MEDICINES IN DEVELOPMENT | 2021 REPORT

ANTIMICROBIAL RESISTANCE

JUST THE FACTS

$5.75 BILLION

ECONOMIC IMPACT ANNUALLY FROM JUST 9 OF 18 AMR THREATS.[1]

AMR RESULTS IN

48,000

DEATHS EACH YEAR IN THE U.S.[1]

AMR AFFECTS AT LEAST

3 MILLION

AMERICANS EACH YEAR.[1]

AMR COULD CAUSE

10 MILLION

DEATHS EACH YEAR WORLDWIDE BY 2050.[2]

ANTIMICROBIAL RESISTANCE (AMR)

AMR and the Challenge of Establishing a Robust Pipeline of New Antimicrobial Products

Nearly **90** Medicines in Development Against Drug-Resistant Infections

As the world confronts the COVID-19 public health crisis, now more than ever is the time to consider preparedness for a growing public health threat: antimicrobial resistance (AMR). AMR is a natural process that occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that make the medicines used to treat the infections they cause ineffective. Therefore, the more we use such medicines, the more resistance we may create. This means a robust and sustained pipeline of new and novel antimicrobial medicines is critical to ensure that new innovations and interventions can keep pace with these evolving pathogens.

While AMR occurs across a range of microorganisms, infections caused by bacteria and fungi in particular have emerged as an urgent public health threat in the U.S and across the globe as people are increasingly dying from drug-resistant infections that were formerly routinely treatable. The discovery and introduction of antibiotics in the 1940s transformed modern medicine and enabled tremendous progress in health care, food production and life expectancy in the 20th century. Unfortunately, increasing rates of AMR and an insufficient pipeline of new medicines threaten to undo this progress.

This urgent threat is driven by a combination of increased exposure of pathogens to the medicines designed to kill them, along with the spread of mechanisms of resistance that these pathogens develop. Though a naturally occurring process, overuse in medical care, animal health and agriculture are all contributing to the growing threat of AMR.[1] During the COVID-19 pandemic, concerns about secondary bacterial infections have given rise to a significant percentage of hospitalized patients receiving broad-spectrum antimicrobials with a yet unknown impact on future microbial resistance rates.[3]

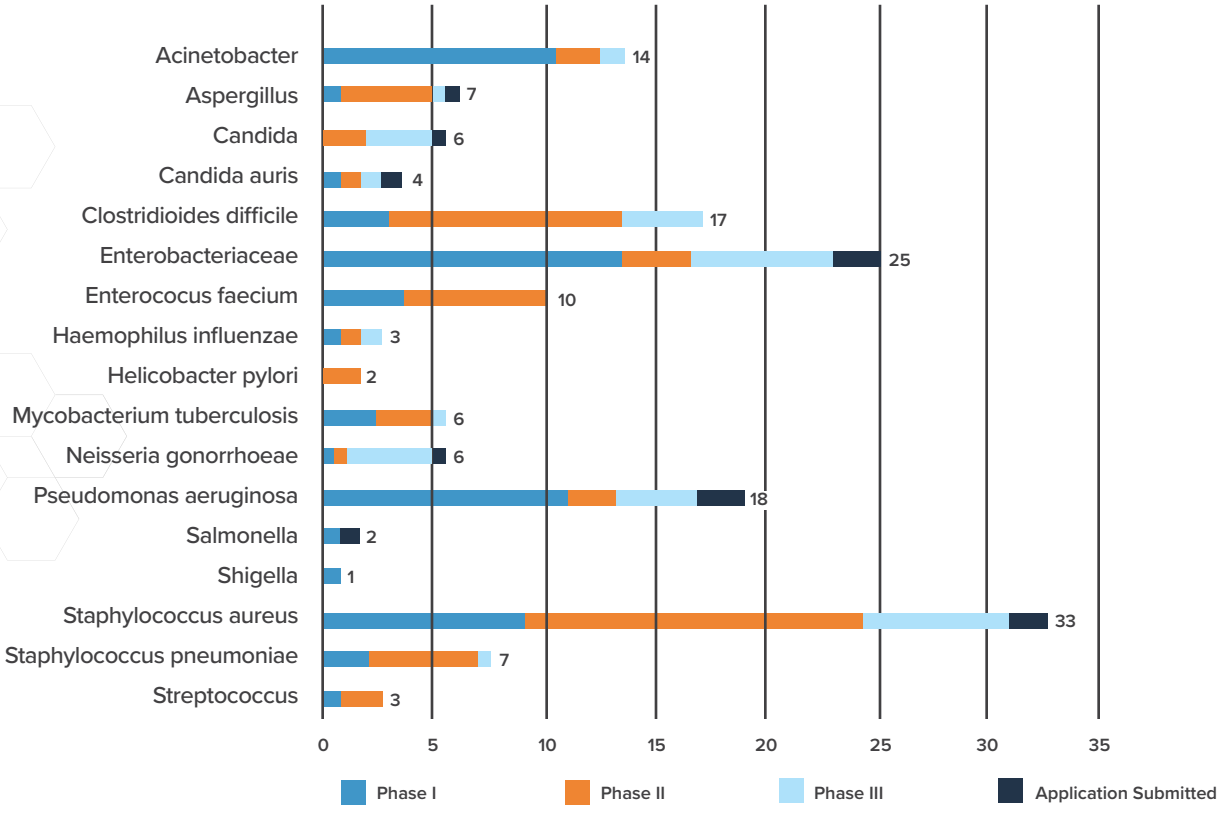
According to the U.S. Centers for Disease Control and Prevention (CDC), AMR affects at least 3 million Americans each year and 48,000 die as a result.[1] Further, a recent Government Accountability Office report finds these may in fact be an underestimate due to inadequate surveillance in the United States.[4] Unless action is taken, around the globe AMR could take 10 million lives annually by 2050, a higher toll than from cancer.[2]

