in one year. If left untreated, it can cause serious complications, particularly in women.

Potential complications caused by gonorrhea include the following:

- Infertility
- Eye (ophthalmic) infections in newborns
- Pelvic inflammatory disease
- Miscarriage
- Five-fold increase in HIV transmission

Prevailing Resistance

Once easily treatable, gonorrhea is now resistant to several antibiotics, including penicillin, tetracycline, fluoroquinolones (such as ciprofloxacin and ofloxacin), and older generations of cephalosporins.

Resistance to extended-spectrum cephalosporins such as cefixime—currently regarded as the “last-line” treatment—has also been documented in Australia, Japan, Norway, and other countries.

Consequences

With no vaccine available and no new drugs in development, it is likely that gonorrhea may soon become untreatable.

Sources: CDC 2019; Wi et al. 2017; WHO 2020a. WHO 2018d; Wi 2017.

Did You Know?

A survey of gonococcal samples in 21 Asia Pacific countries or territories from 2011 to 2016 showed quickly increasing resistance to ceftriaxone and azithromycin. Samples of ceftriaxone meeting WHO's definition of decreased susceptibility increased from 14.3% to 35.3% and the percentage of locations reporting samples with azithromycin resistance increased from 14.3% to 38.9%.

Source: George CRR et al. 2019.

Bacterium: MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) refers to a strain of *S. aureus* (a common cause of skin, wound, and blood infections) that has acquired genes that can withstand the effects of several types of antibiotics.

MRSA began emerging during the 1960s and was primarily seen in hospital-acquired infections. Today, instances of community-acquired MRSA have increased significantly in many countries. Livestock-associated MRSA has also been identified and is now a major concern in many parts of the world. Those who handle livestock have a significantly higher risk of getting colonized and infected by livestock-associated MRSA.

Prevailing Resistance

WHO’s first global report on antibiotic resistance, published in 2014, highlighted the global problem of MRSA. In some parts of the WHO Africa and Western Pacific regions, as many as 80% of staph infections were methicillin-resistant.

While the incidence of MRSA infections has overall been declining in recent years, progress to prevent MRSA bloodstream infections in healthcare has stalled, and as a result, serious health care-associated MRSA infections have not been declining.

Consequences

People with MRSA are estimated to be 64% more likely to die than those with a non-resistant form of the infection.

Source: CDDEP 2017; CDC 2019; CDC 2019a; Chen 2020; Sadiq A. et al. 2020; WHO 2014; WHO 2020a.

Glossary Term:
hospital-acquired infection

Bacterium: Other Bacteria of International Concern

A host of additional bacteria that cause significant death and disability have been identified by the WHO as bacteria of international concern. These pathogens, along with others already discussed in this course (including *S. pneumoniae,* MRSA, and gonorrhea) are frequent causes of community or hospital-acquired

infections.

Prevailing Resistance

Of particular concern is the growing resistance of several bacteria to a class of antibiotics known as cephalosporins and carbapenems, which, for many conditions, represent the last line of effective treatment. Some strains of carbapenem-resistant Enterobacterales (CRE) have developed resistance to most of the available antibiotics, resulting in mortality rates of 50%.

Bacteria	Example of Illness Caused	Showing Resistance to:
Enterococci	• Urinary tract infections • Bloodstream infections • Wound infections	• Vancomycin (called vancomycin-resistant enterococci or VRE)
Escherichia coli (E.coli)	• Urinary tract infections • Bloodstream infections	• Third generation cephalosporins, with production of extended spectrum beta-lactamases (ESBLs)
Klebsiella pneumoniae (K. pneumoniae)	• Pneumonia • Urinary tract infections • Bloodstream infections	• Third generation cephalosporins (with production of ESBLs) • Carbapenems
Nontyphoidal Salmonella	• Foodborne diarrhea and/or • Blood stream infections	• Ceftriaxone • Ciprofloxacin
Pseudomonas aeruginosa	• Pneumonia • Urinary tract infections • Bloodstream infections • Surgical site infections	• Aminoglycosides • Cephalosporins • Fluoroquinolones • Carbapenems

Salmonella typhi	• Typhoid fever	• Azithromycin • Ceftriaxone • Ciprofloxacin
Shigella species	• Diarrhea (“bacillary dysentery”)	• Azithromycin • Ciprofloxacin

The following is a list of antibiotic-resistant bacteria that cause many hospital-acquired infections:

- Carbapenem-resistant Enterobacterales
- Methicillin-resistant *Staphylococcus aureus*
- Extended-spectrum β-lactamase-producing Enterobacterales
- Vancomycin-resistant Enterococci
- Multidrug-resistant *Pseudomonas aeruginosa*
- Multidrug-resistant *Acinetobacter*

Consequences

In Europe from 2007 to 2015, the median number of deaths attributed to carbapenem-resistant *P. aeruginosa, K. pneumoniae*, and *E. coli* increased by a factor of 3.29, 6.16, and 4.76, respectively. Colistin is the last resort treatment for CRE. Resistance to colistin (a crucial antimicrobial agent for some multidrug resistant infections) has recently been detected in several countries and regions, making those infections untreatable. Both CDC and WHO have classified CRE as one of the most critical MDR pathogens of public health significance.

