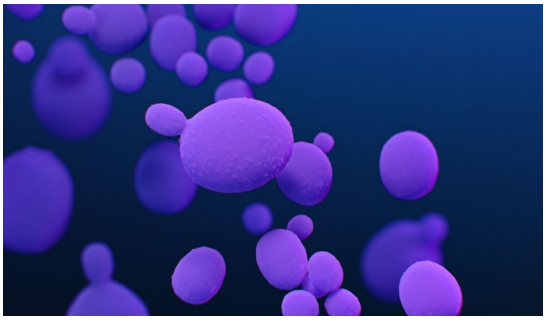
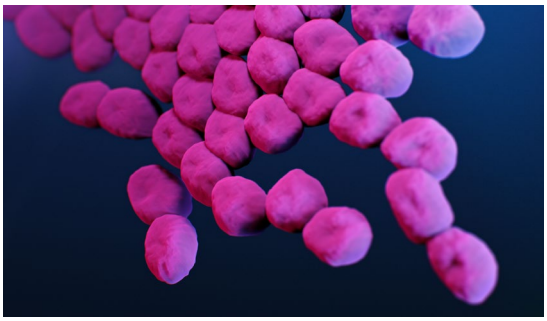
ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

2019





U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

Revised Dec. 2019

This report is dedicated to the 48,700 families who lose a loved one each year to antibiotic resistance or Clostridioides difficile, *and the countless healthcare providers, public health experts, innovators, and others who are fighting back with everything they have.*

Antibiotic Resistance Threats in the United States, 2019 (2019 AR Threats Report) is a publication of the Antibiotic Resistance Coordination and Strategy Unit within the Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention.

Suggested citation: CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

Available online: The full 2019 AR Threats Report, including methods and appendices, is available online at www.cdc.gov/DrugResistance/Biggest-Threats.html.

DOI: http://dx.doi.org/10.15620/cdc:82532.

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The 2019 AR Threats Report is available online at www.cdc.gov/DrugResistance/Biggest-Threats.html.

METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS
(MRSA)

Foreword

In March 1942, Mrs. Anne Miller of New Haven, Connecticut, was near death.* Infectious germs had made their way into her bloodstream. Desperate to save her, doctors administered an experimental drug: penicillin, which Alexander Fleming discovered 14 years earlier. In just hours, she recovered, becoming the first person in the world to be saved by an antibiotic. Rather than dying in her thirties, Mrs. Miller lived to be 90 years old.

Today, decades later, germs like the one that infected Mrs. Miller are becoming resistant to antibiotics. You could have one in or on your body right now—a resistant germ that, in the right circumstances, could also infect you. But—unlike the bacteria that threatened Mrs. Miller—the bacteria may be able to avoid the effects of the antibiotics designed to kill them.

Unfortunately, like nearly 3 million people across the United States, you or a loved one may face an antibiotic-resistant infection.

This report from CDC, the second of its kind, presents data about the top 18 pathogens that require attention now. It emphasizes that antibiotic resistance is a One Health issue that can spread through people, animals, and the environment; threatens our most vulnerable friends and family members; and affects nearly every aspect of life.

Given the chance, these germs will infect our bodies, take up residence in our healthcare facilities, contaminate our food and water supplies, and move across our communities and around the globe. This report shows us, however, that the fight against antibiotic resistance, no matter how complex, is not hopeless.

To stop antibiotic resistance, our nation must:

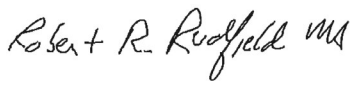
- **Stop referring to a coming post-antibiotic era—**it's already here. You and I are living in a time when some miracle drugs no longer perform miracles and families are being ripped apart by a microscopic enemy. The time for action is now and we can be part of the solution.
- **Stop playing the blame game.** Each person, industry, and country can affect the development of antibiotic resistance. We each have a role to play and should be held accountable to make meaningful progress against this threat.
- **Stop relying *only* on new antibiotics** that are slow getting to market and that, sadly, these germs will one day render ineffective. We need to adopt aggressive strategies that keep the germs away and infections from occurring in the first place.
- **Stop believing that antibiotic resistance is a problem "over there"** in someone else's hospital, state, or country—and not in our own backyard. Antibiotic resistance has been found in every U.S. state and in every country across the globe. There is no safe place from antibiotic resistance, but everyone can take action against it. Take action where you can, from handwashing to improving antibiotic use.

The problem will get worse if we do not act now, but we can make a difference.

Simply, here's what works. Preventing infections protects everyone. Improving antibiotic use in people and animals slows the threat and helps preserve today's drugs and those yet to come. Detecting threats and implementing interventions to keep germs from becoming widespread saves lives.

These actions are protecting us today and will continue to protect us, our families, and our nation from a threat that *will never stop.* I'm proud to serve alongside the experts who refuse to let this threat disarm us and who are diligently protecting our future by putting science and public health into action.

We all have a role to play. We hope the 2019 AR Threats Report inspires you to act now.



Robert R. Redfield, M.D.

Director, U.S. Centers for Disease Control and Prevention

November 13, 2019

*Rothman, L. (March 14, 2016). This Is What Happened to the First American Treated With Penicillin. TIME. https://time.com/4250235/penicillin-1942-history.

Executive Summary

CDC's *Antibiotic Resistance Threats in the United States, 2019* (2019 AR Threats Report) includes updated national death and infection estimates that underscore the continued threat of antibiotic resistance in the United States. **New CDC data show that while the burden of antibiotic-resistance threats in the United States was greater than initially understood, deaths are decreasing since the 2013 report.** This suggests that U.S. efforts—preventing infections, stopping spread of bacteria and fungi, and improving use of antibiotics in humans, animals, and the environment—are working, especially in hospitals. Vaccination, where possible, has also shown to be an effective tool of preventing infections, including those that can be resistant, in the community.

Yet the number of people facing antibiotic resistance in the United States is still too high. More than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result. In addition, nearly 223,900 people in the United States required hospital care for *C. difficile* and at least 12,800 people died in 2017.

Germs continue to spread and develop new types of resistance, and progress may be undermined by some community-associated infections that are on the rise. More action is needed to address antibiotic resistance. While the development of new treatments is one of these key actions, such investments must be coupled with dedicated efforts toward preventing infections in the first place, slowing the development of resistance through better antibiotic use, and stopping the spread of resistance when it does develop to protect American lives now and in the future.

This report is intended to:

- Serve as a reference for anyone looking for recent information on antibiotic resistance
- Provide the latest antibiotic resistance burden estimates for human health in the United States, including a list of 18 germs listed on level of concern to human health—urgent, serious, and concerning
- Highlight emerging areas of concern and additional action needed to address this threat at a national and global level

In 2013, CDC published the first AR Threats Report about the most alarming antibiotic-resistant germs in the United States. Like the 2013 report, the 2019 report does not include viruses (e.g., HIV, influenza) or parasites. Additionally, new data sources that provide a more complete estimate of antibiotic resistance are now available and were used to produce portions of the 2019 report.

The 2019 report also highlights some gaps slowing progress against the antibiotic resistance threat, CDC's aggressive actions taken to combat resistance, and a Watch List with three threats where full burden is unknown and true impact needs to be better understood in the United States. Throughout this report, several themes emerge from the data:

- Dedicated prevention and infection control efforts have helped reduce the number of infections and deaths caused by antibiotic-resistant germs in the United States. Still, the number of people infected and who die is too high.

- CDC used stronger methods and data sources to calculate several estimates, specifically for healthcare-associated germs. Using electronic health data, CDC generated some pathogen estimates from more than 700 geographically diverse U.S. acute-care hospitals and used these data to determine national estimates. This allows CDC to provide a "look back" at the 2013 data to redefine the true burden of resistance for some germs. This is the first time CDC has leveraged these data to estimate the national burden of antibiotic resistance.
- CDC is concerned about rising resistant infections in the community. For example, infections associated with drug-resistant gonorrhea and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae have increased since 2000. Rising infections in the community puts more people at risk and makes spread more difficult to identify and contain—and threatens the progress made to protect patients in healthcare. Rapid detection and prevention strategies have helped protect people from two community-associated germs (i.e., drug-resistant tuberculosis, drug-resistant *Streptococcus pneumoniae),* but a stronger focus and interventions are needed.
- The emergence and spread of new forms of resistance continues to alarm CDC experts, especially resistance shared among germs through genetic mobile elements (antibiotic-resistant germs can share their resistance genes with other germs and can make them untreatable). ESBL-producing Enterobacteriaceae, for example—which are on the rise in the community—can transfer resistance within the Enterobacteriaceae family, which includes germs that can cause common infections such as urinary tract infections. Increased infection prevention domestically and abroad will help slow these new threats.

The first AR Threats Report helped inform the *National Action Plan for Combating Antibiotic-Resistant Bacteria* (CARB) by highlighting the scope of the antibiotic resistance threat in the United States, emphasizing the need for action across the One Health spectrum, and identifying the most critical germs to be addressed.

The resulting investments from Congress to implement CARB enabled the United States to make great strides in addressing these threats. Since the first AR Threats Report released in 2013, data show that the nation has reduced the number of deaths caused by antibiotic-resistant infections by 18 percent overall and by nearly 30 percent in hospitals alone.

As detection and surveillance capabilities increased, awareness of the scope and complexity of antibiotic resistance has also grown. **CDC has taken aggressive action in coordination with other Federal agencies, state and local health departments, patients, public health partners, and the private sector to rapidly detect, prevent spread, and innovate against antibiotic resistance**.

Antibiotics are critical tools for treating common and complex infections among humans, animals, and crops, including infections that can lead to sepsis (the human body's extreme response to an infection and a medical emergency). **Together, more action is needed across settings, industries, and countries to fully protect people from antibiotic resistance threats.**

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CDC's 2019 AR Threats Report:

PREVENTION WORKS.

18% fewer deaths from antibiotic resistance overall since 2013 report

28% fewer deaths from antibiotic resistance in hospitals since 2013 report

AND DECREASES IN INFECTIONS CAUSED BY:

- **41%** Vancomycin-resistant *Enterococcus*
- **33%** Carbapenem-resistant *Acinetobacter*
- **29%** Multidrug-resistant *Pseudomonas aeruginosa*
- **25%** Drug-resistant *Candida*
- **21%** Methicillin-resistant *Staphylococcus aureus* (MRSA)
- **STABLE** Carbapenem-resistant Enterobacteriaceae (CRE) & drug-resistant tuberculosis (TB disease cases)

CDC strategies that work in healthcare:

- Preventing device- and procedure-related infections, such as from urinary catheters or central lines
- Stopping the spread of resistant germs within and between healthcare facilities
- Containing emerging threats through early detection and aggressive response
- Tracking and improving appropriate antibiotic use
- Infection prevention and control in non-hospital settings, such as long-term care facilities

CDC strategies that work in communities:

- Widespread use of vaccines to prevent infections and spread
- Routine tuberculosis and gonorrhea screening for at-risk groups and prompt treatment
- Using safer sex practices (e.g., condoms)
- Safe food handling and preparation
- Improving antibiotic use everywhere

(AR) antibiotic resistance

Despite these gains, CDC's 2019 AR Threats Report shows additional actions are needed to protect people.

2.8M+ antibiotic-resistant infections each year

35k+ deaths from antibiotic resistance each year

Plus: 223,900 cases and 12,800 deaths from *Clostridioides difficile*

AND INCREASES IN INFECTIONS CAUSED BY:

- ↑ **315%** Erythromycin-resistant invasive group A strep
- ↑ **124%** Drug-resistant *Neisseria gonorrhoeae*
- ↑ **50%** ESBL-producing Enterobacteriaceae

Challenges in healthcare:

- Preventing the spread of germs, including in non-hospital settings such as long-term care facilities
- Spread of germs from the healthcare environment (e.g., bedrails, devices, other surfaces)
- Incomplete adoption of the Containment Strategy
- Inconsistent implementation of some CDC recommendations (e.g., Contact Precautions)
- Introduction of emerging threats from outside of the United States
- Continued vigilance against serious threats like "nightmare bacteria" CRE

Challenges in the community:

- Poor hygiene, such as not keeping hands clean or not wiping properly after toileting or diapering
- Spread of resistant threats in the food supply
- Inconsistent use of safer sex practices
- Few vaccines to prevent infections and spread of resistant threats
- Stopping spread of germs in animals
- Understanding the role of antibiotic-resistant germs in the environment
- Improving antibiotic use everywhere

For further progress, the nation must continue to innovate and scale up effective strategies to prevent infections, stop spread, and save lives.

Learn more: www.cdc.gov/DrugResistance/Biggest-Threats

(strep) *Streptococcus*

(ESBL) extended-spectrum beta-lactamase

Revised Dec. 2019

SECTION 1

THE THREAT OF ANTIBIOTIC RESISTANCE

DRUG-RESISTANT
NEISSERIA GONORRHOEAE

MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA

Antibiotic resistance is when germs (bacteria, fungi) develop the ability to defeat the antibiotics designed to kill them. It does not mean your body is resistant to antibiotics.

Introduction

Antibiotic resistance—the ability of germs to defeat the drugs designed to kill them—is one of the greatest global public health challenges of our time. Antibiotics are one of our most powerful tools for fighting life-threatening infections. Their discovery has transformed human and animal health. Unfortunately, we now live in an era when people around the world, including Americans, are dying from untreatable infections because of the emergence and spread of antibiotic resistance.

The threat of antibiotic resistance undermines progress in health care, food production, and life expectancy. Addressing this threat requires preventing infections in the first place, slowing the development of resistance through better antibiotic use, and stopping the spread of resistance when it does develop.

In 2013, CDC published *Antibiotic Resistance Threats in the United States, 2013,* the first snapshot of the burden and threats posed by key antibiotic-resistant germs (bacteria and fungi) on human health and the actions needed to address this challenge. The report's conservative estimates showed that at least 2 million people were infected with antibiotic-resistant germs each year in the United States and at least 23,000 people died as a result.

For the 2013 report, CDC used the best data available at the time, but data limitations led to an underestimate of the true burden of antibiotic resistance. Fortunately, new data sources that provide a more complete estimate of antibiotic resistance are now available and were used to produce portions of the 2019 report. Additionally, CDC was able to apply data from these new sources to recalculate burden estimates for the previous report; the revised estimate shows that more than 2.6 million antibiotic-resistant infections and nearly 44,000 deaths occurred each year when the 2013 report was published. When compared to the previous estimate, the updated 2013 report estimate describing the number of deaths caused by antibiotic resistance each year is nearly two-times higher.

However, deaths decreased by 18 percent since the 2013 report. This suggests that prevention efforts in hospitals are working. Yet the number of people facing antibiotic resistance in the United States is still too high. More than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result.

The AR Threats Report also includes an estimate of the burden of *Clostridioides difficile (C. difficile)* infections, because *C. difficile* is caused by the same factors that drive antibiotic resistance—antibiotic use and the spread of germs. In 2017, nearly 223,900 people in the United States required hospital care for *C. difficile* and at least 12,800 people died.

In this report, CDC listed 18 germs into one of three categories: urgent, serious, and concerning. CDC also developed the Watch List (see page 107), a new resource that includes antibiotic-resistant threats with the potential to spread or become a challenge in the United States. These germs are currently responsible for few, if any, infections in the United States. However, they either cause infections in other countries, have the potential to rapidly spread, or are not well understood yet. Early detection and prevention of these infections could have a large, positive public health impact.

DRUG-RESISTANT
SHIGELLA

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae (S. pneumoniae)*
- Drug-resistant Tuberculosis (TB)

Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Watch List

- Azole-resistant *Aspergillus fumigatus (A. fumigatus)*
- Drug-resistant *Mycoplasma genitalium (M. genitalium)*
- Drug-resistant *Bordetella pertussis (B. pertussis)*

Antibiotics save lives, but any time antibiotics are used—in people, animals, or crops—they can cause side effects and can contribute to the development of antibiotic resistance. Antibiotic-resistant germs can also share their ability to become resistant with other germs that have not been exposed to antibiotics.

Antibiotic resistance is a One Health challenge—the health of people is connected to the health of animals and the environment. Antibiotic-resistant infections can be difficult, and sometimes impossible, to treat. In addition to increasing morbidity and mortality, resistant infections also add considerable costs to the U.S. healthcare system. The total economic cost of antibiotic resistance to the U.S. economy is difficult to calculate. However, in many cases, these infections require extended hospital stays, additional follow-up visits to healthcare providers, and the use of treatments that may be more costly and potentially more toxic.

Antibiotic-resistant infections also affect animals including pets, petting zoo animals, and food animals, which can increase the spread of resistance. Resistant germs can quickly spread across settings—communities, the food supply, healthcare facilities, the environment (e.g., soil, water), and around the world. This spread increases the burden of resistance and antibiotic-resistant infections.