AMR may also have been exacerbated during the COVID-19 pandemic as doctors desperate to save patients are using a large amount of antibiotics to treat hospitalized patients at risk for secondary infections caused by ventilators or weakened immune systems.[5] Initial data suggest that one in seven patients hospitalized with COVID-19 acquired dangerous secondary bacterial infection caused by ventilators or weakened immune systems.[6]

Recent reports from the CDC and the World Health Organization (WHO) have highlighted the serious threats posed by AMR and sought to identify the pathogens which pose the greatest risk to public health that continue to alarm experts both in the U.S. and around the world. This report seeks to examine the medicines in development that target these pathogens and challenges of the antimicrobial marketplace.

Biopharmaceutical researchers are working to develop new and effective treatments to combat AMR and to avoid turning back the clock on the progress made since the mid-century. These medicines represent more than antibiotics and include non-traditional antibacterial treatments, such as bacteriophage products, live therapeutic products and monoclonal antibodies. Today, **89** such medicines are currently in development by biopharmaceutical research companies, all of which are in clinical trials or awaiting review by the U.S. Food and Drug Administration (FDA).[7] A look at these medicines and the pathogens they target are highlighted in the graph below.

Medicines in Development for Antimicrobial Infections by Pathogen



Note: The CDC and WHO have highlighted the serious threats posed by AMR and have identified the pathogens which pose the greatest risk to public health that continue to alarm experts both in the U.S. and around the world. The medicines represented in the chart above have shown activity or possible activity against the specific pathogen. Some medicines are in more than one category.

Examples of Antimicrobials in the Pipeline

- A novel bacterial topoisomerase II inhibitor is being developed to treat *Neisseria gonorrhoeae* infections and uncomplicated urinary tract infections. The drug has a dual mechanism of action by selectively inhibiting two bacterial enzymes—DNA gyrase and topoisomerase IV—that play a role in bacterial DNA replication. The drug may have activity against most target pathogens resistant to established antibiotics.

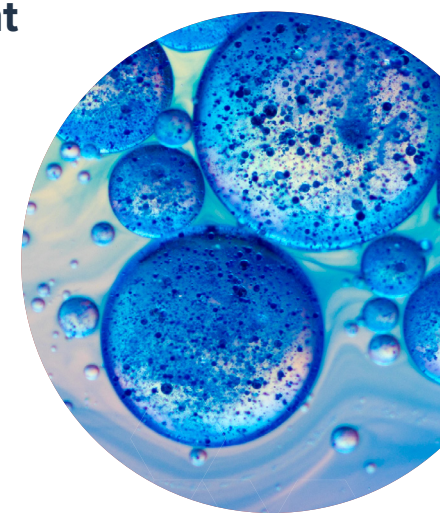
- A combination of a novel, broad-spectrum and potent inhibitor of beta-lactamase and a marketed beta-lactam antibiotic is being studied against **Acinetobacter baumannii**, a gram-negative bacterium that is becoming a common cause of hospital-acquired infections and is increasingly resistant to currently available treatments. Beta-lactamase-mediated resistance is widespread, leaving treatments generally ineffective. In preclinical trials, inhibiting the activity of beta-lactamase found in *Acinetobacter baumannii* in turn restored the effectiveness of the beta-lactam antibiotic.