Sources: Cassini et al. 2019; CDC 2019; WHO 2017b; WHO 2014; Wang M. et al. 2019; WHO 2020a.

Glossary Term:
carbapenem-resistant Enterobacterales (CRE)

> **Highlight**
>
> To read more about how antimicrobial resistance has affected people, visit this page of patient stories from the Infectious Disease Society of America.

Parasite: Malaria

Substantial decreases in the number of both malaria cases and deaths have been observed in recent years, largely due to effective prevention and treatment strategies using:

- Antimalarial medicines
- Vector control
- Insecticide-treated nets

For example, the global number of cases decreased to 228 million in 2018 from 251 million in 2010. However, in 2018, nearly half of the world’s population still remained at risk for malaria and 405,000 people died from the disease.

Prevailing Resistance

Chloroquine, once widely effective in eliminating one of the main malaria-causing parasites, *Plasmodium falciparum*, is now no longer effective across much of Africa (where the disease burden is greatest). Chloroquine was replaced by sulfadoxine-pyrimethamine (SP), which also showed signs of resistance within a few years of mainstream use.

Artemisinin-based combination therapies (ACTs) are the standard for malaria treatment. However, it is worrisome that parasite resistance to and treatment failure with ACTs are being reported from countries in Asia's Greater Mekong Subregion, the same region where chloroquine resistance first emerged. Recent studies suggest a failure rate for dihydroartemisinin-piperaquine (DHA-PPQ) of up to 62% in western Cambodia; 53% in southwestern Vietnam, and 87% in northeastern Thailand. Of great concern are the new findings of emerging artemisinin resistance of *Plasmodium falciparum* in Africa.

Chloroquine is still effective as the first-line treatment for *P. vivax* in many countries; however, resistance or high treatment failure rates are being seen in some countries, such as Ethiopia, Madagascar, Myanmar, and Timor-Leste.

The rise of drug-resistant malaria strains has occurred largely as a consequence of the irrational (i.e., inappropriate) use of antimalarial medicines, including poor treatment practices, poor patient adherence, and the availability of substandard and falsified medicines.

The use of oral artemisinin and its derivatives, such as artesunate, as a monotherapy, is an example of irrational use that contributes to ACT resistance. In addition, the indiscriminate use of chloroquine/hydroxychloroquine as a potential (and later proved ineffective) treatment for COVID-19 caused drug shortages and potentially increased chloroquine resistance, which is still the drug of choice for *Plasmodium* species other than *P. falciparum*.

Consequences

The spread of ACT-resistant malaria to other parts of the world, particularly sub-Saharan Africa, could pose a major health security risk, because no alternative antimalarial medicine has the same level of efficacy and tolerability as ACTs.

Sources: Abena et al. 2020; Mellon 2019; Kozlov 2021; The Lancet 2019; WHO 2019d. WHO 2019e; WHO 2020d.

Glossary Term:

artemisinin-based combination therapy (ACT)
malaria

Highlight

WHO approved the first malaira vaccine (RTS,S vaccine) in October 2021 and recommended its widespread use among children in sub-Saharan Africa.

Source: Maxmen 2021

Virus: HIV

By the end of 2019, 38 million people were living with HIV. Antiretroviral treatment in low- and middle-income countries has expanded dramatically throughout the past decade, with over 25 million now receiving treatment.

As with any antimicrobial agent, with the widespread use of antiretrovirals (ARVs) comes the risk of the development and spread of resistance.

Prevailing Resistance

Surveys in 18 low- and middle-income countries between 2014 and 2018 showed that 12 of those 18 countries had a prevalence of resistance to non-nucleoside reverse transcriptase inhibitors (nevirapine/efavirenz) above 10% for patients who had never previously received antiretroviral treatment.

The burden was much higher in women, with an average prevalence of 11.8% compared with 7.8% for men across the 18 countries.

Consequences

The extremely high rate at which HIV mutates, combined with the difficulties in maintaining optimal and lifelong adherence to ARV treatment, means that a drug-resistant strain can become the predominant circulating strain in just two to four weeks, underscoring the need for pharmacovigilance and other monitoring.

The WHO has identified resistance to antiretroviral agents as a major public health concern. Preventing drug-resistant HIV is one of the strategic objectives of the Global Action Plan on HIVDR: 2017-2021.

The high levels of pretreatment drug resistance that exceed the recommended threshold of 10% highlight the need to fast-track WHO's recommendation in 2018 to adopt a dolutegravir-based regimen to help prevent the negative effects of resistance to nevirapine and efavirenz. In addition, countries need to improve practice quality indicators such as appropriate prescribing and retention on therapy at 12 months, which needs particular attention.

Sources: WHO 2019f; WHO 2019i.