These infections can be stopped by preventing the spread of germs and improving infection prevention and antibiotic use in all settings. U.S. government agencies are leading critical activities with partners to combat antibiotic resistance domestically and globally. Investments from Congress to support actions—such as improving infection prevention and control and antibiotic use—are working, proving the value of continued action against this threat. Coordinated, aggressive action and a One Health approach have been critical to this success.

The United States has worked toward implementing actions and addressing scientific gaps identified in the 2013 report. In 2018, CDC proposed five core actions to better prepare the United States for the resistance that will continue to emerge worldwide:

Infection prevention and control: Prevent infections and reduce the spread of germs

Tracking and data: Share data and improve data collection

Antibiotic use and access: Improve appropriate use of antibiotics, reduce unnecessary use (called antibiotic stewardship), and ensure improved access to antibiotics

Vaccines, therapeutics, and diagnostics: Invest in development and improved access to vaccines, therapeutics, and diagnostics for better prevention, treatment, and detection

Environment and sanitation: Keep antibiotics and antibiotic-resistant threats from entering the environment through actions like improving sanitation and improving access to safe water

Through its Antibiotic Resistance (AR) Solutions Initiative, CDC works with partners to drive aggressive action and empower the nation to respond comprehensively. The AR Solutions Initiative invests in national infrastructure to detect, respond, contain, and prevent resistant infections across healthcare, food, and community settings. Through these investments, CDC is transforming how the nation and world combat and slow antibiotic resistance at all levels.

The Threat of Antibiotic Resistance in the United States

Antibiotic resistance—when germs (bacteria, fungi) develop the ability to defeat the antibiotics designed to kill them—is one of the greatest global health challenges of modern time.

New National Estimate*

Each year, antibiotic-resistant bacteria and fungi cause at least an estimated:

2,868,700 infections

35,900 deaths

+

Clostridioides difficile ** is related to antibiotic use and antibiotic resistance:**

223,900 cases

12,800 deaths

New Antibiotic Resistance Threats List

Updated urgent, serious, and concerning threats—totaling 18

5 urgent threats

2 new threats

NEW: Watch List with **3** threats

Antibiotic resistance remains a significant One Health problem, affecting humans, animals, and the environment. Data show infection prevention and control is saving lives—especially in hospitals—but threats may undermine this progress without continued aggressive action now.

Learn more: www.cdc.gov/DrugResistance/Biggest-Threats.html

*National burden reflects de-duplicated infection and death estimates.
**_Clostridioides difficile_ cases from hospitalized patients in 2017

Revised Dec. 2019

Common Words in the 2019 AR Threats Report

Germs are microbes—very small living organisms including bacteria, fungi, parasites, and viruses. Most microbes are harmless and even helpful to people, but some can cause infections. The harmful germs are called **pathogens.**

In this report, CDC uses "germ" to describe bacteria and fungi, including pathogens.

Antimicrobials are drugs that treat infections by killing or slowing the growth of microbes causing infection. **Bacteria** cause infections such as strep throat and foodborne illnesses. **Bacterial infections** are treated with drugs called **antibiotics. Fungi** cause infections like athlete's foot and yeast infections. Fungal infections are treated with drugs called **antifungals.** People sometimes use "antibiotic" and "antimicrobial" interchangeably.

In this report, CDC uses "antibiotic" to describe antibacterial and antifungal drugs, which kill bacteria and fungi.

Susceptible infections are infections that can be treated effectively with antibiotics.

Antibiotic resistance happens when germs develop the ability to defeat the drugs designed to kill them. That means the germs are not killed and continue to grow. **Multidrug-resistant germs** are resistant to multiple antibiotics available for treatment. **Pan-resistant infections** are caused by germs resistant to all antibiotics available for treatment.

Infection control prevents or stops spread of infections.

Antibiotic stewardship is improving the way antibiotics are prescribed and used.

One Health is a collaborative, multisectoral, and trans-disciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment.

Resistance mechanisms are defense strategies that germs develop to help them survive and avoid the effects of antibiotics.

Colonization refers to a person carrying germs, but they do not have symptoms of an infection. However, they are still able to spread the germs to others.

Isolates are pure samples of a germ.

Gram-negative bacteria are a group of germs that are increasingly resistant to many available antibiotics. They often find new ways to develop resistance and can sometimes share these abilities with other bacteria, increasing the spread of resistance. Examples of Gram-negative bacteria include *Acinetobacter* species, *P. aeruginosa,* and *Escherichia coli (E. coli).*

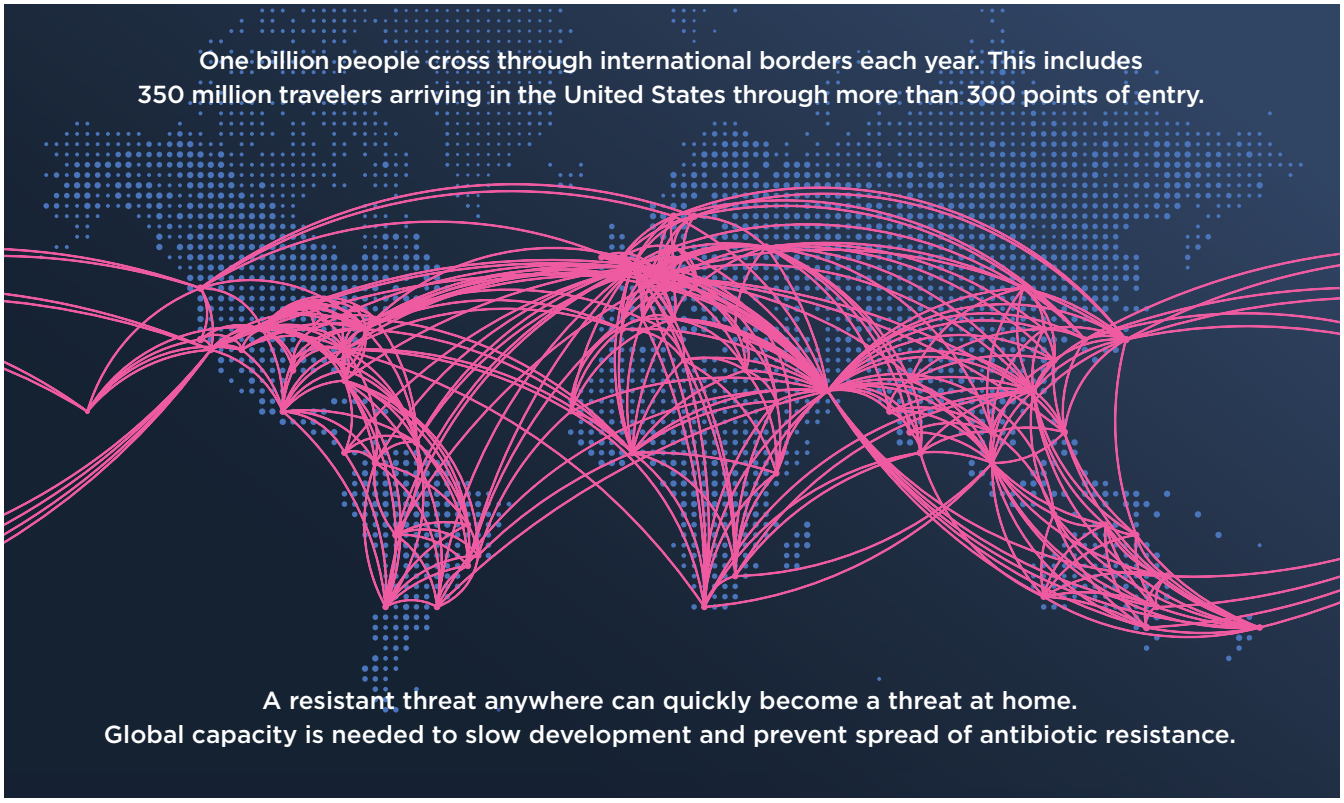
Everyone is at Risk

Antibiotic resistance can affect any person, at any stage of life. People receiving health care or those with weakened immune systems are often at higher risk for getting an infection. Moreover, antibiotic resistance jeopardizes advancements in modern health care that we have come to rely on, such as joint replacements, organ transplants, and cancer therapy. These procedures have a significant risk of infection, and patients won't be able to receive them if effective antibiotics are not available.

Antibiotic resistance is not only a U.S. problem—it is a global crisis. Resistance has been identified across the world. New forms of resistance emerge and can spread with remarkable speed between continents through people, goods, and animals. Inappropriate antibiotic use and inadequate infection prevention can increase the chance that resistance develops, spreads, and puts the world at risk. It is critical that the United States continue to take a global, One Health approach to combating antibiotic resistance.

Antibiotic Resistance Spreads Easily Across the Globe

Resistant bacteria and fungi can spread across countries and continents through people, animals, and goods.



Detect Resistant Threats

Prevent & Contain Resistant Germs

Improve Antibiotic Use

Stopping Spread of Antibiotic Resistance Saves Lives

Addressing this threat requires continued aggressive action:

- Preventing infections in the first place
- Slowing the development of resistance through improved antibiotic use
- Stopping the spread of resistance when it does develop

Without action, these germs can spread like wildfire—infecting and killing more people every year.

Antibiotic-resistant germs can spread between people with and without symptoms of infection. Depending on the germ, germs can spread to people in many ways:

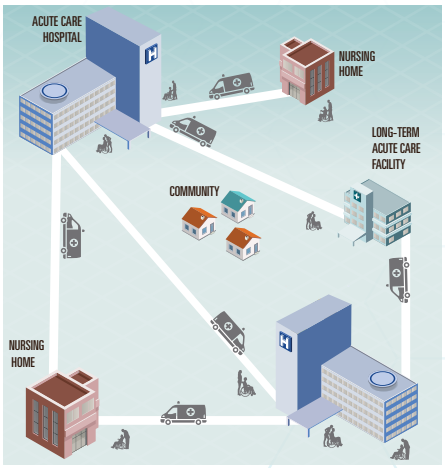
- **Close contact** (direct or indirect) with a person carrying a resistant germ—for example, this can happen when healthcare providers move from one patient to the next without washing their hands
- **In the air**—for example, TB bacteria can enter the air when a person with TB disease of the lungs or throat coughs, speaks, or sings
- **Contaminated water,** which may include sewage systems, hospital plumbing, or recreational water
- **Contact with contaminated surfaces,** such as hospital bedrails, kitchen counters, shared equipment (e.g., ultrasound machines), or personal items (e.g., towels)
- **Animals**—for example, eating contaminated food or touching animals carrying resistant germs
- **Sexual contact** with a person carrying a resistant germ (e.g., *N. gonorrhoeae or Shigella)*

Resistance Threats are Amplified in Health Care

Antibiotic resistance disproportionally impacts the most vulnerable—the young, elderly, and sick—who often receive medical care. Often, the most deadly, resistant healthcare-associated germs spread from patient to patient and across healthcare facilities through patient transfer. When not stopped, these resistant healthcare-associated germs can spill over into communities, becoming much harder to control.

CDC's expertise and resources have supported the implementation of vital healthcare prevention programs that incorporate actions to prevent infections and control their spread. When launched at the first sign of a problem, CDC's Containment Strategy—aggressive detection and response activities—keeps new or rare forms of antibiotic resistance from spreading. For the "nightmare bacteria" CRE alone, aggressive containment responses could prevent 1,600 cases in just one state over three years.[1]

CDC recognizes that hospital prevention programs have already seen successes. From 2012 to 2017, the number of antibiotic-resistant infections seen in hospitals dropped 27 percent and the number of deaths from antibiotic-resistant infections fell nearly 30 percent. Nonetheless, without continued action and vigilance these gains will only be temporary.



Potentially Deadly Resistance Contained in Orange County, CA

In 2019, a patient in a long-term care facility tested positive for *C. auris.* An extensive, aggressive containment response followed that involved screening hundreds of patients. When a new patient was identified as carrying or infected with *C. auris,* they were immediately put under special precautions to prevent spread. This vigilant action by public health officials and healthcare facilities helped control the spread of *C. auris* in Orange County, protecting hundreds of vulnerable patients.

Resistance Also Spreads in Communities

Resistance is increasing in the community—when infections occur, more are resistant. Stopping the spread of resistant threats in the community requires tailored interventions, such as good hygiene, routine vaccination, safer sex practices, and safe food preparation. Many of these interventions have already proven successful.

Vaccination Saves Lives

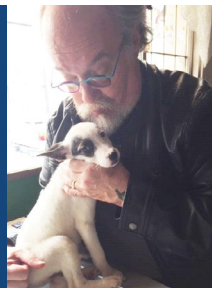
Pneumococcal infections are common in young children, but older adults are at greatest risk of serious illness and death. The PCV13 vaccine, which the U.S. Food and Drug Administration (FDA) licensed in 2010, protects people from 13 types of pneumococcus, including resistant forms. This vaccine prevented more than 30,000 cases of invasive pneumococcal disease and 3,000 deaths from 2010 to 2013 alone.

Preventing Infections & Slowing Spread of Germs

Without appropriate use of infection prevention and control practices, germs can spread across all settings. While the development of new drugs is important to treat resistant threats, public health prevention programs targeting resistant germs can and have worked to slow spread and save lives. But more needs to be done. The U.S. and global community must scale up these effective strategies and develop new strategies to prevent infections and save lives. In the United States, infection prevention activities have proven effective in slowing the spread of resistant germs. This includes:

- Strategies to decrease spread within healthcare settings (e.g., implementing hand hygiene)
- Vaccinating
- Implementing biosecurity measures on farms
- Responding rapidly to unusual genes and germs when they first appear, keeping new threats from spreading

Mike was hospitalized soon after bringing home his puppy, Mabel. Mike was one of 133 people in 17 states who was sickened with multidrug-resistant *Campylobacter* in an outbreak linked to pet store puppies. Read Mike's story on page 80.



Revised Dec. 2019

Antibiotic-Resistant Infections Threaten Modern Medicine

Millions of people in the United States receive care that can be complicated by bacterial and fungal infections. Without antibiotics, we are not able to safely offer some life-saving medical advances.

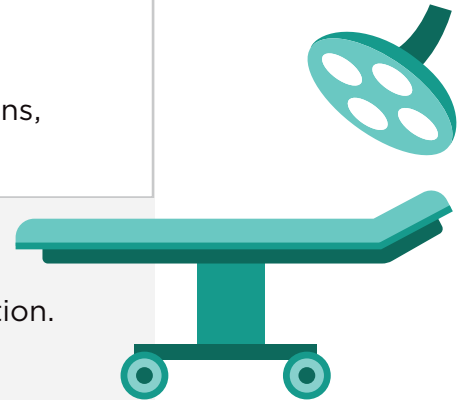
Sepsis Treatment

Anyone can get an infection and almost any infection can lead to sepsis — the body's extreme response to an infection. Without timely treatment with antibiotics, sepsis can rapidly lead to tissue damage, organ failure, and death.

AT LEAST 1.7M adults develop sepsis each year.

Surgery

Patients who have surgery are at risk for surgical site infections. Without effective antibiotics to prevent and treat surgical infections, many surgeries would not be possible today.



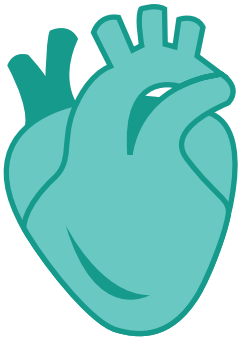
1.2M women had a cesarean section (C-section) in 2017. Antibiotics are recommended to help prevent infection.

Chronic Conditions

Chronic conditions (e.g., diabetes) put people at higher risk for infection. These conditions and some medicines used to treat them can weaken the immune system (how the body fights infection).

MORE THAN 30M people have diabetes. Antibiotics are used to treat common infections in these patients.

Antibiotic-Resistant Infections Threaten Modern Medicine



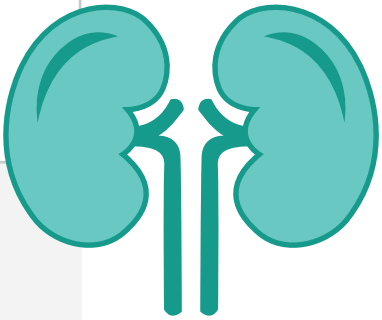
Organ Transplants

Organ transplant recipients are more vulnerable to infections because they undergo complex surgery. Recipients also receive medicine to suppress (weaken) the immune system, increasing risk of infection.

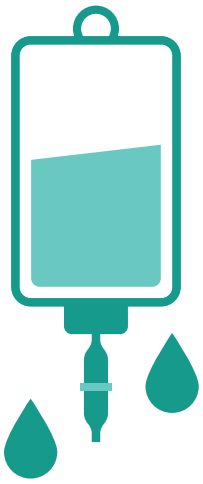
MORE THAN 33,000 organ transplants were performed in 2016. Antibiotics help organ transplants remain possible.