- A monobactam antibiotic is in development for the treatment of bacterial infections and has demonstrated potent activity against serine and metallo-beta-lactamase expressing **carbapenem-resistant Enterobacteriaceae (CRE)**. The antibiotic inhibits bacterial peptidoglycan synthesis primarily through inhibition of penicillin-binding protein 3.

- A fixed combination treatment is being studied for the treatment of bacterial infections and complicated urinary tract infections caused by **multi-drug resistant gram-negative bacteria**, including ESBL-producing organisms, carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*; suspected polymicrobial infections caused by both gram-negative and gram-positive pathogens. The medicine is a combination of a broad-spectrum beta-lactamase inhibitor that directly inhibits all four major classes of beta-lactamases and a fourth-generation cephalosporin.

- An antibacterial targeting **Clostridioides difficile** for the treatment of *Clostridium difficile (C. difficile)* infections is an orally administered, narrow-spectrum antibacterial to specifically target *C. difficile* at the infection site, without causing damage to the healthy gut flora, to reduce the risk of recurrent infection.

The Challenging R&D and Reimbursement Environment for Antimicrobial Medicines



AMR presents a national security concern and is a threat to the everyday practice of medicine and patients around the world. Nearly all the antibiotics brought to market over the past 30 years have been improved versions of previously approved drugs, and every currently available antibiotic is a derivative of a class discovered between the early 1900s and 1984.[8] Recognizing the growing challenges with the AMR pipeline, in 2012, Congress passed the Generating Antibiotic Incentives Now (GAIN) Act, which sought to stimulate research into new antibiotics by creating incentives for the development of qualified infectious disease product (QIDP), antibacterials and antifungals that treat serious or life-threatening infections . Since that time, the FDA has approved nearly 20 new drugs with a QIDP designation.

While the medicines approved under GAIN were very much needed for patients with infections that were resistant to available antibiotics, these medicines emanated from existing classes of medicines. In order to manage the growing threat that AMR presents, we need a robust and diverse pipeline of treatments. Experts believe it will be necessary to generate new chemical substances as well as a better understanding of how to overcome the most difficult-to-treat infections in order to make progress on new research and development.

Unfortunately, the treatments we need to combat this growing threat are dwindling and the current pipeline is insufficient to deal with the growing threat of AMR as many biopharmaceutical companies have abandoned research into new infectious disease treatments. The findings here confirm what has been warned about by others: there are too few antimicrobial medicines in development targeting priority pathogens identified by the CDC and WHO as posing the greatest risk to public health to meet current and anticipated needs.[9]

Developing new medicines is a long, complex and risky process taking anywhere from 10 to 15 years and cost on average $2.6 billion for a single medicine. Among antibiotics, this process is fraught by even more risk. Developing new antimicrobial medicines can take anywhere from 10-20.5 years and $568-$700 million to develop a single new medicine. In fact, among antibiotics in existing classes of antibiotics in preclinical development just one in 15 will ultimately be approved and reach patients. And among new classes of antibiotics these odds are even slimmer with just one in 30 ultimately obtaining FDA approval. Recruiting sufficient numbers of volunteers to participate in the necessary clinical trials is especially challenging, because only a small number of patients contract infections from highly resistant pathogens and meet the requirements to participate.[11] Recognizing this challenge, Congress created the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway) to provide stakeholders with a tool to help with the approval of antibacterial and antifungal drugs to treat serious and life-threatening infections in a limited population of patients with unmet needs.[12]

In addition, unlike other medicines, the incentives necessary to allow companies to take these risks is lacking in the antimicrobials market. Stewardship policies designed to reduce the rise of resistance necessarily limit the use of new products, making it very challenging for biopharmaceutical research companies to recoup the substantial costs of research and development in subsequent sales.

Our current reimbursement system also reinforces misguided incentives which discourage appropriate use of new antimicrobials even when they are the most clinically appropriate treatment option to treat drug-resistance infections. That is because newer antimicrobial medicines are often more expensive than older generic options and providers are often discouraged from prescribing these new medicines due to financial disincentives that exist in a reimbursement system in which hospitals are reimbursed for inpatient services via bundles, or capitated amounts.