Glossary Term:
non-nucleoside reverse transcriptase inhibitor (NNRTI)
pharmacovigilance
human immunodeficiency virus (HIV)

Highlight

The prevalence of resistance to nevirapine/efavirenz among women was over 30% in three countries—Cuba, Honduras, and Nicaragua—highlighting the urgency of changing first-line treatment there.

Source: WHO 2019f.

Did You Know?

People with HIV are at an increased risk for TB. In fact, TB accounts for one-third of all AIDS deaths worldwide and is one of the most common causes of morbidity among people living with HIV/AIDS.

Source: WHO 2019g.

Fungi: Candida

Some infections, like candidiasis, are caused by fungi. Candidiasis frequently develops in patients receiving intensive antibacterial therapy and is caused by the yeast *Candida*, which is the most common cause of fungal infections worldwide.

Three primary antifungal classes of medicines exist to treat *Candida* and other fungal infections.

Prevailing Resistance

Some fungi have developed resistance and no longer respond to these medications—*Candida auris* and *Candida glabrata*, for example, can be resistant to all three classes:

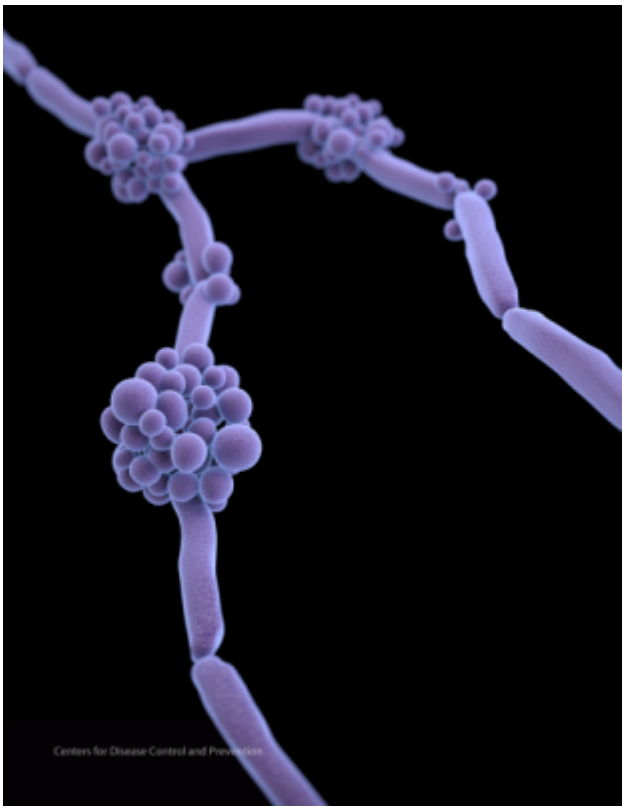
- Azoles (e.g., fluconazole)
- Echinocandins, (anidulafungin, caspofungin, and micafungin)
- Polyene (e.g., amphotericin B)

Global rates of fluconazole and echinocandins resistance appear to be rising. However, resistance varies widely depending on the *Candida* species. In addition to clinical use, the increasing use of these compounds in agricultural pesticides may also contribute to resistance.

Consequences

For patients who develop *Candida* infections that are multidrug resistant, there are few remaining treatment options, some of which can be toxic for patients who are already extremely sick. An average of one in four patients with *Candida* bloodstream infections die.

Sources: Hendrickson JA et al. 2019; Ostrowsky B 2019; Toda M et al. 2019; Whaley SG et al., 2017.



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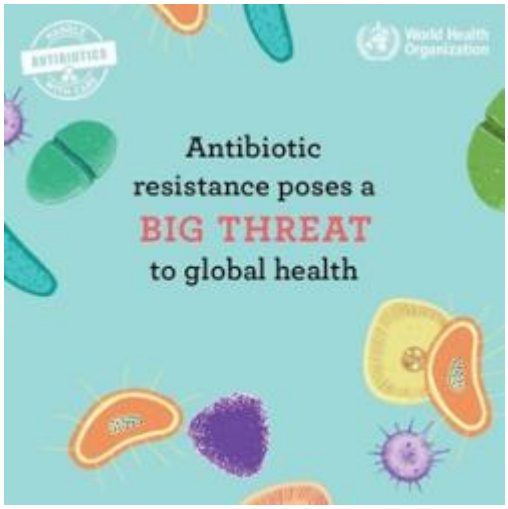
Session Summary



Antimicrobial resistance is not only a concern for one disease or due to one type of microorganism. This session described how antimicrobial resistance has wide-ranging effects across disease-causing bacteria, viruses, parasites, and fungi of major public health importance. As the case study of Thandiwe showed, becoming infected with a resistant organism (or multiple resistant organisms) can have severe and lasting effects on an individual's health and wellbeing.

In the next session, we will discuss the impact AMR has on individuals, health systems, societies, and global public health goals, as well as identify some of the key international responses to AMR.