Dialysis for Advanced Kidney Disease

Patients who receive dialysis treatment have a higher risk of infection, the second leading cause of death in dialysis patients.



MORE THAN 500,000 patients received dialysis treatment in 2016. Antibiotics are critical to treat infections in patients receiving life-saving dialysis treatment.



Cancer Care

People receiving chemotherapy for cancer are often at risk for developing an infection during treatment. Infection can quickly become serious for these patients.

AROUND 650,000 people receive outpatient chemotherapy each year. Antibiotics are necessary to protect these patients.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

A ONE HEALTH CHALLENGE

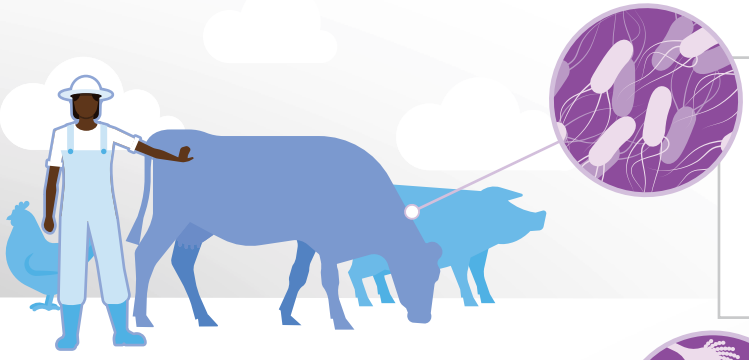
The Interconnected Threat of Antibiotic Resistance

Resistance happens when germs (bacteria and fungi) defeat the drugs designed to kill them. Any antibiotic use—in people, animals, or crops—can lead to resistance. Resistant germs are a One Health problem—they can spread between people, animals, and the environment (e.g., water, soil).

Examples of How Antibiotic Resistance Affects Humans, Animals & the Environment

People

Some types of antibiotic-resistant germs can spread person to person. "Nightmare bacteria" carbapenem-resistant Enterobacteriaceae (CRE) can also survive and grow in sink drains at healthcare facilities and spread to patients and to the environment through the wastewater.



Animals

Resistant germs can spread between animals and people through food or contact with animals. For example, *Salmonella* Heidelberg bacteria can make both cattle and people sick.

Environment

Antibiotic-resistant germs can spread in the environment. *Aspergillus fumigatus*, a common mold, can make people with weak immune systems sick. In 2018, resistant *A. fumigatus* was reported in three patients. It was also found in U.S. crop fields treated with fungicides that are similar to antifungals used in human medicine.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Estimating Burden Data

For this report, CDC used the best available data (as late as 2018) and, for some germs, new methods to update the national burden estimates for 18 listed threats. Data sources and methods varied by germ and are described in detail in the Technical Appendix. The following sections include details on the new data sources for healthcare-related germs and how CDC assessed the threat level for the 18 germs.

New Data Source For Healthcare Threats

CDC used electronic health databases to assess the burden of antibiotic-resistant germs commonly associated with health care. CDC generated the estimates with de-identified information from three databases including more than 700 geographically diverse U.S. acute-care hospitals. This included results identified from the hospitals' microbiology data.

Compared to the methods used for the 2013 report, these databases have advantages:

- Allows for the estimation of a broader group of infection types (e.g., cultures involving both sterile (e.g., blood) and nonsterile (e.g., urine, skin) body sites).
- Includes both hospital-onset and community-onset infections (among hospitalized patients)
- Promotes better precision in estimates
- Offers the ability to assess trends in incidence between 2012 and 2017

The use of databases also has important advantages over methods that utilize International Classification of Diseases (ICD) diagnosis codes or death certificate data, which likely underreport the true burden of cases and death from antibiotic resistance. ICD codes are primarily designed for billing purposes. They can provide helpful information about cause of death, but there is no simple way to code for an antibiotic-resistant infection. The definition varies by germ and will continue to vary as new drugs are introduced and new resistance emerges. Given these limitations, CDC does not use death certificates to determine mortality estimates related to antibiotic-resistant infections.

Threats Assessed with Electronic Health Databases

- Carbapenem-resistant *Acinetobacter*
- Drug-resistant *Candida*
- CRE
- ESBL-producing Enterobacteriaceae
- VRE
- MRSA
- Multidrug-resistant *P. aeruginosa*

Limitations of Counting Resistant Infections in People

Many limitations exist when calculating the burden of disease associated with antibiotic-resistant germs. This is why the totals are an estimate of the true burden of illness. CDC continues to refine methods for greater precision. This report does not provide a specific estimate for the financial cost of antibiotic-resistant infections on a national scale. Some germs in this report show germ-specific costs—either antibiotic-resistant related or total infection costs. There is no consensus on methodology for making monetary estimates for many germs included in this report. See the Technical Appendix for details, such as how resistance is defined for each germ included in this report.

How CDC Assessed and Assigned Threat Level

In 2013, CDC assessed antibiotic resistance threats and categorized the threat level of each germ as urgent, serious, or concerning. Like the 2013 report, the 2019 report assesses threats according to seven factors:

- Clinical impact
- Economic impact (when available)
- Incidence
- 10-year projection of incidence (new infections over the next 10 years)
- Transmissibility (how easily a germ spreads or causes infections)
- Availability of effective antibiotics
- Barriers to prevention

The assessment focused on domestic impact, but the international context of antibiotic resistance was taken into account in the 10-year incidence projection. Threats assigned to the urgent and serious categories require greater attention and action. Regardless of category, CDC efforts are tailored to address challenges associated with each germ.

Since the 2013 report, the ranking of three germs has shifted.

C. auris

Not listed in 2013. Listed as Urgent in 2019.

C. auris emerged after the 2013 report was published. It is a multidrug-resistant yeast that can cause invasive infection and death. It spreads easily between hospitalized patients and nursing home residents. Particularly concerning, some strains (types) of *C. auris* are resistant to all three antibiotic classes used to treat fungal infections.

Carbapenem-resistant *Acinetobacter*

Listed as Serious (as Multidrug-resistant Acinetobacter) in 2013. Listed as Urgent in 2019.

Acinetobacter often causes infections in people who have weakened immune systems, such as hospitalized or very sick patients. The previous report measured and listed this germ as multidrug-resistant *Acinetobacter,* but the 2019 report focuses on carbapenem-resistant *Acinetobacter,* which is often resistant to many antibiotics. The threat level was escalated to Urgent because of the emergence of easily spread resistance in *Acinetobacter* and the lack of current antibiotics, and antibiotics in development, to treat these infections.

Vancomycin-resistant *Staphylococcus aureus* (VRSA)

Listed as Concerning in 2013. Removed as a threat in 2019.

Since 2002, 14 cases of VRSA have been identified in the United States. These are isolated cases and spread from patient to patient has never been documented. CDC removed VRSA as a threat and will continue monitoring it as part of ongoing work to reduce *Staphylococcus* infections in health care and the community.

Threat Estimates

This following table summarizes the 2019 AR Threats Report estimates, and compares these estimates to the 2013 report when applicable.

Resistant germ	Threat Estimate, 2019 report	What CDC Counted, 2019 report	What CDC Did Not Count, 2019 report	Threat Estimate, 2013 report	New 2013 Threat Estimate, 2019 report	Can Data be Compared? 2013 vs 2019 reports	Year-to-Year Comparison Provided, 2019 report	Resistant Infection Increase/ Decrease, 2019 report
Drug-resistant *Neisseria gonorrhoeae*	550,000 infections	All infections	N/A	246,000 infections & <5 deaths	N/A	Yes	Resistance over time from 2000–2017	↑ Increase
Candida auris	323 clinical cases	Clinical cases	Colonization/ screening cases	N/A—was not listed in 2013 report	N/A	N/A	Cases over time from 2015–2018	↑ Increase
ESBL-producing Enterobacteriaceae	197,400 cases & 9,100 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	26,000 healthcare associated infections & 1,700 deaths	131,900 cases & 6,300 deaths (2012 estimates)	No	Cases over time from 2012–2017	↑ Increase
Erythromycin-resistant group A *Streptococcus*	5,400 infections & 450 deaths	Invasive infections	Non-invasive infections including common upper-respiratory infections like strep throat	1,300 infections & 160 deaths	N/A	Yes	Invasive infection rates over time from 2010–2017	↑ Increase
Carbapenem-resistant Enterobacteriaceae	13,100 cases & 1,100 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	9,300 healthcare associated infections & 600 deaths	11,800 cases & 1,000 deaths (2012 estimates)	No	Cases over time from 2012–2017	Stable
Carbapenem-resistant *Acinetobacter* (formerly multidrug-resistant *Acinetobacter)*	8,500 cases & 700 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	N/A—was listed as multidrug-resistant in 2013 report	11,700 cases & 1,000 deaths (2012 estimates)	No	Cases over time from 2012–2017	↓ Decrease
Drug-resistant *Candida* (formerly fluconazole-resistant *Candida)*	34,800 cases & 1,700 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	N/A—was listed as fluconazole-resistant Candida in 2013 report	44,800 cases & 2,200 deaths (2012 estimates)	No	Cases over time from 2012–2017	↓ Decrease
Vancomycin-resistant *Enterococcus*	54,500 cases & 5,400 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	20,000 healthcare associated infections & 1,300 deaths	84,800 cases & 8,500 deaths (2012 estimates)	No	Cases over time from 2012–2017	↓ Decrease

Resistant germ	Threat Estimate, 2019 report	What CDC Counted, 2019 report	What CDC Did Not Count, 2019 report	Threat Estimate, 2013 report	New 2013 Threat Estimate, 2019 report	Can Data be Compared? 2013 vs 2019 reports	Year-to-Year Comparison Provided, 2019 report	Resistant Infection Increase/ Decrease, 2019 report
Multidrug-resistant *Pseudomonas aeruginosa*	32,600 cases & 2,700 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	6,700 healthcare associated infections & 440 deaths	46,000 cases & 3,900 deaths (2012 estimates)	No	Cases over time from 2012–2017	⬇ Decrease
Methicillin-resistant *Staphylococcus aureus*	323,700 cases & 10,600 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	80,000 healthcare associated infections & 11,000 deaths	401,000 cases & 13,600 deaths (2012 estimates)	No	Cases over time from 2012–2017	⬇ Decrease
Drug-resistant Tuberculosis	847 cases & 62 deaths	Cases	N/A	1,042 cases & 50 deaths	N/A	Yes	Cases over time from 2012–2017	Stable
Clostridioides difficile	223,900 estimated cases in hospitalized patients & 12,800 deaths	Infections requiring hospitalizations or in already hospitalized patients	Non-hospitalized infections	250,000 infections & 14,000 deaths	N/A	No	Cases over time from 2012–2017	⬇ Decrease*
Drug-resistant *Campylobacter*	448,400 infections & 70 deaths	All infections	N/A	310,000 infections & 28 deaths	N/A	No	Percentage of resistance over time from 1997–2017	N/A
Drug-resistant non-typhoidal *Salmonella*	212,500 infections & 70 deaths	All infections	N/A	100,000 infections & 38 deaths	N/A	No	Percentage of resistance over time from 2009–2017	N/A
Drug-resistant *Salmonella* Serotype Typhi	4,100 infections & <5 deaths	All infections	N/A	3,800 infections & <5 deaths	N/A	Yes	Percentage of resistance over time from 1999–2017	⬆ Increase
Drug-resistant *Shigella*	77,000 infections & <5 deaths	All infections	N/A	27,000 infections & <5 deaths	N/A	No	Percentage of resistance over time from 2009–2017	N/A
Drug-resistant *Streptococcus pneumoniae*	900,000 infections & 3,600 deaths	All infections	N/A	1,200,000 infections & 7,000 deaths	N/A	No	Invasive infection rates over time from 2005–2017	N/A
Clindamycin-resistant group B *Streptococcus*	13,000 infections & 720 deaths	Invasive infections	Non-invasive infections & asymptomatic intrapartum colonization requiring prophylaxis	7,600 infections & 440 deaths	N/A	No	Invasive infection rates over time from 2012–2016	N/A

*This report includes all *Clostridioides difficile* infections requiring hospitalizations or in already hospitalized patients (*C. difficile* is not a resistant infection but is related to antibiotic use and antibiotic resistance).

N/A: not applicable

Revised Dec. 2019

How Antibiotic Resistance Happens

Antibiotic Exposure and the Spread of Germs

Increases in antibiotic resistance are driven by a combination of germs exposed to antibiotics, and the spread of those germs and their mechanisms of resistance. This naturally occurring process is accelerated when antibiotics are constantly present in the environment or in the germs' hosts (e.g., patients).

This is why antibiotics for medical care, animal health, and agriculture should be used only when necessary and only for appropriate durations. Patients should always be promptly treated with antibiotics when the drugs are needed for infections and to prevent sepsis.

Antibiotic Use Across Settings

Environment

Antibiotics and fungicides are sometimes applied as pesticides to manage crop disease. The effect of this on human health is not well understood. Human and animal waste (poop), along with pharmaceutical manufacturing waste, can also introduce antibiotics and antibiotic resistance into the environment.

People

Antibiotics were first used to treat serious infections in the 1940s. Since then, antibiotics have saved millions of lives and transformed modern medicine. CDC estimates that U.S. doctors' offices and emergency departments prescribe about 47 million antibiotic courses each year for infections that don't need antibiotics. That's about 30% of all antibiotics prescribed in these settings.[2]

Animals

Antibiotics are used to treat infections in pets and food animals. Since 2017, veterinary oversight has been required for the use of medically important antibiotics in the feed and drinking water of food animals for treatment, control, or prevention of infection.[3,4]

Dalene was diagnosed with a multidrug-resistant tuberculosis (TB) infection. Treatment took 19 harrowing months. Dalene had to make potentially life-threatening decisions to stop treatment to preserve her hearing and career. Read Dalene's story on page 97.

DRUG-RESISTANT
STREPTOCOCCUS PNEUMONIAE

Improving Antibiotic Use Resources

Human Health: CDC Resources

Core Elements of Antibiotic Stewardship

Antibiotic Prescribing and Use in the U.S.

Be Antibiotics Aware educational materials

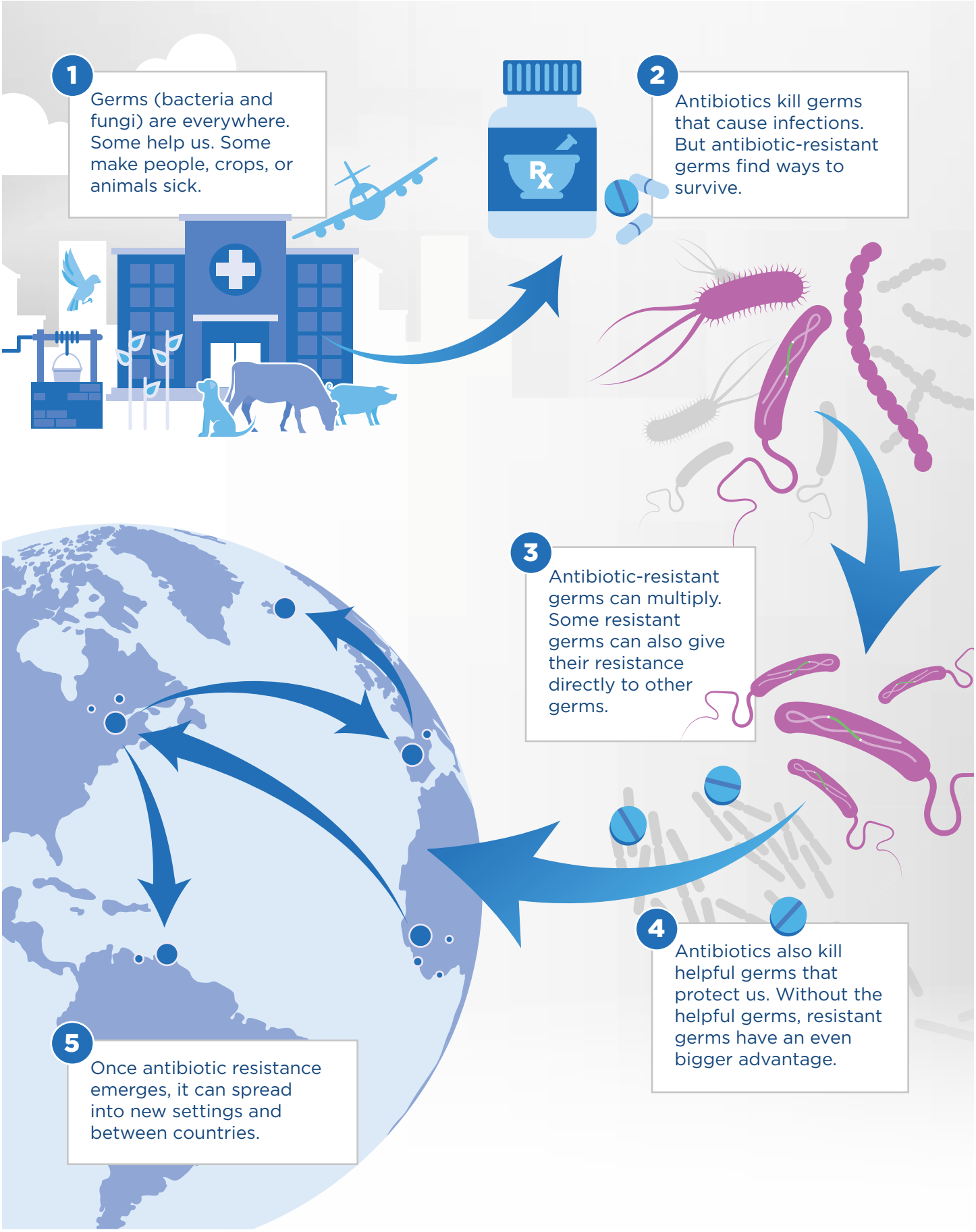
Animal Health: American Veterinary Medical Association (AVMA) Resources

Judicious Therapeutic Use of Antimicrobials

Antimicrobial Stewardship Definition and Core Principles

CDC participates in the AVMA Committee on Antimicrobials, which established improving use principles and encourages development of antibiotic stewardship plans in every veterinary practice setting.