Many manufacturers have given up and have stopped working on innovative antibiotics because they cannot afford to take the substantial risks necessary to develop these products without some assurance of earning back the investment. While some companies are still trying to develop new antibiotics, it is hard to make an investment with no guarantee companies will ever recover what they have to spend to develop these antibiotics. Many small biotechnology companies focused on antibiotics that have tried to navigate the challenging market dynamics have gone bankrupt. Without policy interventions this market failure will persist at the expense of patients and global public health.

Selected Diseases Affected by Drug-Resistance

Antimicrobial medicines are critical to the care and treatment of patients with conditions other than infectious diseases. The drug resistance issue affects patients with cancer, Crohn's disease and liver disease, among others. Below are ways AMR can affect the treatment of some of these diseases.

- **Sepsis**, a life-threatening condition, occurs when the body aggressively responds to an infection, such as pneumonia, influenza or urinary tract infections. Without timely treatment, sepsis can rapidly lead to tissue damage, organ failure and death. Antibiotics are used, along with other therapies, to treat sepsis. Because controlling infections that can lead to sepsis, the use of antibiotics is the cornerstone of sepsis prevention and treatment. Resistance to antibiotics is damaging to the future of sepsis treatment and survival. Worldwide, one-third of people who develop sepsis die.[13] In the U.S., at least 1.7 million adults in America develop sepsis annually and nearly 270,000 Americans die as a result of sepsis. One in three patients who dies in a hospital has sepsis.[14]

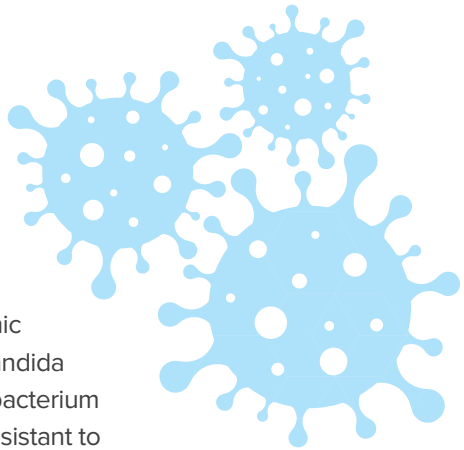
- Antibiotics are commonly used in the management of inflammatory bowel disease (IBD), which includes **Crohn's disease** and **colitis**. Antibiotics are used to treat infections that arise as a complication of IBD itself, as a treatment of infections that occur from the medicines used to treat IBD and sometimes to help treat the disease-causing inflammation of the intestines. *Clostridium difficile* infections are common in patients with IBD, where the infection attacks the intestines.[15] *Clostridium difficile* which can cause life-threatening diarrhea, is categorized as an urgent threat by the CDC. In 2017, C. difficile caused an estimated 223,900 hospitalizations and 12,800 deaths.[1]

- For **cancer** patients undergoing treatment—resulting in weakened immune systems—effective antibiotics are critical. Cancer patients are at a higher risk of contracting serious infectious diseases and rely on antibiotics for the prevention and treatment of infections, which is one of the most common life-threatening complications of their illness and treatment. A recent survey found that 95% of the oncologists worry antibiotic resistant bacteria will negatively impact the viability of chemotherapy.[16]

Resistance in Intensified in Health Care Settings

Antibiotic resistance disproportionally impacts the most vulnerable—the young, elderly and sick—who often receive medical care.[1] When not stopped, these resistant health care-associated germs can spill over into communities, becoming much harder to control.[1] For the "nightmare bacteria" CRE alone, aggressive containment responses could prevent 1,600 cases in just one state over three years.[1] From 2012 to 2017, the number of antibiotic-resistant infections seen in hospitals dropped 27% and the number of deaths from antibiotic-resistant infections fell nearly 30%.[1]

COVID-19 Response and its Impact on AMR



Antibiotic resistance has also been exacerbated during the COVID-19 pandemic, as doctors desperate to save patients are using a large amount of antibiotics to treat hospitalized patients at risk for secondary infections caused by ventilators or weakened immune systems.[5] Initial data suggest that one in seven patients hospitalized with COVID-19 acquired dangerous secondary bacterial infection caused by ventilators or weakened immune systems.[6] Focus on battling the COVID-19 pandemic has also caused certain drug-resistance organisms to take root and spread, such as Candida auris, a particularly dangerous fungus and Acinetobacter baumannii, a gram-negative bacterium that is becoming a common cause of hospital-acquired infections and is increasingly resistant to currently available treatments.[6]