Impact of AMR and International Response

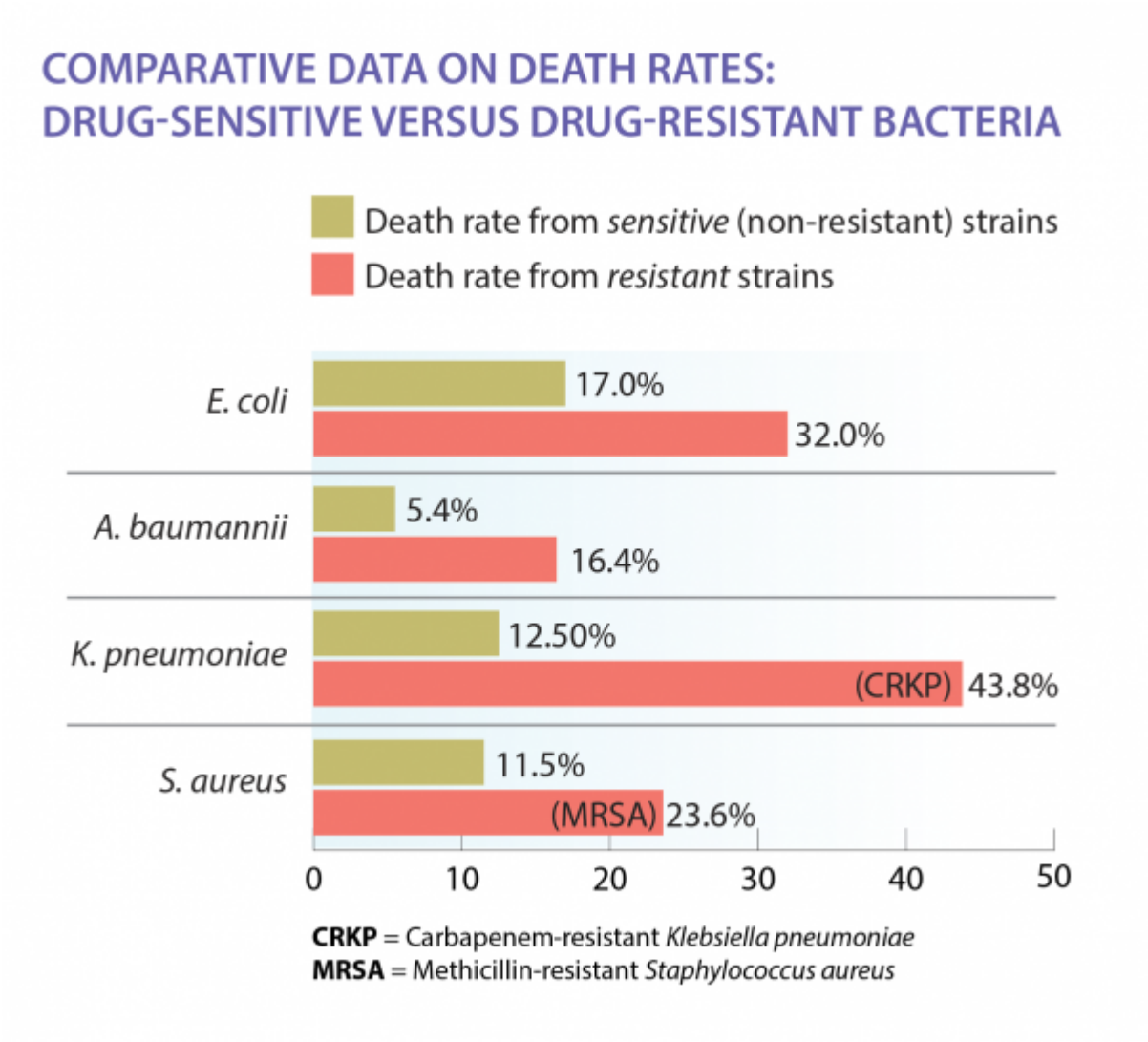
After completing this session, learners will be able to do the following:

- Describe the impact of AMR on individuals, society, health systems, and global health goals
- Identify key international responses to AMR

Impact on Individuals: Increased Mortality

Based on what we have seen so far in the course, you might find it easy to conclude that AMR has drastic implications for patients in terms of their health outcomes; however, it also has potentially devastating financial, social, and psychological effects.

Patients who are infected with pathogens that are resistant to standard treatments typically require more complicated treatment, take longer to recover, and are more likely suffer treatment failure and death (see figure below).



Now we will dive into specific impacts we have not discussed yet.

Sources: ReAct 2012; President's Council of Advisors on Science and Technology 2014

Highlight

A 10-hospital study from India analyzed results from antimicrobial susceptibility testing for Enterococcus spp., *E. coli, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa*, and Enterobacter spp. The 5,103 patient samples showed a significant relationship between multidrug resistance (MDR) and mortality: patients with MDR or extremely drug-resistant (XDR) *E. coli*, XDR *K. pneumoniae*, and MDR *A. baumannii* infections had two to three times higher mortality.

Source: Gandra S et al. 2019.