How Antibiotic Resistance Spreads



Germs Fight Back: Resistance Mechanisms

To survive the effects of antibiotics, germs are constantly finding new defense strategies, called "resistance mechanisms." DNA tells the germ how to make specific proteins, which determine the germ's resistance mechanisms. These mechanisms can change over time and lead to more resistant infections. Alarmingly, antibiotic-resistant germs can share their resistance genes with other germs that have not been exposed to antibiotics.

Bacteria and fungi can carry genes for many types of resistance. When already hard-to-treat germs have the right combination of resistance genes, it can make all antibiotics ineffective, resulting in untreatable infections. For example, since the dawning of the antibiotic era, the beta (β)-lactam class of antibiotics have been critically important to modern medicine. These include the earliest-developed and narrow-spectrum penicillins, increasingly broader-spectrum cephalosporins, and the most recently introduced and broadest-spectrum carbapenems (see page 36 for descriptions of narrow- and broad-spectrum antibiotics).

Beta-lactam antibiotics kill bacteria by binding to proteins to stop the germ from creating a cell wall or prevent the cell wall from properly forming. The cell wall is essential for the germ to survive because it offers protection and gives the cell its structure. Enterobacteriaceae are a large family of germs that are a common cause of infections in hospitals and in the community. Some Enterobacteriaceae can produce enzymes called extended-spectrum beta-lactamases (ESBL), which break down and destroy beta-lactam antibiotics.

Carbapenems are one of the few remaining antibiotics that can treat ESBL-producing bacteria, but resistance enzymes are on the rise and destroying the antibiotics. Some Enterobacteriaceae can produce an enzyme called a carbapenemase that makes carbapenems, penicillins, and cephalosporins ineffective. For this reason, CRE have been called "nightmare bacteria"—there are few alternative antibiotics, if any, left to treat the infections these germs cause.

Many bacteria from the Enterobacteriaceae family, including *Klebsiella pneumoniae (K. pneumoniae)* and *Escherichia coli,* can produce a carbapenemase and become CRE. Carbapenemase enzymes that CRE produce include:

- *K. pneumoniae* carbapenemase (KPC)
- Oxacillinase-48 (OXA-48)
- New Delhi Metallo-beta-lactamase (NDM)
- Verona integron-encoded metallo-beta-lactamase (VIM)

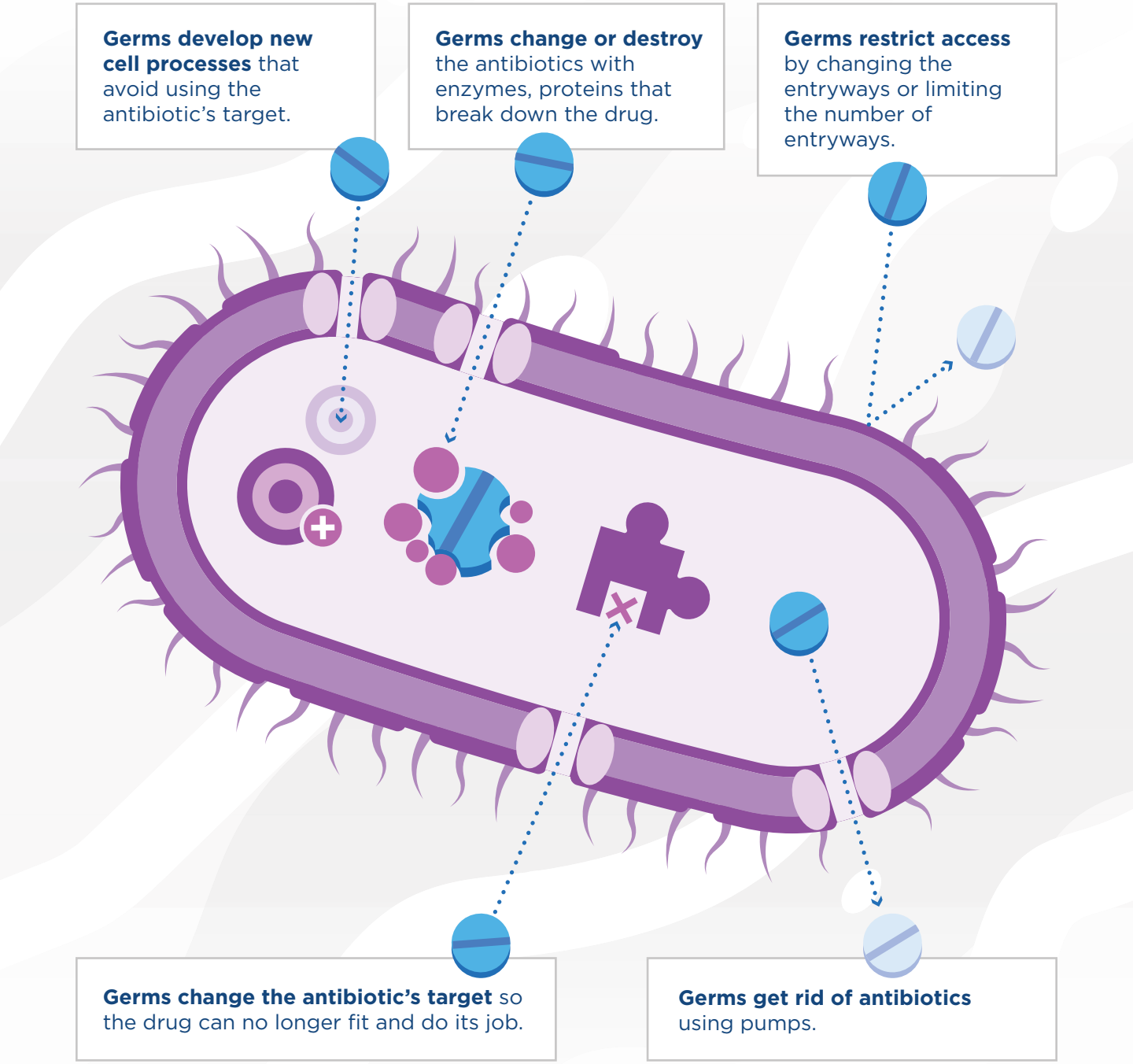
Antibiotic Use Pressures Bacteria & Fungi to Adapt

Germs evolve all the time, developing new ways to avoid the effects of antibiotics. Once new resistance develops, exposure to antibiotics wipes out susceptible germs and allows the resistant germ to survive and multiply.

The surviving germs have resistance traits in their DNA. This genetic information can pass from generation to generation in germs and can also move between germs via mobile genetic elements and other processes. This creates more resistant germs, which continue to spread.

How Bacteria and Fungi Fight Back Against Antibiotics

Antibiotics fight germs (bacteria and fungi). But germs fight back and find new ways to survive. Their defense strategies are called **resistance mechanisms**. Only germs, not people, become resistant to antibiotics.

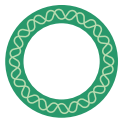


How Antibiotic Resistance Moves Directly Germ to Germ

Any antibiotic use can lead to antibiotic resistance. Antibiotics kill germs like bacteria and fungi, but the resistant survivors remain.

Resistance traits can be inherited generation to generation. They can also pass directly from germ to germ by way of **mobile genetic elements**.

Mobile Genetic Elements

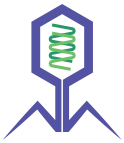


Plasmids

Circles of DNA that can move between cells.

Transposons

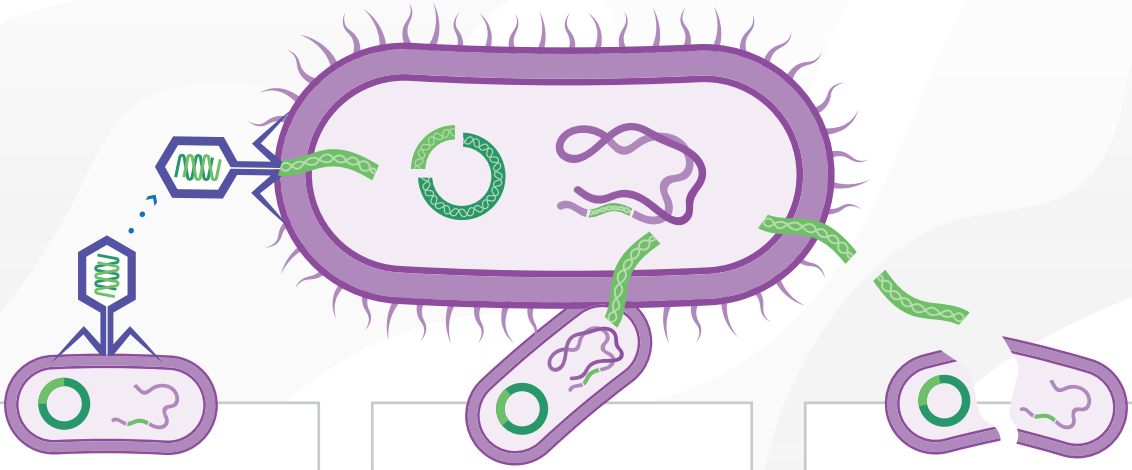
Small pieces of DNA that can go into and change the overall DNA of a cell. These can move from chromosomes (which carry all the genes essential for germ survival) to plasmids and back.



Phages

Viruses that attack germs and can carry DNA from germ to germ.

How Mobile Genetic Elements Work



Transduction

Resistance genes can be transferred from one germ to another via phages.

Conjugation

Resistance genes can be transferred between germs when they connect.

Transformation

Resistance genes released from nearby live or dead germs can be picked up directly by another germ.

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A Complex Web:
Everything is Connected

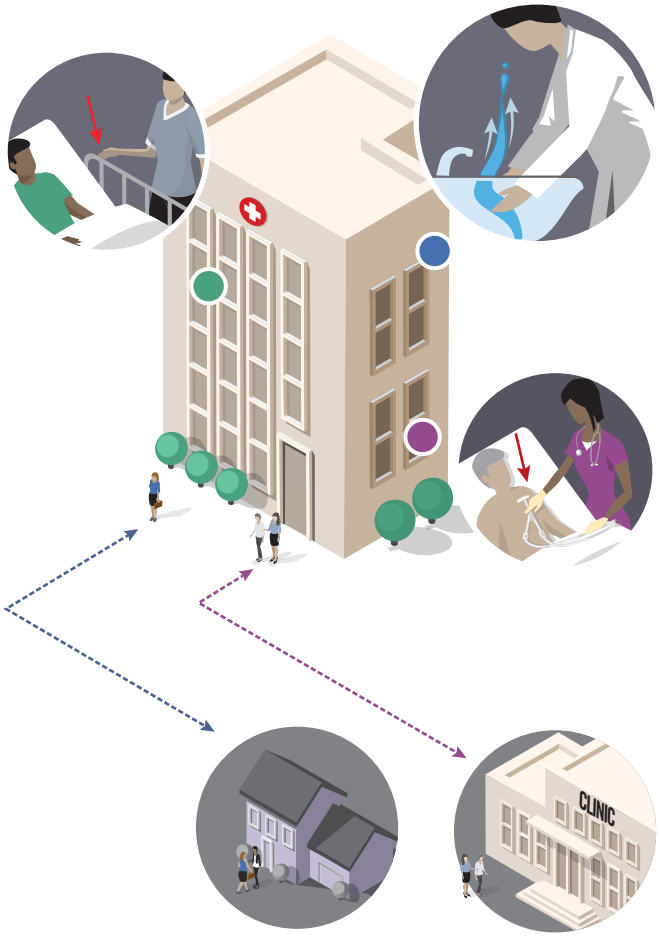
Antibiotic resistance, when germs defeat the antibiotics designed to kill them, can develop and spread across settings. It can affect our progress in health care, food production, and life expectancy.

Antibiotic resistance is a One Health problem—the health of people is connected to the health of animals and the environment (soil, water).

SCHOOL
NURSING HOME

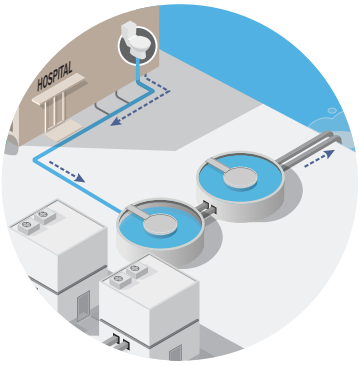
Healthcare Facilities

Antibiotic-resistant germs, including new and emerging resistance, can spread within and between healthcare facilities. These germs can cause infections in patients, called healthcare-associated infections (HAIs), and can spread to the community or environment (soil, water).



- Antibiotics save lives. However, any time antibiotics are used, the drugs can cause side effects and contribute to the development of antibiotic resistance.
- Germs can survive in plumbing (e.g., sink drains, toilets). The germs can splash back onto people, or move to wastewater treatment plants.
- Without appropriate infection control actions, germs can spread to people from other people on surfaces like bedrails or the hands of healthcare workers.
- Procedures and medical devices (e.g., catheters) help treat patients, but can be pathways for germs to enter the body and cause infections.

- Germs can move with patients when they are transferred from one healthcare facility to another, or go home.
- Germs can cause infections in the community when healthcare settings do not stop their spread.



- Human waste (poop) can carry traces of previously consumed antibiotics and antibiotic-resistant germs. Waste goes to treatment plants and is released as treated waste water. This can contribute to antibiotic resistance in the environment, including contaminating lakes and streams.

A COMPLEX WEB: EVERYTHING IS CONNECTED

Community & the Environment

Germs, including antibiotic-resistant germs, live and spread within our community and sometimes make people sick. Human activity can introduce antibiotics and antibiotic-resistant germs into the environment (soil, water), but it remains unclear how spread in the environment impacts human and animal health.

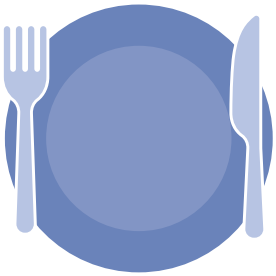
- Germs spread person to person, even during activities like handshaking, working out, having sex, or going to school.
- Resistant germs can spread between people and animals, including pets and petting zoos.
- Antibiotics save lives. However, any time antibiotics are used, the drugs can cause side effects and contribute to the development of antibiotic resistance.

- People can get infections when traveling internationally from other people, animals, contaminated food or water, or through receiving medical care. People can spread germs when they return.

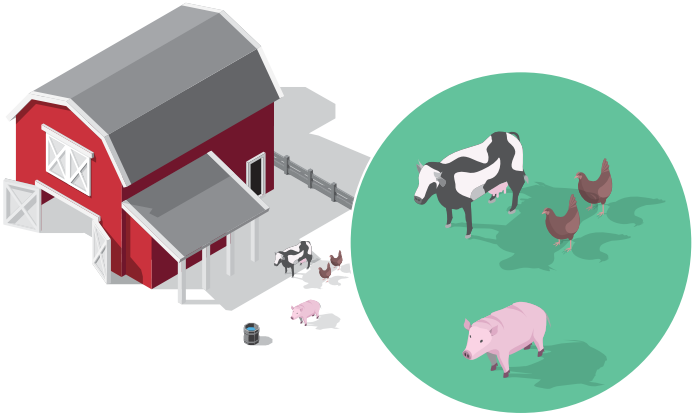
- Antibiotics and resistant germs can spread through wildlife and through the environment, including bodies of water, and can make people sick.
- Waste (poop) from people in hospitals and animals on farms, applying antibiotics as pesticides, and antibiotic manufacturing (commonly occurs outside of the United States) can result in antibiotics and resistant germs in the environment. This contributes to the spread of resistance across the globe.
- Untreated sewage from septic systems and sewer leaks can contaminate the environment.