CDC/WHO Reported Emerging and Remerging Threats

CDC Urgent Threats[1]
- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridioides difficile*
- Carbapenem-resistant *Enterobacteriaceae*
- Drug-resistant *Neisseria gonorrhoeae*

CDC Serious Threats[1]
- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*
- Vancomycin-resistant *Enterococci (VRE)*
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Staphylococcus pneumoniae*
- Drug-resistant Tuberculosis

CDC Concerning Threats[1]
- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

CDC Watch List[1]
- Azole-resistant *Aspergillus fumigatus*
- Drug-resistant *Mycoplasma genitalium*
- Drug-resistant *Bordatella pertussis*

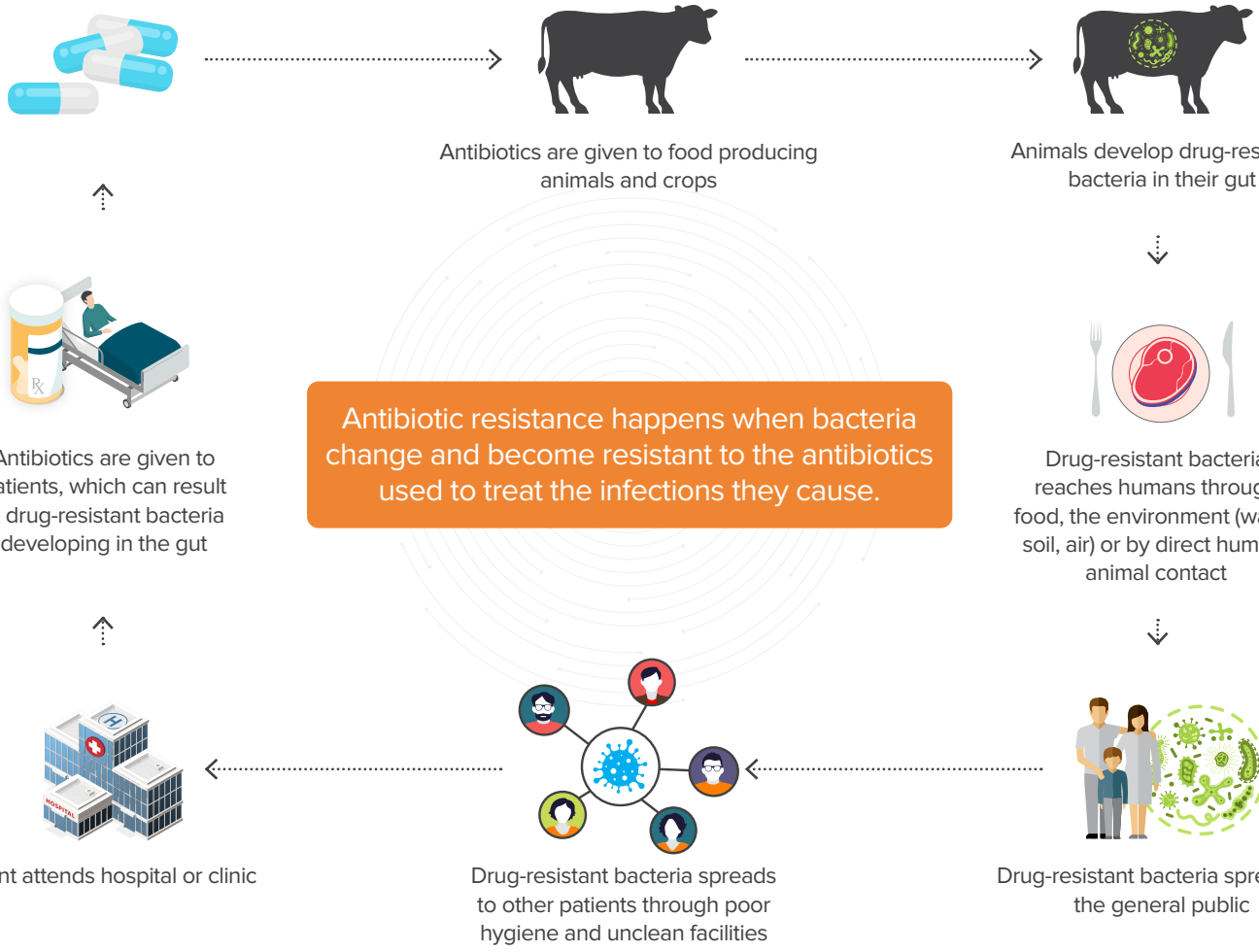
WHO Priority 1: Critical[2]
- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, Carbapenem-resistant
- *Enterobacteriaceae*, Carbapenem-resistant, 3rd gen. cephalosporin-resistant