Impact on Individuals: Financial and Psychological Consequences

Drug resistance results in increased costs to patients for several reasons, including:

- More expensive second- or third-line drugs, which may require more sophisticated administration techniques
- Need for longer hospitalizations
- Closer monitoring of treatment
- Management of potentially more frequent or severe drug side effects

Patients with AMR-related illnesses may miss work for longer periods, which results in loss of productivity and income.

Managing drug-resistant infections may bring catastrophic financial hardship to patients and their families and can prevent people from ever seeking care. AMR therefore represents a significant barrier to achieving the Sustainable Development Goals and universal health coverage. Drug-resistant infections may also increase anxiety and have other psychological effects on patients and their families. Stigma around certain diseases, such as HIV or TB, may also affect a patient's ability to seek care or remain adherent to their treatment regimens, which can further exacerbate poor health outcomes. Long-term treatment regimens, especially those with medicines that may cause side effects, can have drastic psychological implications that may also negatively influence health outcomes.

Source: van der Heijden M et al. 2019.

Glossary Term:
universal health coverage
Sustainable Development Goals

> **Highlight**
>
> A study of 220 patients in a hospital in India showed notable differences in experience for patients who had drug-resistant sepsis vs. those that had drug-susceptible sepsis. The total median cost difference was $700, representing approximately 442 days of wages of a rural male casual worker in India. Further, the antibiotic cost difference was $139 and pharmacy cost difference was $358. The differences in health consequences were also significant: admission to the intensive care unit—44% vs. 21%; complications—56% vs. 37%; length of stay—14 vs. 11 days; and mortality—12% vs. 2%.
>
> *Source*: Chandy SJ et al. 2014.

Impact on Health Systems and Societies: Increased Mortality and Cost

The negative effects of AMR are not borne by patients alone, but also by health systems. Societal impacts may also result, as patients with prolonged drug-resistant infections may inadvertently put family and other community members at risk of illness, not to mention the long-term effects due to loss of productivity and increased morbidity.

Mortality

Globally, the current estimated number of deaths due to drug-resistant infections is already approximately 700,000 each year. This figure is likely to reach as high as 10 million per year by 2050 if AMR remains unchecked.

Costs

AMR also imposes enormous financial burdens on society as a whole from increased morbidity and mortality, but also as a result of longer hospital stays, more expensive treatment, and personal financial losses. AMR costs the US health system $20 billion per year. Globally, it is estimated that $5.8 trillion is lost annually in productivity. Some estimates indicate that, if left unchecked, AMR may lead to a cumulative global cost of $100 trillion by the year 2050 and thrust an additional 24 million people into extreme poverty by 2030—mainly individuals living in low-income countries.

Sources: CDC 2019; Review on Antimicrobial Resistance 2016; World Bank 2017.

The Potential for Catastrophic Effects

The consequences of antimicrobial resistance already discussed in this course are just part of the issue.

AMR has clear implications for medical advances that rely on antibiotics to prevent infections, including complex surgeries, cancer treatment, and organ transplantation. These advanced procedures could become increasingly risky or infeasible, which would increase morbidity and mortality around the world.

If a particular AMR strain were to reach pandemic levels, food shortages could occur due to untreatable infections in farm animals and restrictions could be imposed on travel, migration, and trade. Such scenarios could lead to serious market failures, challenges in global governance, and huge social impacts. Low-income countries would suffer the most, resulting in greater income inequality. The World Bank estimated that the global economic losses would rival those of the 2008-2009 global financial losses, but last for many more years.

Of additional concern is the potential for existing drug-resistant bacteria (or bacteria engineered with resistant genes) to be intentionally released as a weapon.

Creating a world safe and secure from infectious disease threats was the impetus behind the 2014 launch of the Global Health Security Agenda. The agenda outlines 19 areas of action and leverages country commitments and cooperation to advance long-term global health security. AMR is one of the 19 technical areas.

Sources: van der Heijden M et al. 2019; World Bank 2017.

AMR: A Challenge to Achieving the SDGs

Adopted by all UN Member States in 2015, the 17 Sustainable Development Goals (SDGs) are a call to improve the lives of everyone, everywhere by 2030. The goals cover a range of issues from poverty to health, to the environment.

There is a direct connection between AMR and achieving SDG 3—Good Health and Well-being. However, because many of the SDGs are intertwined, lack of progress on SDG 3, also affects others. For example, without good health of the family provider, the entire family is more likely to go hungry. Without AMR containment, SDGs 1, 2, 3, 8, and 10, among others, are likely not achievable.

Source: IISD/SDG Knowledge Hub 2019; United Nations N.D.; van der Heijden M et al. 2019.

Glossary Term:

Sustainable Development Goals

AMR: A Challenge to Achieving UHC

Under universal health coverage (UHC), everyone receives the health services they need without financial hardship.