Food, Farms, & Animals

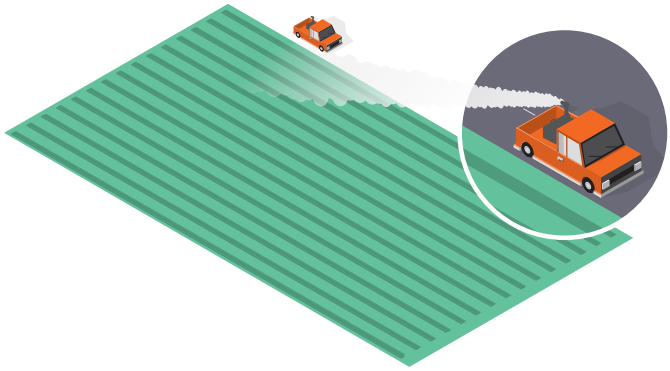
Animals, like people, carry germs in their gut, including antibiotic-resistant germs. The U.S. food supply is among the safest in the world, but these germs can get into the food supply and people can get sick.



- When animals are slaughtered and processed for food, germs in the animal gut, including resistant germs, can contaminate meat or other animal products.
- People can get sick from eating or handling contaminated food or from contact with animals or their surroundings.



- Antibiotics save lives. However, any time antibiotics are used, the drugs can contribute to the development of antibiotic resistance.
- Animal waste (poop) can carry traces of previously consumed antibiotics and antibiotic-resistant germs. Sometimes animal waste is used as fertilizer on farms.
- Food, such as fruits and vegetables, can become contaminated through contact with soil or water containing waste from animals.



- Antibiotics and antifungals are sometimes applied as pesticides to manage crop disease. This may speed up the development and spread of resistant germs by contaminating surrounding soil and water.
- Stormwater and irrigation water from farmland can contaminate nearby lakes and rivers.

Revised Dec. 2019

CLOSTRIDIOIDES DIFFICILE

Take Action: Combat Antibiotic Resistance

Addressing this threat requires preventing infections in the first place, slowing the development of resistance through better antibiotic use, and stopping the spread of resistance when it does develop.

The capacity and resources—such as infection prevention, access to antibiotics, diagnostic testing, and vaccines—to fight antibiotic resistance vary worldwide. CDC is working with partners to strengthen prevention efforts and improve antibiotic use so that the world benefits.

We all have a role to play—let's take action.

Peggy was admitted to the hospital one week after being prescribed antibiotics. She had a *C. difficile* infection brought on by antibiotic use, was diagnosed with sepsis, and passed away.

Learn more about Peggy and the Peggy Lillis Foundation—established by her sons, Christian and Liam—which works to bring awareness to *C. difficile*.

Protect Yourself & Your Family

Infections caused by antibiotic-resistant germs are difficult, and sometimes impossible, to treat—but we can help stop the spread of these germs. Antibiotic resistance happens when germs like bacteria and fungi develop the ability to defeat the drugs designed to kill them.

No one can completely avoid getting an infection, but there are steps you can take to reduce your risk.

Know Your Risks, Ask Questions, & Take Care

Ask your healthcare provider about risks for certain infections and sepsis. Speak up with questions or concerns. Keep cuts clean and covered until healed, and take good care of chronic conditions, like diabetes or heart disease.

Clean Your Hands

Keeping your hands clean is one of the best ways to prevent infections, avoid getting sick, and prevent spreading germs.

Get Vaccinated

Vaccines are an important step to prevent infections, including resistant infections.

Be Aware of Changes in Your Health

Talk to your healthcare provider about how to recognize signs and symptoms of infections, or if you think you have an infection. If an infection isn't stopped, it can lead to additional complications like sepsis, a life-threatening medical emergency.

Use Antibiotics Appropriately

Talk with your healthcare provider or veterinarian about the best treatment when you, your family, or your animal is sick. Antibiotics save lives, but any time they are used they can cause sides effects and lead to antibiotic resistance.

Practice Healthy Habits Around Animals

Always clean your hands after touching, feeding, or caring for animals, and keep your animals healthy.

Prepare Food Safely

Follow four simple steps to avoid foodborne infections. Clean your hands, cooking utensils, and surfaces. Separate raw meat from other foods. Cook foods to safe temperatures. Chill leftovers and other foods promptly.

Stay Healthy When Traveling Abroad

Be vigilant when traveling abroad. Know what vaccinations are needed, check health alerts, stick to safe food and drinks, plan in advance in case you get sick, and learn about the risks of medical tourism.

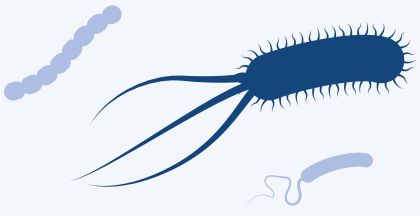
Prevent STDs

Gonorrhea, a common STD, can be resistant to the drugs designed to treat it. The only way to avoid STDs is to not have sex. If you have sex, lower your risk by choosing safer sexual activities and using condoms the right way from start to finish. You and your partner should be treated right away if you test positive to keep from getting infected again.

PROTECT YOUR PATIENTS, COMBAT ANTIBIOTIC RESISTANCE

Actions For Healthcare Providers

You can protect your patients from antibiotic-resistant germs such as bacteria and fungi, which can cause difficult and sometimes impossible to treat infections.



Prevent Infections & the Spread of Germs

Follow infection prevention and control recommendations, including screening at-risk patients when indicated.

Ask patients if they recently received care in another facility or traveled to another country (germs can be spread easily across borders).

Ensure your patients receive recommended vaccines.

Alert receiving facilities when transferring patients who are colonized or infected with antibiotic-resistant germs.

Educate patients on ways to prevent spread.

Stay informed of current outbreaks.

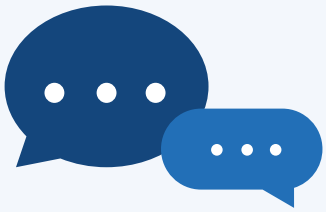
Improve Antibiotic Prescribing

Follow clinical and treatment guidelines. Support CDC's Core Elements of Antibiotic Stewardship to ensure appropriate antibiotic use.

Consider fungal infections for patients with respiratory infections that do not respond to antibiotics.

Watch for signs and symptoms of sepsis. If you suspect sepsis, start antibiotics as soon as possible and reassess antibiotic therapy.

Perform appropriate diagnostic tests to guide antibiotic therapy, including correct drug, dose, and duration.



Be Alert & Take Action

Be aware of infections and resistance patterns in your facility and community.

Ensure you are notified by the lab immediately when antibiotic-resistant germs are identified in your patients.

Inform patients and families if they have an antibiotic-resistant infection, as well as sexual partners when appropriate (e.g., gonorrhea).

Know when to report cases and submit resistant isolates to the health department to help identify unusual resistance or treatment failures.

Actions For Veterinarians

Veterinarians are leaders and stewards in preserving the effectiveness of antibiotics for animals and people. Working with animal owners and producers, veterinarians can slow antibiotic resistance by implementing disease prevention strategies and improving the use of antibiotics while also guaranteeing high-quality medical care for animal patients.

Prevent Disease

Implement best practices for animal husbandry, vaccination, nutrition, and biosecurity (e.g., infection control). Educate people who engage with animals on how to prevent disease.

Clean Your Hands & Equipment

Wash your hands regularly to remove germs, avoid getting sick, and prevent spread of germs between animals and people. Disinfect equipment to help prevent spread among animals and between farms.

Maintain Accurate Records of Treatment & Outcomes

Document and review diagnostic test results and patient response to therapy. Re-evaluate reason for prescribing, dose, and duration as needed.

Select & Use Antibiotics Appropriately

Follow regulatory requirements (antibiotic use should involve veterinary oversight per U.S. guidance). Use current established guidelines and diagnostic tests to assess the need, selection, dose, frequency, and duration of antibiotics.

Stay Current

Stay up-to-date on disease prevention tools; consensus and prescribing guidelines; local, state, and federal requirements; and professional standards for antibiotic use.

Prevent Environmental Contamination

Dispose of unused or expired antibiotics appropriately.

Commit to Antibiotic Stewardship

Implement practice-level stewardship activities, including documenting antibiotic use data, examining use practices, and serving as an educational resource for clients. Engage veterinary diagnostic labs to provide antibiograms to help determine which antibiotics will effectively treat infections. Become familiar with and use the American Veterinary Medical Association established antibiotic use principles to build an antibiotic stewardship plan for your practice settings.

SECTION 2

CHALLENGES AND OPPORTUNITIES IN DETECTION AND TREATMENT FOR ANTIBIOTIC-RESISTANT INFECTIONS

CLOSTRIDIOIDES DIFFICILE

Introduction

Untreatable or pan-resistant infections are no longer a future threat—they are a reality. Around the world, including in the United States, people are dying from infections for which effective antibiotics are not available. In fact, many experts, including at CDC, believe we are already in a "post-antibiotic" era.[5]

Bacteria and fungi do not have to be resistant to every antibiotic to be dangerous. Resistance to even one antibiotic can mean serious problems. Antibiotic-resistant infections that require the use of second- and third-line treatments harm patients and prolong care and recovery, sometimes for months. Healthcare providers may need to treat these infections with antibiotics that have serious side effects, such as organ failure. In some cases, these infections have no treatment options.

Developing new antibiotics is important but we cannot rely on new drugs alone. Antibiotics, even new ones, improve our chances of surviving a resistant infection, but they do not guarantee it. Bacteria and fungi continuously change and develop new ways to resist antibiotics. Once a new antibiotic is used, the countdown starts for how long it will be effective.

Preventing the infection in the first place and stopping spread is the only way to make sure patients are not harmed or killed by these resistant threats. That is why prevention, containment, and antibiotic stewardship are vital.

We Can't Rely on Antibiotics Alone to Fix this Problem

As a result of difficult scientific obstacles and challenging business incentives, many pharmaceutical companies are getting out of the antibiotic business altogether.

- Between 1962 and 2000, **no new major classes** of antibiotics were approved to treat common and deadly Gram-negative infections.[6]
- Since 1990, **78% of major drug companies** have scaled back or cut antibiotic research due to development challenges.[7]
- Historical data show that, generally, only **1 out of 5** infectious disease drugs that reach the initial phase of testing in humans will receive approval from the FDA.[8]

Germs Develop Antibiotic Resistance

Select Germs Showing Resistance Over Time

Since the discovery of penicillin more than 90 years ago, germs have continued to develop new types of resistance against even our most powerful drugs. While antibiotic development has slowed, antibiotic resistance has not. This table demonstrates how rapidly important types of resistance developed after approval and release of new antibiotics, including antifungals.

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant *Staphylococcus aureus*[20, 21]	1942
		Penicillin-resistant *Streptococcus pneumoniae*[9,10]	1967
		Penicillinase-producing *Neisseria gonorrhoeae*[11]	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant *Enterococcus faecium*[12,13]	1988
		Vancomycin-resistant *Staphylococcus aureus*[14]	2002
Amphotericin B	1959	Amphotericin B-resistant *Candida auris*[15]	2016
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*[16]	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing *Escherichia coli*[17]	1983
Azithromycin	1980	Azithromycin-resistant *Neisseria gonorrhoeae*[18]	2011
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*[19]	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*[20]	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant *Candida*[21]	1988
Caspofungin	2001	Caspofungin-resistant *Candida*[22]	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*[23]	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*[24]	2015

Revised Dec. 2019

How Antibiotics Work

Antibiotics are critical tools for preventing and treating infections caused by specific bacteria or fungi in people, animals, and crops. Antibiotics are sometimes classified by how many germs they kill:

- Narrow-spectrum antibiotics target specific types of germs
- Broad-spectrum antibiotics target a wide range of germs

Effective narrow- and broad-spectrum antibiotics target specific parts or processes of susceptible (i.e., not resistant) germs to kill or stop growth. Some antibiotics, such as penicillins and cephalosporins, target a germ's cell wall or membrane to either keep the cell from multiplying or to disrupt the protection these structures provide. This results in death of the organism. Other antibiotics target other cellular functions:

- Macrolides and tetracyclines stop protein synthesis
- Fluoroquinolones stop DNA replication, making it hard for the bacteria to multiply

When a patient has an infection for which an antibiotic is recommended, **the benefits of giving the antibiotic generally outweigh the risks.**

Antibiotics can be administered in many ways to people, animals, and crops.

Intravenously (IV): Through a needle or catheter placed in a vein. This is often used for patients staying overnight in healthcare facilities (inpatients), sometimes for outpatients, in veterinary offices for pets, and on farms for large animals. Healthcare professionals for people or animals oversee it. IV antibiotics are often used for more serious infections because they quickly deliver high levels of the drug to the infection site through the bloodstream.

Intramuscularly: Through injection or a shot into a muscle. This is most helpful when antibiotics cannot be given orally, like using the antibiotic ceftriaxone for gonorrhea.

Orally: By mouth in pill or liquid form. In people, oral antibiotics are often used in outpatient health care—the patient must swallow the medication at the times and doses prescribed. In animals, antibiotics can be placed in food (feed) or water.

Topically: Applied directly to the body (e.g., superficial skin wounds) in the form of a cream, ointment, or liquid. This is often used for skin, eye, and ear infections.

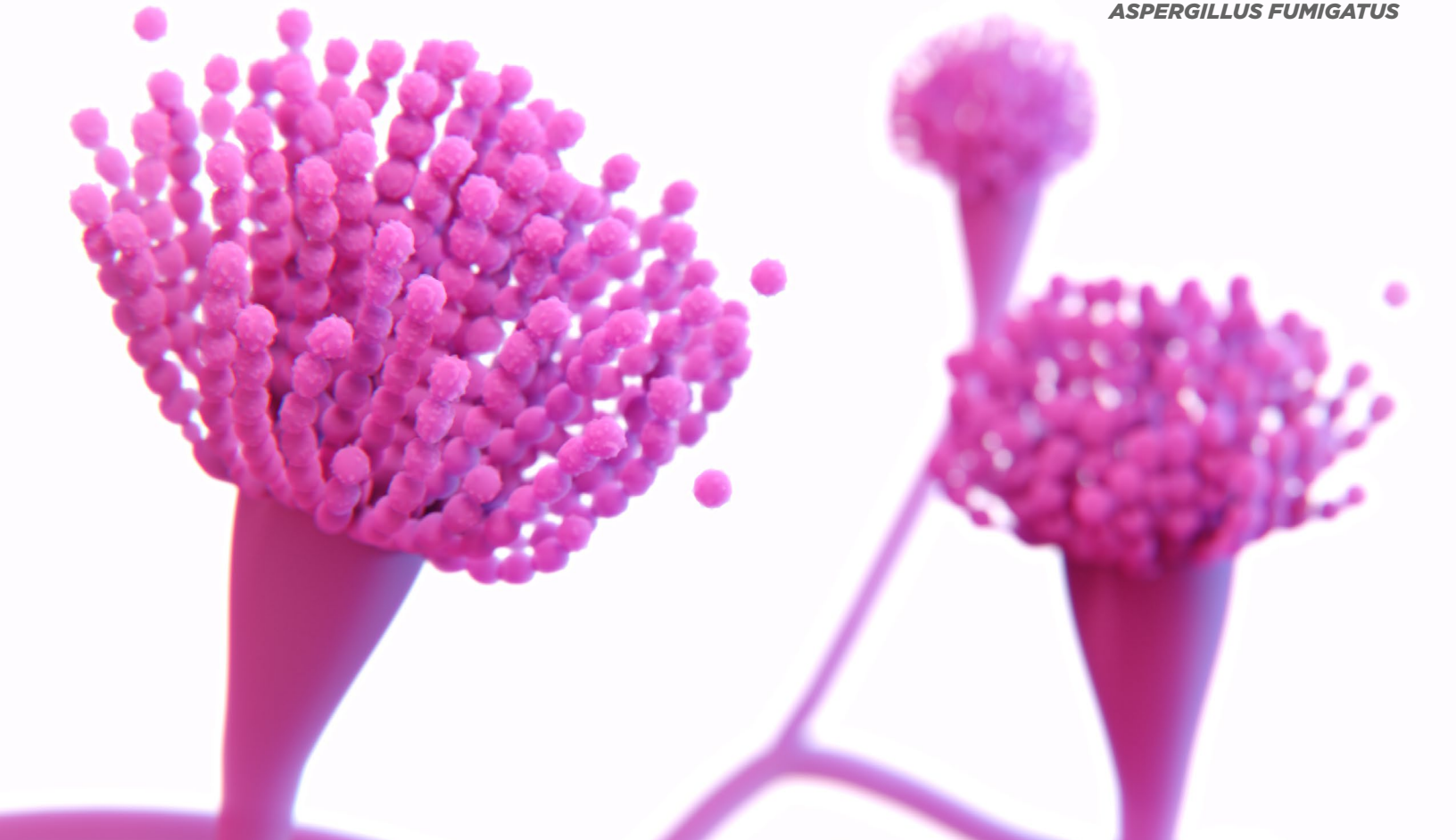
Spraying: Crops can also be sprayed with pesticides that include antibiotics and fungicides important to human medicine to prevent or treat plant diseases. The pesticide can be applied by trucks or airplanes over crop land.