WHO Priority 2: High[2]
- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and -resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter spp.*, fluoroquinolone-resistant
- *Salmonella species*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, 3rd gen. cephalosporin-resistant, fluoroquinolone-resistant

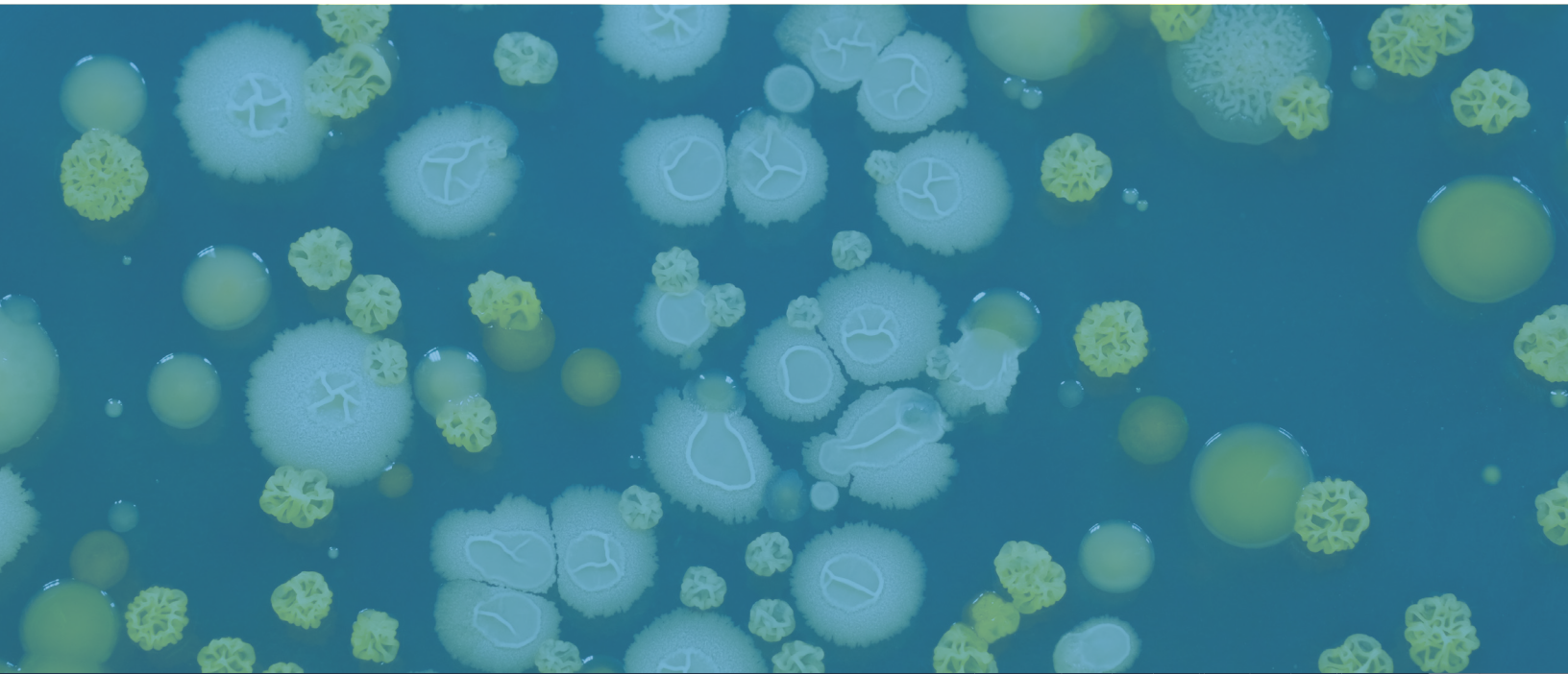
WHO Priority 3: Medium[2]
- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella species*, fluoroquinolone-resistant