Sustainable Development Goal 3 targets achieving universal health coverage, including:

- Financial risk protection
- Access to quality essential health care services
- Access to safe, effective, quality, and affordable essential medicines and vaccines for all

AMR makes it more difficult for countries to provide UHC by:

- Making first- and second-line antimicrobials ineffective, affecting supply chains, access, and treatment efficacy
- Diverting scarce health system resources, affecting supply chain and affordability of treatment and health services
- Translating into expensive treatment, affecting affordability and causing financial hardship
- Making treatment difficult and complex, affecting health service quality and treatment effectiveness

Although many think of UHC primarily as a health financing issue that if achieved would provide access to essential health services, the service quality is also of utmost importance as is the inclusion of medical products in the basic package of care provided under UHC. The complex dynamics and relationships at play require a systems approach to achieve UHC and to contain AMR. There is growing international effort to use the momentum behind UHC efforts to simultaneously address AMR.

Sources: ReAct 2019; Tayler E. et al. 2019; Joshi MP 2016; WHO. 2019h; WHO 2020e.

Highlight

The first national TB patient cost survey carried out in Lao People's Democratic Republic in 2018-2019 showed that 86.7% of people with drug-resistant TB faced catastrophic costs (>20% of household annual income) compared with 62.2% of people with drug-susceptible TB.

Source: Chittamany P. et al. 2020.

The World Health Organization's Response to AMR

Recognizing the potentially grave impact of AMR on global health outcomes, the World Health Organization (WHO) has taken several steps toward catalyzing coordinated global action toward the containment of AMR.

In 2015, following the World Health Assembly, the WHO adopted a global action plan to help address, build awareness, and promote coordinated global action to keep AMR from eroding the progress of modern medicine.

Part 2 of this course lists the objectives of the WHO Global Action Plan and some of the key actions to meet those objectives.

The chart below provides a chronology of the major actions WHO and the tripartite--WHO, Food and Agriculture Organization (FAO), and World Organsiation for Animal Health (OIE)--have taken to fight AMR, along with links to each respective document.

Year	Select WHO Responses to AMR
2015	Global Action Plan to Combat AMR [S1]
2016	Antimicrobial resistance: A manual for developing national action plans
2017	Antimicrobial priority pathogen list
2019	Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and selected indicators
2019	Antimicrobial Resistance Multi-Partner Trust Fund
2015 - 2020	Annual World Antibiotic Awareness Week (WAAW) events
2017 - 2019	AWaRe (Access, Watch, Reserve) classification of antibiotics in Model EML (2017) and AWaRe portal and database (2019
2019 - 2020	Tripartite AMR Country Self-assessment Survey (TrACSS) Global Analysis Report

Year	Select WHO Responses to AMR
2020	The One Health Global Leaders Group on Antimicrobial Resistance
2014 - 2021	Multiple guidance documents, discussion papers, and other tools on surveillance of AMR and antimicrobial use, IPC, AMS, and multisectoral coordination on AMR.
2021	Tripartite AMR Country Self-assessment Survey (TrACSS) 2021 data

One Health Approach to AMR

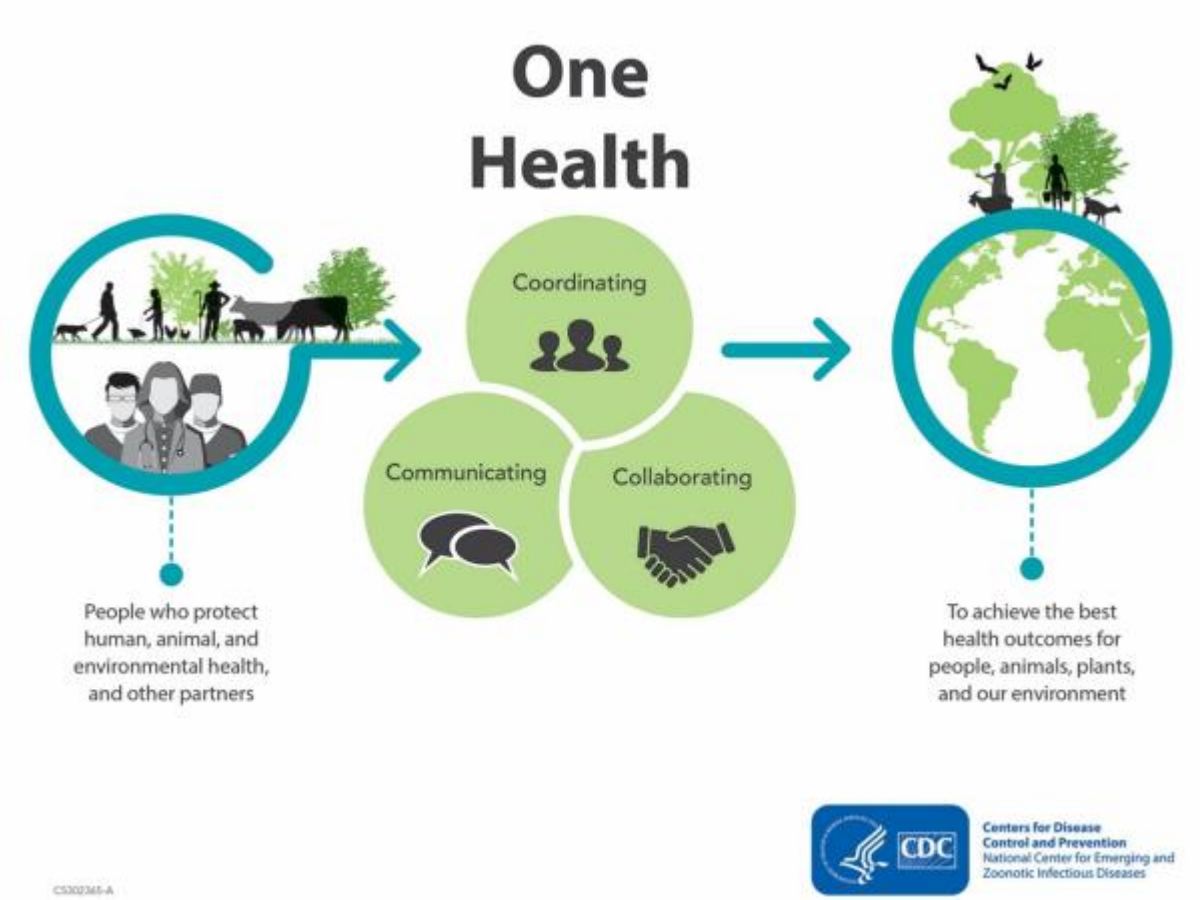
Because the drivers of AMR come from humans, animals, plants, and the environment and are intertwined, controlling AMR requires coordination among these sectors. For example, misuse and overuse of antimicrobials not just in humans, but also in animal husbandry, agriculture, and aquaculture, can lead to resistant microbes circulating among these various sectors, including the environment. Being a multifaceted and multifactorial issue, AMR requires a coordinated and concerted approach.