Antibiotics save lives but using them is not free from risk. It is important to note that even when used properly, antibiotics can have side effects and contribute to the development of resistant germs. When a patient (human or animal) takes an antibiotic they do not need, it unnecessarily makes the problem even worse. Not only does the patient get no benefit, but they are also put at risk for side effects (e.g., allergic reactions, toxicity that affects organ function, or *C. difficile).* Unnecessary antibiotic use can also select for antibiotic-resistant germs, which can then spread to other people.

Antibiotic use can also disrupt the human or animal microbiome, the community of naturally occurring germs in and on the body. A healthy microbiome is important for staying healthy and preventing disease. When a patient takes antibiotics, these drugs kill the infection-causing "bad" germs, but "good" germs that protect against infection can also be destroyed at the same time. It can take weeks to months for these "good" bacteria to return. A disrupted microbiome can put people and animals at risk for getting some types of infection, such as *C. difficile*.

Twenty percent of all hospitalized patients who received an antibiotic experienced an adverse drug event (ADE) as a result.[25] In the community, antibiotic-associated adverse events often require emergency treatment. Among children, antibiotics are involved in 46 percent of emergency department visits for ADEs.[26] Among adults, antibiotics are involved in 14 percent of emergency department visits for ADEs.[27] This amounts to more than 214,000 emergency department visits each year. Because any antibiotic use has the potential to cause harm, clinicians should prescribe their patients these powerful drugs only when the benefits outweigh the potential risks.

AZOLE-RESISTANT
ASPERGILLUS FUMIGATUS



What Will That Antibiotic Do?

Common Side Effects of Select Common Antibiotics

Any antibiotic use carries the potential for side effects, such as diarrhea and yeast infections that naturally result from disrupting our microbiome. Some antibiotics can also lead to side effects that are severe, disabling, and even deadly. ADEs are harms resulting from the use of medication and include allergic reactions, side effects, overmedication, and medication errors.

Antibiotics are designed to perform specific functions and treat people with potentially deadly infections. Using the right antibiotic, at the right time, dose, and duration, helps protect people and helps slow the development of antibiotic resistance and the spread of germs.

This table provides examples of important side effects and ADEs of some commonly used and key antibiotics. It is not a comprehensive list. Talk with your healthcare provider for more information, or visit FDA's Index to Drug-Specific Information.

CLINDAMYCIN-RESISTANT
GROUP B *STREPTOCOCCUS*

What Will That Antibiotic Do? Common Side Effects of Select Common Antibiotics

Generic Drug Name	Drug Class	Example Brand Name	Often Used to Treat...	How Drug is Given (Administered)	Often Used at Home, a Healthcare Facility, or Both†	Concerning Side Effects & Adverse Events
Amoxicillin	Penicillins	Amoxil	Ear infections Strep throat	Orally	Home	Rash *C. difficile* infection
Amphotericin B	Polyenes	AmBisome	Fungal infections	Intravenously (IV)	Healthcare Facility	Fever Sweats Electrolyte disturbances Kidney damage
Azithromycin	Macrolides	Zithromax (Z-Pak)	Pneumonia STDs Severe or complicated enteric (gut) infections	Orally IV	Home Healthcare Facility	Irregular heartbeat
Caspofungin	Echinocandin	Cancidas	Fungal infections	IV	Healthcare Facility	Nausea, vomiting
Ceftriaxone	Cephalosporins	Rocephin	Respiratory infections STDs Severe or complicated enteric infections	IV Intramuscularly	Healthcare Facility	Rash *C. difficile* infection
Cephalexin	Cephalosporins	Keflex	Skin infections	Orally	Home	Rash *C. difficile* infection
Clindamycin	Lincosamides	Cleocin	Dental infections	Orally Intramuscularly IV Topically	Home Healthcare Facility	Rash Nausea, vomiting *C. difficile* infection
Daptomycin	Lipopeptides	Cubicin	Antibiotic-resistant Staphylococcus infections	IV	Healthcare Facility	Muscle inflammation and damage
Doxycycline	Tetracyclines	Doryx	Acne STDs	Orally IV	Home Healthcare Facility	Sensitivity to sunlight Esophagus inflammation
Fluconazole	Azoles	Diflucan	Fungal infections	Orally IV	Home Healthcare Facility	Liver toxicity Drug interactions
Gentamicin	Aminoglycoside	Gentak	Antibiotic-resistant Gram-negative infections	IV	Healthcare Facility	Kidney damage Vertigo Hearing loss

What Will That Antibiotic Do? Common Side Effects of Select Common Antibiotics

Generic Drug Name	Drug Class	Example Brand Name	Often Used to Treat...	How Drug is Given (Administered)	Often Used at Home, a Healthcare Facility, or Both†	Concerning Side Effects & Adverse Events
Isoniazid	Antimycobacterials	Nydrazid	Tuberculosis	Orally Intramuscularly	Home Healthcare Facility	Liver toxicity Nerve damage
Levofloxacin	Fluoroquinolones	Levaquin	Pneumonia Urinary tract infections Severe or complicated enteric infections	Orally IV Topically	Home Healthcare Facility	Risk of ruptures or tears in aorta Achilles tendon rupture *C. difficile* infection Altered sugar levels Abnormal heartbeat
Linezolid	Oxazolidinones	Zyvox	Antibiotic-resistant Staphylococcus infections	Orally IV	Home Healthcare Facility	Blood cell complications Nerve damage (long-term)
Meropenem	Carbapenems	Merrem	Sepsis Antibiotic-resistant Gram-negative infections	IV	Healthcare Facility	Seizure risk *C. difficile* infection
Metronidazole	Nitroimidazoles	Flagyl	Trichomoniasis (a type of vaginitis) Abdominal infections	Orally IV Topically	Home Healthcare Facility	Nerve damage
Nitrofurantoin	Nitrofurans	Macrobid	Urinary tract infections	Orally	Home	Rash Lung damage
Piperacillin-Tazobactam	Penicillin-based combination	Zosyn	Sepsis	IV	Healthcare Facility	Rash *C. difficile* infection
Trimethoprim-sulfamethoxazole	Antifolates	Bactrim	Urinary tract infections	Orally IV	Home Healthcare Facility	Rash Electrolyte disturbances
Vancomycin	Glycopeptides	Vancocin	Antibiotic-resistant Staphylococcus infections *C. difficile* infections	Orally IV	Home Healthcare Facility	Rash Kidney damage

†Some drugs prescribed to patients to be taken when not admitted to or outside of a healthcare facility can also be prescribed for patients who are admitted to a healthcare facility

STD: Sexually transmitted disease

Gram-negative bacteria: A group of germs that are increasingly resistant to many available antibiotics

Visit FDA's Index to Drug-Specific Information for the comprehensive list of adverse events associated with antibiotics

Development Pipeline For Human Medicine:
Antibiotics, Diagnostics, and Other Innovations

Drug development can take many years and can cost antibiotic developers millions of dollars. This table shows the extensive process. The FDA must approve all drugs and medical devices to ensure that they are safe and effective when they reach the public.

The Drug Development Process[28]

STEP 1	**Discovery and Development:** Research for a new drug begins in the laboratory.
STEP 2	**Preclinical Research:** Drugs undergo laboratory and animal testing to answer basic questions about safety.
STEP 3	**Clinical Research:** Drugs are tested on people to make sure they are safe and effective.

PHASE 1	PHASE 2	PHASE 3
Purpose Safety and dosage	**Purpose** Efficacy and side effects	**Purpose** Efficacy and monitoring adverse reactions
Study Participants 20–100 healthy volunteers or people with the disease/condition	**Study Participants** Up to several hundred people with the disease/condition	**Study Participants** 300–3,000 volunteers who have the disease or condition
Length of Study Several months	**Length of Study** Several months to 2 years	**Length of Study** 1 to 4 years
Approximately 70% of drugs move to the next phase	Approximately 33% of drugs move to the next phase	Approximately 25–30% of drugs move to the next phase

STEP 4	**FDA Review:** FDA review teams thoroughly examine all the submitted data related to the drug and make a decision to approve or not to approve it.
STEP 5	**FDA Post-Market Safety Monitoring & Phase 4 Studies:** FDA and the product developer monitor all drug and device safety once products are available for use by the public. Additional Phase 4 studies may be performed after the drug is approved.

Pew's Analysis of Antibiotics in Clinical Development

42	4	17	11	1 in 4
Antibiotics in development	Have new drug applications submitted	Could treat infections caused by certain Gram-negative bacteria	Could address urgent threats gonorrhea or *C. difficile*	Is a novel drug class or novel mechanism of action

As of June 2019[8]

Antibiotic Development

New antibiotics, including antifungals, may help improve patient treatment options and outcomes, especially against resistant infections, but the fight against antibiotic resistance cannot rely on drug development alone. CDC encourages everyone who uses antibiotics important for human and animal medicine to improve how these drugs are used to protect their effectiveness.

New antibiotics are an important piece of the fight against antibiotic resistance. Unfortunately, there is not enough novel activity in the drug development pipeline. Of the resistance threats listed in this report, the challenges in drug development for human health include:

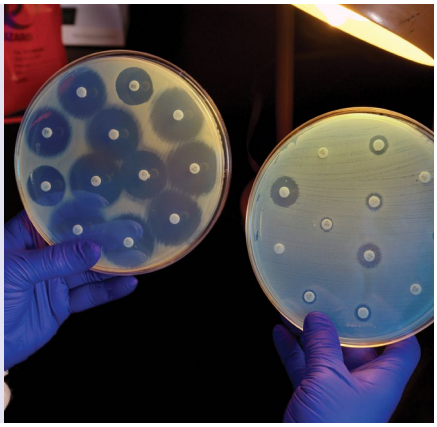
- **Gram-negative Germs:** Ten of the 18 antibiotic-resistant threats listed in this report are Gram-negative, but few antibiotics are available or in development to treat the infections they cause. For example, treatment with ceftriaxone for *N. gonorrhoeae* infections is highly effective, but there is growing concern about antibiotic resistance.
- **Fungi:** Therapeutic options for fungal infections are limited even before considering antifungal resistance. Only three classes of drugs are available to treat systemic *Candida* and *Aspergillus* infections. New antifungals are needed that are broad spectrum and are low toxicity.
- **Multidrug-resistant (MDR-TB) and Extensively Drug-resistant Tuberculosis (XDR-TB):** Drug development for *Mycobacterium tuberculosis* is focused on shortening drug regimens and reducing toxicity, such as hearing loss caused by intravenous antibiotics.

Developing new drugs will require stronger, different, and better discovery strategies. Hopefully, drug discovery will focus on infections of greatest need, like those caused by carbapenemase-producing bacteria (e.g., CRE, carbapenem-resistant *Acinetobacter baumannii,* carbapenem-resistant *P. aeruginosa*). It is critical to improve use of the effective antibiotics available today, as well as implement the infection prevention and control tools we have at our disposal. Focusing on stopping spread and containing spread of rare and emerging resistance is important. We will need fewer drugs if we can prevent infections through proper measures.

> "...resistance will eventually develop to those [antibiotics] that are approved, it is clear that there are too few drugs in development to meet current and anticipated patient needs."
>
> —Pew Charitable Trusts, September 2019[8]

How Susceptibility Testing Works

Antibiotic susceptibility testing is a way to describe how sensitive germs are to particular antibiotics. An antibiotic can stop the growth of or kill a susceptible germ. This image shows two petri dish culture plates growing bacteria. Discs containing various antibiotics were placed on the bacteria. The bacteria growing on the left plate appear to be susceptible to the antibiotics on the discs since it was unable to grow next to them. However, the bacteria on the right was able to grow nearer the discs, showing potential resistance.



Diagnostic Development

Appropriate treatment and prevention of antibiotic-resistant infections relies on diagnostic tools to detect resistant germs as soon as they emerge. Identifying resistance allows healthcare providers to promptly use effective antibiotics or alternative therapies and implement infection control measures to prevent spread. The United States' response to antibiotic resistance cannot rely on these tools alone.

In addition to therapeutics like antibiotics, we also need improved use and development of diagnostics—laboratory tests that help determine the germ causing an infection—to detect resistant infections earlier and guide appropriate antibiotic use. Diagnostics can be just as critical for fighting infections as antibiotics. These tools help human and animal healthcare providers identify infections as soon as possible and guide selection of the best treatment option for their patient. In addition, they help sound the alarm that alerts local infection control programs and health departments to emerging threats. Diagnostic tools can:

- Improve the accuracy and speed of a patient's diagnosis, improving appropriate antibiotic selection and reducing unnecessary antibiotic use
- Identify when germs spread, so that infection prevention and control can improve
- Support public health tracking to rapidly identify threats and infection trends, informing public health response

Resistance or susceptibility tests are diagnostic tools that give healthcare providers, laboratorians, and epidemiologists specific information to help select the best treatment for an infection and prevent the spread of resistant germs in people or animals. The cost, expertise, and time varies for each test. The various tests provide different kinds of data. Laboratory technicians perform the test depending on the question the healthcare provider is trying to answer:

- What is causing the infection, and has new resistance emerged?
- Which antibiotics will be effective?
- Is the germ spreading?

Helpful Resources

Tracking Drug Development Progress

Nature Reviews: Drug Discovery

Treatment Action Group's Pipeline Report

The Pew Charitable Trusts

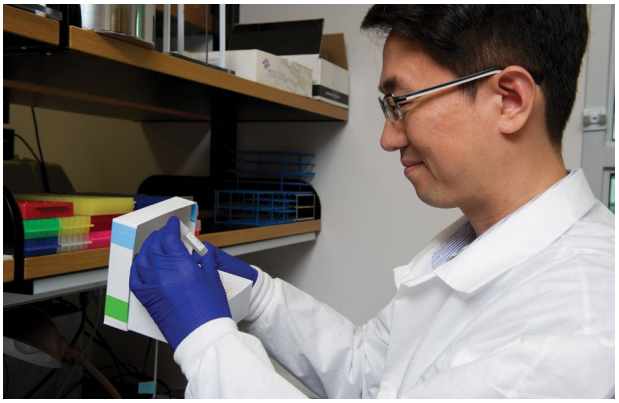
Working Group of New TB Drugs

U.S. Government Agency Websites

Biomedical Advanced Research and Development Authority

National Institute of Allergy and Infectious Diseases

FDA



CDC's AR Lab Network

The Antibiotic Resistance Laboratory Network (AR Lab Network) provides healthcare facilities and state health departments with access to gold-standard public health lab testing.

Supported by CDC's AR Solutions Initiative, the AR Lab Network provides testing capacity in every U.S. state, several large cities, and Puerto Rico.

The network works in a tiered structure—necessary, basic testing at the local level, with more complex, specialized testing at seven regional labs and a TB lab that supports the country. CDC supports the labs by performing additional testing when needed.

This testing complements other testing CDC performs, including through the National Antimicrobial Resistance Monitoring System (NARMS). NARMS is an interagency partnership among CDC, FDA, and the U.S. Department of Agriculture that tracks antibiotic resistance in foodborne and other enteric bacteria.

AR Isolate Bank

The CDC & FDA Antibiotic Resistance Isolate Bank (AR Isolate Bank) provides information on resistance to support innovation in diagnostics and drug development. It helps:

- Strengthen diagnostics by validating lab tests
- Perform testing to ensure drug effectiveness
- Study biology and pathogenic mechanisms
- Detect new and unusual public health resistance threats
- Inform research and development to
- Develop drugs such as antibiotics and antifungals
- Develop diagnostic devices, tests, or assays
- Satisfy a request or support an application to FDA

This work ultimately improves patient care and builds solutions against resistance threats.

As of August 2019, the AR Isolate Bank provided

24	810	1,872	955
Panels Available	Isolates Available	Orders Filled	Registered Users

The following table highlights types of diagnostic tests and tools that CDC and public health experts use in the fight against antibiotic resistance.