WHO Other Concerns[2]
- *Mycobacterium* Tuberculosis
- *Clostridioides difficile*

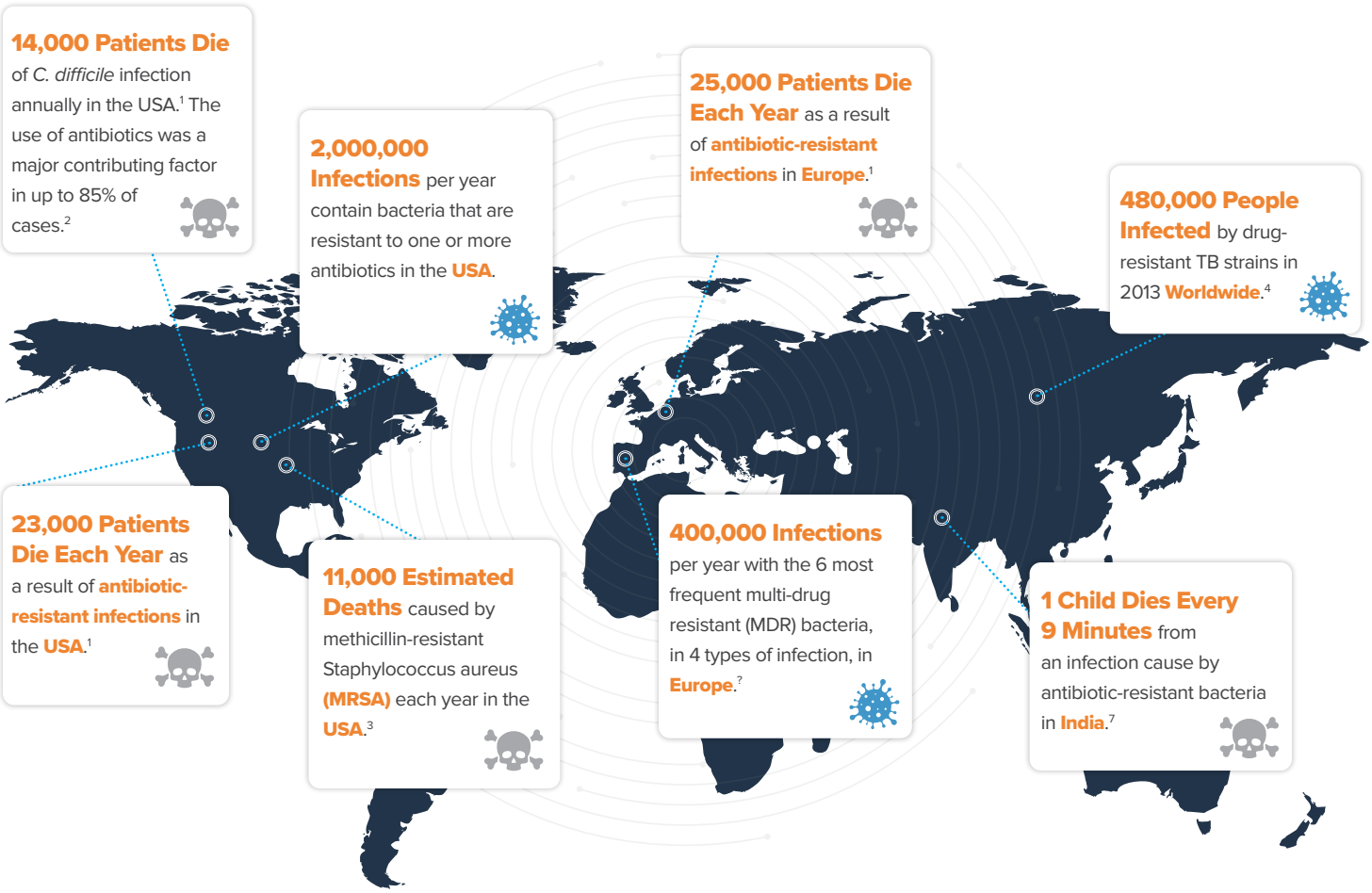
Antibiotic Resistant How It Spreads



Source: Graphic repurposed from the World Health Organization.



AMR Worldwide



Source: Graphic repurposed from the bioMerieux Connection. Updated version available here: https://www.biomerieuxconnection.com/wp-content/uploads/2017/12/antibiotic-resistance-worldwide-infographic.pdf

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