Previous efforts to combat AMR were highly siloed with little collaboration between players and sectors. One Health is the concept of multisectoral coordination to ensure optimal health for people, domestic animals, wildlife, plants, and our environment. In the context of One Health, the Food and Agriculture Organization (FAO), the World Organisation for Animal Health (OIE), and the World Health Organization (WHO) committed to support governments; health care workers; veterinary, plant, and environmental professionals; and other stakeholders to promote multisectoral activities to contain AMR.

Examples of One Health actions include the following:

- Joint assessments, planning, and reviews
- Joint budgeting
- One global surveillance AMR repository, e.g. Global Antimicrobial Resistance and Use Surveillance System (GLASS)
- Integrated education (e.g. One Health competency)
- Policy review and coherence between sectors
- Intersectoral communication and coordination

For example, many countries now have multisectoral coordination bodies on AMR that include members from various sectors, including the human, animal, and environmental sectors. The main objective of these bodies is to help implement their national action plans on AMR through multisectoral meetings, reviews, collaborations, and actions.



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Source: Alas M 2020; Collingnon PJ and McEwen SA 2019; Interagency Coordination Group on Antimicrobial Resistance 2019; Joshi MP et al. 2021.

Glossary Term:
nosocomial infections

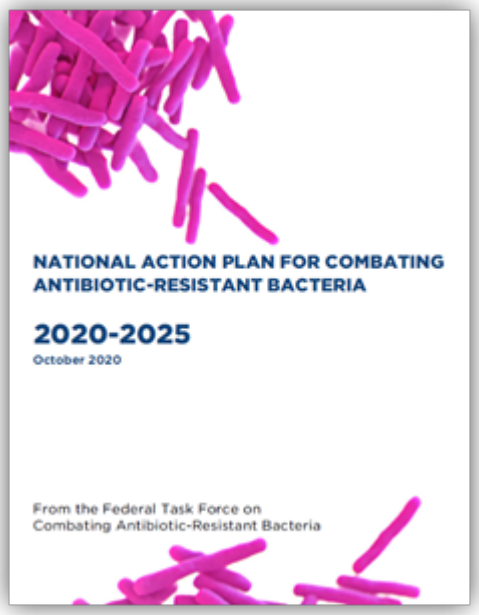
National Action Plans on AMR

As of January 2021, 143 countries had finalized national plans to help combat AMR and 43 were in the process.

Côte d'Ivoire launched its national action plan (2019-2020) with an accompanying AMR policy and governance manual. The action plan for the US National Strategy for Combating Antibiotic-Resistant Bacteria has been updated for 2020-2025. It takes a One Health approach and expands activities that have proven effective in combating AMR such as infection prevention and control and antimicrobial usage.

Source: WHO 2021a.

The Global Health Security Agenda



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Launched in 2014, the Global Health Security Agenda (GHSA) is a partnership of more than 70 nations, international organizations, and non-governmental stakeholders and private sector entities to strengthen the world's ability to prevent, detect, and respond to infectious disease threats. The GHSA includes 19 technical areas or action packages, including one specifically focused on addressing antimicrobial resistance.