Type of Lab Test	Primary Use	Primary User	Description
Pathogen Identification: Culture & Molecular Tests	Identify the germ causing an infection.	Clinical labs and public health labs in the AR Lab Network. Testing is conducted by all AR Lab Network labs—in every state, several large cities, and Puerto Rico, including regional labs.	Labs work to identify and confirm the genus and species of germs with suspected resistance, which can inform the response to stop spread and treat the infection. This is done through one of many methods: **Mass spectrometry:** A specialized technique that looks for a pathogen's protein profile **Biochemical tests:** Classifying a particular species by the way it uses different biological chemicals, like proteins or sugars **Nucleic acid amplification tests (NAATs):** Detection of a specific DNA or RNA target that is specific for a particular pathogen. **Subtyping tests:** Classify organisms within a species (i.e., strains) that are genetically-related often by sequencing a subset of antigens or genes. **Whole genome sequencing:** Identifying a pathogen by comparing its sequence to a database of known pathogens to find the closest relative.
Colonization Screening	Identify if the germ has or is being spread, even if no infections have occurred.	Healthcare providers and public health authorities use colonization screening in or across healthcare facilities. CDC supports colonization screening of pathogens, such as CRE and *Candida auris*, through the AR Lab Network.	Some people can carry germs without becoming sick or showing symptoms, known as colonization. People who are colonized can be a source of spread of these germs to others without knowing it. When unusual resistance is identified in a patient, healthcare workers can screen other patients to see if they are colonized with the same resistant germ, indicating spread. This can prompt additional infection control actions to reduce the risk of spread and protect patients.
Asymptomatic Infection Screening	Identify if the germ is causing an asymptomatic infection.	Healthcare providers and public health authorities use screening in healthcare clinics and in community settings. CDC and the U.S. Preventive Services Task Force (USPSTF) support screening for STDs, such as gonorrhea.	Some people can be infected without showing symptoms, known as asymptomatic infection. People who have asymptomatic sexually transmitted diseases (STDs), such as gonorrhea, can spread these germs to others without knowing it. Public health programs support timely treatment of patients and their sexual partners to reduce burden and spread of STDs in a community. When unusual resistance is identified in a patient, healthcare workers can screen and treat sexual and social networks to reduce the risk of spread of the resistant germ to protect patients and communities.

Type of Lab Test	Primary Use	Primary User	Description
Antimicrobial Susceptibility Testing (AST)	Identify which antibiotics the germ may be resistant or susceptible to. Germs may be deemed "multidrug-resistant" or "pan-resistant" with this test. Since most laboratories do not test all existing antibiotics, the term "pan-resistant" often means the germ is resistant to all antibiotics used against it during lab testing; not necessarily to all antibiotics available on the market.	For healthcare-associated infections: Hospital labs and public health labs perform these tests. In the AR Lab Network, AST is conducted by all labs—in every state, several large cities, and Puerto Rico, including regional labs. Expanded AST is performed by regional labs to test drugs that have recently or are soon to come to market for which no standard lab test yet exists. For enteric (gut) infections: CDC NARMS performs these tests on a subset of isolates submitted to public health labs.	Susceptibility testing is a type of lab test that uses a culture to show how susceptible (sensitive) a germ is to different amounts of different antibiotics. These tests can be used to help select the right drug for an antibiotic-resistant infection, and also provide data to monitor how a germ's resistance profile might change over time.
Phenotypic Carbapenemase Test	Identify if a germ produces a specific resistance enzyme called carbapenemase.	Some clinical labs perform this testing, but many do not. In the AR Lab Network, this is conducted by all labs—in every state, several large cities, and Puerto Rico, including regional labs.	A phenotypic carbapenemase test uses a culture (a medium to grow bacteria) to determine if the pathogen produces a carbapenemase enzyme. Carbapenamase-producing bacteria are more likely to spread their resistance to other bacteria.
Genotypic Test	Identify the type of resistance genes a germ carries.	Some clinical labs and all public health labs in the AR Lab Network—in every state, several large cities, and Puerto Rico, including regional labs.	Molecular testing techniques detect specific genes within a germ, including those that have and can share resistance. These tests can be used to diagnose infections, guide treatment for patients, prioritize foodborne and zoonotic disease investigations, and help inform the need for infection control interventions.
Whole Genome Sequencing (WGS)	Identify germs that may be related, predict resistance, and/or identify underlying causes of resistance in a germ. WGS can also be used to predict resistance in certain germs by looking at the genes and mechanisms that are identified.	Rarely performed in hospital or clinical labs. In the AR Lab Network, conducted by a regional lab, a state lab participating in PulseNet, or the National Tuberculosis Molecular Surveillance Center.	WGS is a laboratory procedure that provides a precise DNA profile of a germ that can help identify resistance genes and link cases to one another, allowing an outbreak to be detected, prioritized for investigation, and stopped sooner.

Many current diagnostic technologies are:

- Effective but costly
- Time-consuming
- Do not detect emerging resistance markers
- Do not yield a live, pure culture of the bacteria
- Do not rapidly discriminate bacterial or fungal infections from viral ones

Additional research and investments are needed to improve diagnostic tests and the data they generate. Having information about resistance at the time when the patient is first treated helps to target broad-spectrum antibiotic use to those patients with resistant infections when they need it and avoiding unnecessary use of broad-spectrum antibiotics in those patients who do not. See analysis of the diagnostic pipeline in the Technical Appendix.

In addition, reimbursement challenges in human and animal healthcare can prevent some diagnostic use (e.g., colonization testing has often not been reimbursed by health insurance). Diagnostic test manufacturers also can consider tests that will work in low- and middle-income countries with limited testing materials and supplies.

Future tests could be performed at or near the bedside or on the farm, or at the time of the clinic visit (i.e., with a point-of-care device). These simple, quick tests could give healthcare providers enough information to act immediately. Additional information will still be needed for surveillance and outbreak detection and investigation. Finally, a test that can differentiate bacterial, viral, or fungal infection from other causes of symptoms, and which can be used across healthcare settings (inpatient and outpatient), can significantly improve appropriate antibiotic use and reduce unnecessary antibiotic use.

The current diagnostic test pipeline shows innovation, but more is needed to significantly change how infections are managed.

Diagnostic Stewardship

Diagnostic stewardship is critical in improving patient care and combating antibiotic resistance. Ordering the wrong tests, ordering tests at the wrong time, or interpreting tests incorrectly harms patients by, for example:

- Performing unnecessary tests
- Providing unnecessary treatment, including unnecessary antibiotic use
- Missing opportunities to provide the right treatment in a timely manner

It can result in delayed diagnosis or wrong diagnosis that can impact lives. For example, there is a strong link between over-testing nursing home patients with urine cultures and unnecessary antibiotic use, which can lead to *C. difficile* infection and other adverse events.

Antibiotic resistance, antibiotic stewardship, and outcomes of infections, such as sepsis, are all tied together.

CDC plays several critical roles in promoting diagnostic stewardship:

- Data analyses that drive appropriate diagnostic testing and monitor diagnostic use
- Measurement of diagnostic stewardship impact
- Help to mitigate harms that could result from using diagnostics
- Development of best practices to educate healthcare providers

Other Tools to Combat Resistant Infections

According to Pew Charitable Trusts, unlike many antibiotics in development, most nontraditional products (i.e., antibiotic alternatives) are active against a limited range of germs. As of June 2019, 29 nontraditional products were in clinical development and only seven were in Phase 3 clinical trials.[29]

Alternative treatment and prevention options may potentially be as effective as antibiotics. Because they do not deplete the microbiome of "good bacteria," they can also be lower risk.

In addition to working with partners to improve how antibiotics are used, CDC collaborates with academic researchers to identify alternative treatment and prevention solutions. More innovation and research are needed to identify, develop, implement, and evaluate novel therapies for antibiotic-resistant infections.

Vaccines

Vaccines work by causing the immune system to prevent and target threats to the body, including antibiotic-resistant germs. Vaccines can significantly reduce infection rates, which decreases antibiotic use and the number of resistant germs. From 2000 to 2016, many Member States of the World Health Organization (WHO) increased the use of the pneumococcal conjugate vaccine, which helped protect against infection by *Streptococcus pneumoniae*. This reduced the rate of death in children substantially—more than 250,000 children had a new chance at life. Specifically, resistant strains of *Streptococcus pneumoniae* fell sharply after widespread introduction of the vaccines in both children and older adults.

Pneumonia caused by other bacteria, including MRSA, is a leading cause of complications and death in patients who get the flu. The influenza vaccines can decrease the risk of these potentially deadly MRSA pneumonias. Researchers are also testing vaccines to prevent other types of *Streptococcus* infections (e.g., those caused by groups A and B) and *C. difficile* infection.

Vaccination of food-producing animals can also lower the chances of infection in consumers. The United States has seen fewer human *Salmonella* Typhimurium infections (a type of nontyphoidal *Salmonella*), which might be due to U.S. poultry producers vaccinating against *Salmonella* Typhimurium.[30]

Improving the use of vaccination for those at risk is a challenge. The vaccine pipeline is fragile, and the development process is difficult. It can take many years and significant resources to develop a safe and effective vaccine and bring it to market, particularly for some germs like *Staphylococcus aureus*.

Antibodies

Antibodies are naturally occurring proteins that the body produces in response to invading germs. In some instances, antibodies can be harvested and used as medicines. These medicines work differently than vaccines. A vaccine stimulates antibody production within a few weeks. Antibody therapy, however, provides an immediate level of immunity. Healthcare providers can give antibody treatment to patients with recurrent *C. difficile* infections. New antibody-based therapies to treat and prevent bacterial-associated pneumonia are being developed.

According to Pew Charitable Trusts, as of June 2019, 29 nontraditional products were in clinical development and only seven were in Phase 3 clinical trials.[29]

Bacteriophages[31–35]

Bacteriophages, also called "phages," are viruses that infect and replicate within bacteria. In some cases, phages can kill bacteria. There have been cases in which individuals dying of multidrug-resistant infections made complete recoveries through phage therapy, in one instance involving genetically engineered phages. Researchers are also testing phages for use in burn patients, infected left ventricular assist devices (LVADs), the treatment of bacteremia (bacteria in the blood), and endocarditis (infection in the heart). Phages have also been successfully used to decontaminate food that might carry disease-causing bacteria, such as *Listeria.* Like antibiotics, bacteria can become resistant to phages, but this is managed through different treatment regimens. To date, phage therapy has not been applicable to fungi.

Fecal Microbiota Transplant (FMT)/Live Biotherapeutics (LB)[36]

FMT and LB use helpful bacteria that may assist in restoring a person's microbiome when it becomes disrupted for any reason, including antibiotic use. These "good" bacteria help protect a patient from becoming colonized with infectious bacteria like *C. difficile* and resistant germs. (Colonization is often a first step before infection.) These methods and other similar products are being studied further, especially to stop *C. difficile* infections and to prevent neonatal sepsis.

FMT and LB may help to prevent infections and have been used to stop *C. difficile* infections and shorten the time people are colonized with resistant germs. However, they have also been associated with adverse outcomes. (These therapies are different than probiotics, which have not been approved by FDA for safety and efficacy as a treatment.)[37]

Other Alternative Agents

Most alternative agents fall into one of the categories above. However, some experts have hypothesized that a few other alternatives in development may help. This includes peptides (small proteins) that boost the patient's immune response to an infection, as well as agents that target virulence factors (characteristics that help the germ cause damage) of germs like *Pseudomonas,* both with the goal of reducing the bacteria's ability to cause disease and make patients sick. Strong clinical trials will help test and inform these hypotheses.

With so few novel antibiotics and the number of effective antibiotics dwindling, it is clear we cannot rely on traditional antibiotics alone to treat infections. Alternative antibiotic agents and improved testing are key components to our national healthcare strategy to prevent and treat infections in new ways. Like antibiotics, these solutions will have specific applications but—when applied for life-threatening resistant infections—should save lives and help preserve the remaining antibiotics that are still effective today.

Greater focus on infection prevention and control, using antibiotics only when needed, as well as innovations in diagnostic testing, alternative treatments, and effective vaccines, will better prepare the United States for the resistance that will continue to emerge worldwide.

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SECTION 3

NATIONAL ACTION TO COMBAT ANTIBIOTIC RESISTANCE

U.S. Action

In 2013, CDC published *Antibiotic Resistance Threats in the United States, 2013,* the first snapshot of the burden and threats posed by antibiotic-resistant germs on human health. The report sounded the alarm of this growing threat, spurring unprecedented action and investment by the U.S. government to combat antibiotic resistance.

Following the release of the report, involvement at the highest levels of the government led to the release of the *National Action Plan for Combating Antibiotic Resistant Bacteria* (CARB), a five-year goal-driven roadmap of actions to detect, prevent, and respond to resistant threats. Beginning in Fiscal Year 2016, Congress has supported CARB activities across the U.S. government.

Today, government agencies are leading critical activities with partners to combat antibiotic resistance domestically and globally. Agencies have already achieved key successes by focusing on collaboration, innovation, and early adoption of aggressive action.

A global leader in the fight against antibiotic resistance, the United States spearheads One Health actions and partnerships to combat antibiotic resistance, including:

- Leading the Antimicrobial Resistance (AMR) Challenge
- Advancing the antibiotic resistance call-to-action at the 2016 United Nations General Assembly
- Collaborating with WHO and other nations
- Serving as a founding member of the Global Antimicrobial Resistance Research & Development Hub
- Joining experts from the European Union, Canada, and Norway to form the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)
- Implementing national programs to detect, prevent, and treat antibiotic-resistant infections

Implementing this work across settings addresses the global challenge to prevent antibiotic-resistant infections and slow their spread.

Left: U.S. Secretary of Health and Human Services Alex Azar speaking at the 2018 AMR Challenge

Right: CDC's Principal Deputy Director Anne Schuchat speaking at the 2018 TATFAR meeting

ANTIBIOTIC RESISTANCE:

The United States Is Fighting Back

U.S. government agencies are tackling the complex threat of antibiotic resistance. The comprehensive and coordinated response implements the *U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria*. The response includes cooperation with the U.S. Department of Health and Human Services, Department of Veterans Affairs, Department of Defense, Department of State, and Department of Agriculture.

Tracking and Data

Using **data to detect and track** resistance through, for example, national lab networks

Providing **tools for healthcare** facilities to track and report resistance threats and antibiotic use

Leveraging **new technologies** (e.g., whole genome sequencing) to better understand resistance

Infection Prevention and Containment

Using **national alert systems** to rapidly identify resistance

Providing resources and expertise in outbreak response, infection prevention and control, and lab detection to implement recommendations

Advancing research to improve current healthcare practices and identify new interventions

Improving Antibiotic Use

Working with partners to improve antibiotic use across populations (e.g., outpatient antibiotic prescribing to children has decreased 16% from 2011 to 2017)

Providing evidence and tools for facilities to **implement antibiotic stewardship practices and programs** (e.g., more than 80% of hospitals report having a stewardship program meeting CDC's Core Elements)

Collaborating with food partners to ensure optimal veterinarian antibiotic use to treat, control, or prevent infections (e.g., food animal antibiotic sales and distribution has decreased 33% from 2016 through 2017)

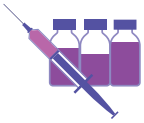
Environment (e.g., water and soil) and Sanitation

Collaborating to **identify gaps in knowledge** related to resistance, the environment, and human and animal health

Piloting **data-driven solutions** to guide long-term public health interventions

Promoting better **sanitation and access to safe water globally** to help prevent infections and reduce need for antibiotics

Vaccines, Diagnostics, and Therapeutics



Investing millions of dollars in **drug, diagnostic, and vaccine development**

Supporting basic research to identify promising new treatments and improve understanding of resistance

Identifying **innovative ways to prevent infections** using novel therapeutics

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VANCOMYCIN-RESISTANT
ENTEROCOCCI
(VRE)

CDC Leads Fight Against Antibiotic Resistance

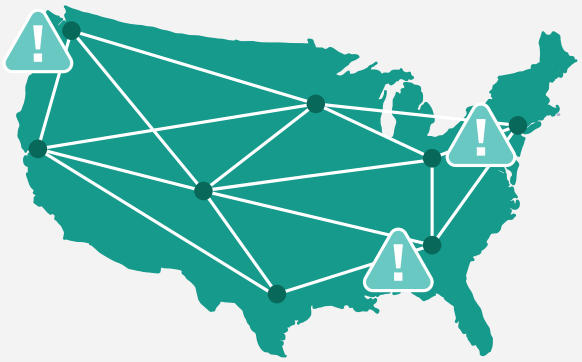
CDC leads the U.S. public health response to combat antibiotic resistance. CDC's Antibiotic Resistance Solutions Initiative has heavily invested in domestic capacity to detect, respond, contain, and prevent the spread of resistance across health care, food, environment, and communities. This includes sounding the alarm, and providing the data for action, technical expertise, and support for a domestic infrastructure to respond to antibiotic resistance. To accomplish this work, CDC successfully collaborates with partners across health care, industry, academia, and government.