The AMR Action Package of GHSA seeks to support the WHO Global Action Plan on AMR by building country capacity related to multisectoral coordination, AMR surveillance, infection prevention and control, and antimicrobial stewardship in human and animal sectors, and maintaining AMR as a priority on political agendas.

The GHSA 2024 target is to strengthen 100 countries to a level of "Demonstrated Capacity" in at least five technical areas as measured by relevant health security assessments, such as the WHO's Joint External Evaluation (JEE) tool.

Source: GHSA 2018.

WHO Joint External Evaluation (JEE) Tool

The WHO developed the International Health Regulations Joint External Evaluation (JEE) tool in 2016 (revised in 2018) to measure progress in all elements of the GHSA assessment. The JEE process is voluntary, collaborative, multisectoral, and transparent and rates country capacity across five levels:

- No Capacity (Level 1)
- Limited Capacity (Level 2)
- Developed Capacity (Level 3)
- Demonstrated Capacity (Level 4)
- Sustainable Capacity (Level 5)

As of November 2020, 113 countries had completed a JEE.

The four indicators of AMR country capacity in the JEE tool are:

- P.3.1 Effective multisectoral coordination (MSC) on AMR
- P.3.2 Surveillance of AMR
- P.3.3 Infection prevention and control (IPC)
- P.3.4 Optimize use of antimicrobials in human and animal health and agriculture (antimicrobial stewardship, AMS)

Source: WHO 2018; CDC 2020a; de la Rocque 2021

Highlight

In its 2017 JEE, Kenya scored 2 (“Limited Capacity”) for indicator 3.4 related to antimicrobial stewardship. The evaluators found that Kenya’s national plan for the prevention and containment of AMR had been approved and included antimicrobial stewardship, its national action plan for antimicrobial stewardship was complete, and development of antibiotic use guidelines for veterinary practice was complete.

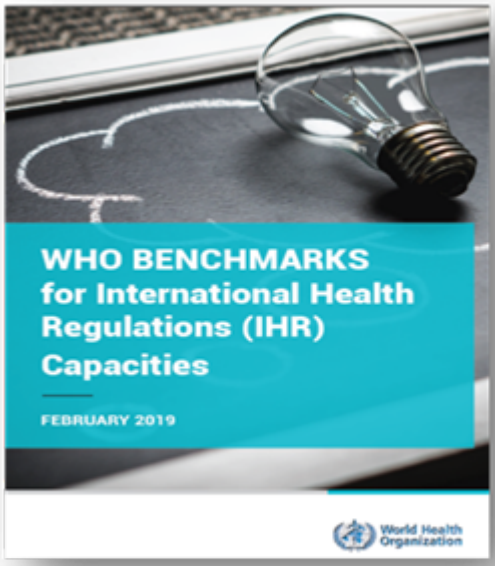
The evaluators made the following recommendations for Kenya to advance its capacity level score:

- There is a need for systematic implementation of existing treatment guidelines.
- There is a need to develop training curriculum for antimicrobial stewardship for pre-service and in-service training to reinforce the provisions for prudent/correct use of antimicrobials at all levels.
- An evaluation of antibiotic use patterns is required.
- There is a need for full implementation of antimicrobial stewardship activities in the human and animal health sector.

Source: WHO 2017c.

WHO Benchmark Actions

In 2019, WHO published a complementary list of benchmark actions designed to help improve the International Health Regulations capacities. This tool provides recommended actions for each JEE capacity level for the different technical areas, including AMR.



For example, the following are the recommended actions to achieve capacity level 3 for the indicator P.3.1. (multisectoral coordination on AMR):

- Develop a plan of action to address AMR in line with the Global Action Plan (GAP) on AMR
- Submit a plan for approval through relevant governance mechanisms (such as office of head of state, cabinet, or ministries of health and agriculture)
- Develop terms of reference for a multisectoral governance mechanism, with clear lines of accountability between the AMR coordinating committee and the high level One Health group making strategic and resourcing decisions
- Organize effective coordination through regular meetings

Sources: WHO 2019; Alliance for Health Security Co-operation 2019.

Session Summary

As shown in this session, AMR affects not only individuals, but also entire health systems and societies. Moreover, AMR impedes the achievements of key global public health goals such as the Sustainable Development Goals and universal health coverage. AMR's wide-reaching consequences have elicited major global initiatives aimed at curbing its development and spread, including its inclusion in the Global Health Security Agenda, which is a growing partnership of over 70 countries and other stakeholders.

Part 2 of this course explains, in more detail, the major factors contributing to AMR and the range of interventions that can help contain it.

Learning More about AMR

Part 2 of the AMR Course

This course is Part 1 of 2 on antimicrobial resistance available on the Global Health eLearning Center. Building on this course, Antimicrobial Resistance, Part 2 explains the major factors that contribute to the development and spread of AMR and the interventions available to help address these factors. We encourage you to take Part 2!

Additional Resources and Reading

Included in the References tab at right is a list of additional resources and relevant reading materials that can help you continue learning about AMR.