However, antibiotic resistance continues to emerge and spread. The drug, diagnostic, and vaccine discovery pipeline are also complex and increasingly fragile. The world needs heightened vigilance and public health engagement to contain resistance threats whenever and wherever they emerge. Swift public health action is fundamental to save lives.

CDC Actions to Combat Antibiotic Resistance (AR)*

The United States is positioned for a better and faster response to antibiotic resistance because of the strategic leadership and investment of CDC's AR Solutions Initiative.

Every 4 hours, CDC's AR Lab Network detected a resistant germ that required a public health investigation *(as of 2018)*



106,000+

bacteria tested by the AR Lab Network, and 2,238 alerts sent about unusual resistance requiring a containment response

NEARLY 13,000

swabs tested to detect resistant germs in healthcare—many launched a containment response

WHOLE GENOME SEQUENCING

15,300

tuberculosis, *C. difficile*, and gonorrhea germ samples

101,511

foodborne germ samples since 2016 (e.g., *Salmonella* via Pulsenet)

CDC invested $300M+ in 59 state & local health departments to detect and prevent resistant threats

500+ local AR experts

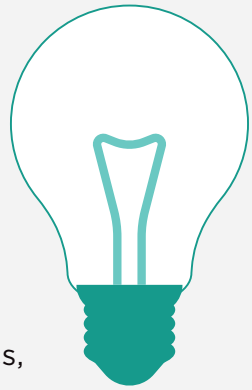
8 SURRG sites to enhance response to drug-resistant gonorrhea outbreaks

SURRG: Strengthening the United States Response to Resistant Gonorrhea

CDC Supports Innovations

158

public health research projects to better understand and combat AR



NEARLY $110M

to 96 institutions for innovations, therapeutics, and diagnostics

125,000+ GERM SAMPLES

sent by CDC & FDA AR Isolate Bank to diagnostic test makers, academic researchers, and drug companies

*As of Fiscal Years 2016-2019

CDC Actions to Combat Antibiotic Resistance (AR)*

The United States is positioned for a better and faster response to antibiotic resistance because of the strategic leadership and investment of CDC's AR Solutions Initiative.

28

countries fighting antibiotic resistance together with CDC

26

infection control experts from CDC give technical assistance and support globally

300+

partners engaged globally through the Antimicrobial Resistance Challenge

84% of U.S. hospitals report having a stewardship program meeting all seven of CDC's *Core Elements of Hospital Antibiotic Stewardship*

Antibiotic prescribing in outpatient settings declined (2011–2016) **↓5%**

Outpatient prescribing to children also declined (2011-2017) **↓16%**

188M+

impressions from *Be Antibiotics Aware* PSAs

15,900+

learners registered for CDC's free training course on improving antibiotic use

3,461

completed regimens using drugs from the Tuberculosis Emergency Stockpile

*As of Fiscal Years 2016-2019

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CDC Leads the Public Health Fight Against Antibiotic Resistance (AR)

2013

CDC releases *Antibiotic Resistance Threats in the United States, 2013*

2014

CDC publishes *Core Elements of Hospital Antibiotic Stewardship Programs*, other settings followed

White House Executive Order 13676 establishes *National Strategy for CARB*[1] and Presidential Advisory Council

2015

U.S. government releases *National Action Plan for CARB*

CONGRESS APPROPRIATES

$160 MILLION

for AR Solutions Initiative*

(CDC's initial request was $264M)

CDC launches CDC & FDA AR Isolate Bank

ARLABnetwork

2016

CDC establishes AR Lab Network and funds local AR experts in every state, some major cities, and Puerto Rico

CDC awards first innovation funding ($40M) to academic, industry, and healthcare investigators, including CDC's Prevention Epicenters Program

CDC launches the Antibiotic Use and Antibiotic Resistance tracking modules through the National Healthcare Safety Network

United Nations (UN) General Assembly holds high-level meeting on AR

2017

CDC begins supporting innovation to combat AR globally

*as part of funding across the U.S. government to implement CARB

1 Combating Antibiotic-Resistant Bacteria

CDC Leads the Public Health Fight Against Antibiotic Resistance (AR)

2017

CDC adds National Tuberculosis Molecular Surveillance Center to AR Lab Network

FDA[2] releases Veterinary Feed Directive to help ensure antibiotics only used to treat and prevent infections in food animals

2018

CDC co-hosts forum to publish report, *Initiatives for Addressing Antimicrobial Resistance in the Environment*

CDC RELEASES

CONTAINMENT STRATEGY

to stop the spread of new or emerging resistance

CDC co-hosts AMR[3] Challenge, a global one-year initiative to drive meaningful action worldwide

2019

PulseNet laboratories transition to whole genome sequencing for foodborne germs, enabling routine surveillance to predict resistance

CDC and HHS[4] conclude AMR Challenge Year with

300+ PARTNER COMMITMENTS WORLDWIDE

UN Interagency Coordination Group on AR calls for urgent action

CDC publishes second *Antibiotic Resistance Threats in the United States, 2019*

[2] Food and Drug Administration
[3] Antimicrobial resistance
[4] U.S. Department of Health & Human Services

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DRUG-RESISTANT
BORDETELLA PERTUSSIS

Health Departments:
Critical Partners

State and local health departments are critical partners in the complex and evolving response to antibiotic resistance, working to rapidly detect and respond to antibiotic resistance threats.

To address the uncertainty of when or where new resistance might emerge, the U.S. government is supporting health departments to establish a foundation with the ability and flexibility to detect, respond, and contain the unique variety of resistant threats state and local jurisdictions face.

As new resistance emerges, state and local health departments will need a more robust workforce, increased laboratory expertise, and the infection prevention control capacity that has proven critical to overcome the threats that antibiotic resistance poses to American lives.

Partnering to Combat Resistance

Through CDC's Antibiotic Resistance Solutions Initiative, CDC partners with state and local health departments to build a domestic antibiotic resistance infrastructure that is more advanced than any other in the world.

Health Departments Are Combating Antibiotic Resistance (AR)

State and local health departments fight antibiotic resistance, but more support is needed as new resistance continues to emerge.

Lab Data are Enhancing Local Response

- Rapidly detect AR through CDC's Antibiotic Resistance Laboratory Network
- Inform local responses to prevent spread

Gaps in Lab Capacity can Allow Germs to Spread Undetected

- New types of resistance are constantly emerging and spreading
- Labs need specialized workforce to implement and use new technologies

Prevention & Containment are Stopping Spread

- Support aggressive responses to all unusual resistance
- Work with local partners and healthcare facilities to track and prevent healthcare-associated, foodborne, and community infections caused by antibiotic-resistant germs

More Boots on the Ground Needed to Stop Transmission

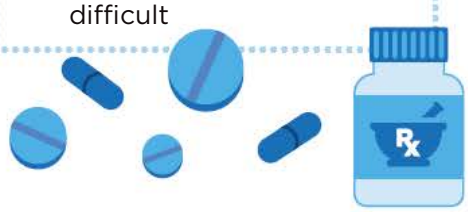
- More infection control responses are needed as new threats emerge in healthcare and the community
- Poor access to the best data tools can hurt efforts to learn about resistant germs and affected people
- Containment responses can be labor intensive and lab-epidemiology coordination is essential to stop the spread of new threats

Improving Antibiotic Use Slows Development of AR

- Use data to improve antibiotic use and keep antibiotics effective for life-threatening infections, including those that can lead to sepsis
- Lead or support improvements to antibiotic use in humans, animals, and the environment

Changing Prescribing Habits & Expectations Require Investment

- Improving antibiotic use across settings (healthcare, farms, the environment) is complex and needs tailored interventions
- Tracking antibiotic use in settings like nursing homes and long-term care facilities often does not exist or is difficult



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More Action Needed: Furthering the Domestic and Global Fight

CDC's 2013 report highlighted significant gaps in knowledge related to antibiotic resistance. As a result of investments made through CARB, the United States has made great strides in addressing these gaps.

As detection and surveillance capabilities increase, awareness of the scope and complexity of antibiotic resistance has also grown. More action is needed across industries, countries, and settings to fully protect people from resistance threats.

In 2018, CDC updated and proposed five core actions to better prepare the United States for the resistance that will continue to emerge worldwide:

- Infection prevention and control
- Tracking and data
- Antibiotic use and access
- Vaccines, therapeutics, and diagnostics
- Environment and sanitation

Addressing the following needs will help the United States and global community combat antibiotic resistance.

Gaps in Knowledge Identified in 2013

- Limited capacity to detect and respond to urgent and emerging threats
- No systematic international surveillance
- Data on antibiotic use in human health and agriculture not systematically collected
- Programs to improve antibiotic use not widely used in the United States
- Advanced technologies can identify threats faster than current practice

Domestic Gaps to Fight Antibiotic Resistance

The United States needs:

- Greater implementation of programs for infection prevention and control and antibiotic stewardship across the One Health spectrum
- State and local access to tools and technology to detect and respond to antibiotic-resistant threats in health care, food, the environment, and the community
- National data on antibiotic use across settings
- Local antibiotic resistance data to help public health departments identify where antibiotic resistance is on the rise and inform outbreak response
- Expanded workforce in health departments to help identify where antibiotic resistance is spreading locally and implement an aggressive local response
- Increased collaboration between public health and health care to prevent the spread of germs and improve antibiotic use

Innovation Gaps to Fight Antibiotic Resistance

The global community, including the United States, needs new solutions that can enhance current practices and protect people and animals:

- New antibiotics, vaccines, and therapeutics to prevent or treat antibiotic-resistant infections
- Reliable diagnostics, including at point of care, to support early detection and improved antibiotic use and enhance healthcare provider and veterinarian decision-making
- Better understanding of the microbiome and how it can be leveraged to prevent and treat infection
- Better strategies for preventing spread in healthcare and community settings
- Better strategies to improve antibiotic stewardship wherever antibiotics are used
- Better understanding of antibiotic resistance in the environment and its impact on human and animal health
- Predictive analytics to help identify actions needed to prevent the spread of resistance across human and animal healthcare facilities, food, the community, and the environment

Global Gaps to Fight Antibiotic Resistance

The global community, including the United States, needs:

- Robust infection prevention and control everywhere health care is provided to stop spread (health care, food, community)
- Broader use of and access to vaccines that can prevent infections and reduce antibiotic use in people and animals
- Improved use of and access to antibiotics worldwide
- Universal access to safe water and sanitation to prevent resistant germs from spreading
- Expanded lab capacity to identify and detect new and emerging antibiotic resistance threats to inform local containment and prevention efforts, and global awareness to stop spread where it is detected

SECTION 4

PATHOGEN SUMMARIES

CARBAPENEM-RESISTANT
ACINETOBACTER

DRUG-RESISTANT
MYCOPLASMA GENITALIUM

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridioides difficile*
- Carbapenem-resistant Enterobacteriaceae
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- ESBL-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci*
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus*
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

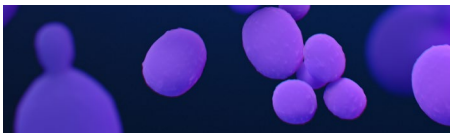
Watch List

- Azole-resistant *Aspergillus fumigatus*
- Drug-resistant *Mycoplasma genitalium*
- Drug-resistant *Bordetella pertussis*

Urgent Threats

These germs are public health threats that require urgent and aggressive action:

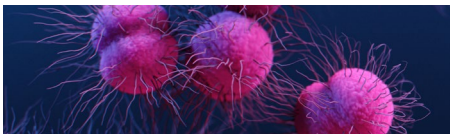
CARBAPENEM-RESISTANT
ACINETOBACTER



CANDIDA AURIS

CLOSTRIDIOIDES DIFFICILE

CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE



DRUG-RESISTANT
NEISSERIA GONORRHOEAE

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CARBAPENEM-RESISTANT *ACINETOBACTER*

THREAT LEVEL **URGENT**

8,500 Estimated cases in hospitalized patients in 2017

700 Estimated deaths in 2017

$281M Estimated attributable healthcare costs in 2017

Acinetobacter **bacteria can survive a long time on surfaces. Nearly all carbapenem-resistant** ***Acinetobacter*** **infections happen in patients who recently received care in a healthcare facility.**

WHAT YOU NEED TO KNOW

- Carbapenem-resistant *Acinetobacter* cause pneumonia and wound, bloodstream, and urinary tract infections. These infections tend to occur in patients in intensive care units.
- Carbapenem-resistant *Acinetobacter* can carry mobile genetic elements that are easily shared between bacteria. Some can make a carbapenemase enzyme, which makes carbapenem antibiotics ineffective and rapidly spreads resistance that destroys these important drugs.
- Some *Acinetobacter* are resistant to nearly all antibiotics and few new drugs are in development.

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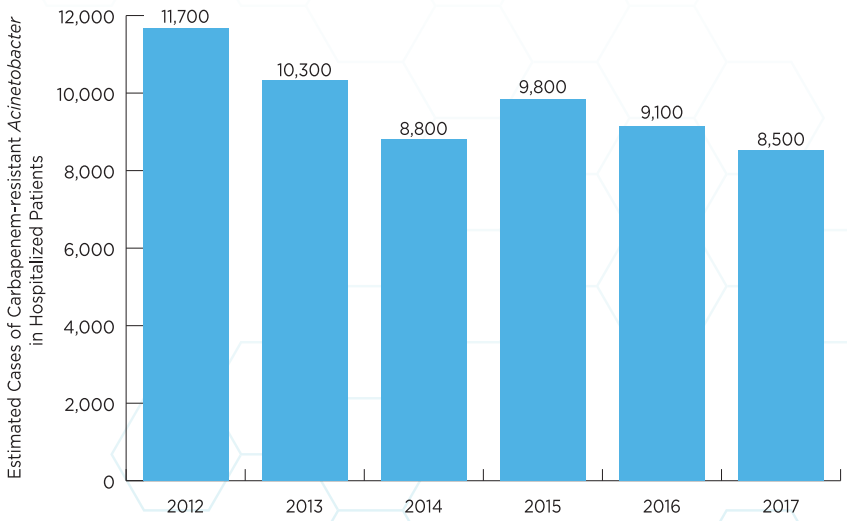
CASES OVER TIME

Continued infection control and appropriate antibiotic use are important to maintain decreases in carbapenem-resistant *Acinetobacter* infections.



A THREAT IN HEALTHCARE

Acinetobacter is a challenging threat to hospitalized patients because it frequently contaminates healthcare facility surfaces and shared medical equipment. If not addressed through infection control measures, including rigorous cleaning and disinfection, outbreaks in hospitals and nursing homes can occur.

Acinetobacter is already resistant to many antibiotics. Resistance to carbapenems further reduces patient treatment options. Overall rates of carbapenem-resistant *Acinetobacter* cases have decreased; however, carbapenem-resistant *Acinetobacter* that can produce carbapenemases, which can spread to other germs and amplify the problem of resistance through mobile resistance elements (e.g., DNA), appear to be increasing.

This increase of carbapenemase production threatens to reverse decreases of carbapenem-resistant *Acinetobacter* cases. Infections caused by carbapenem-resistant *Acinetobacter baumannii* are of particular concern because they are frequently difficult to treat with available antibiotics.

TREATMENT OVER TIME

Treatment options for infections caused by carbapenem-resistant *Acinetobacter baumannii* are extremely limited. There are few new drugs in development.

PERCENT OF GERMS THAT TESTED NON-SUSCEPTIBLE (NOT SENSITIVE) TO OTHER TYPES OF ANTIBIOTICS

Select Antibiotics	2013	2014	2015	2016	2017
Any fluoroquinolone	98%	93%	97%	92%	89%
Any extended-spectrum β-lactam	80%	75%	81%	79%	75%
Ampicillin/sulbactam	62%	62%	59%	64%	61%
Trimethoprim/ sulfamethoxazole	84%	74%	81%	77%	66%

Germs refer to isolates (pure samples of germs) from eight of CDC's Emerging Infections Program sites. See Technical Appendix for antibiotic susceptibilities details.

ONLINE RESOURCES

About *Acinetobacter* in Healthcare Settings
www.cdc.gov/hai/organisms/acinetobacter.html

Surveillance of Gram-negative Healthcare Infections
www.cdc.gov/hai/eip/mugsi.html

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
The full report, including data sources, is available at www.cdc.gov/DrugResistance/Biggest-Threats.html.

CS298822-A

DRUG-RESISTANT *CANDIDA AURIS*

THREAT LEVEL **URGENT**

323 Clinical cases in 2018

90% Isolates resistant to at least **one** antifungal

30% Isolates resistant to at least **two** antifungals

Candida auris (C. auris) **is an emerging multidrug-resistant yeast (a type of fungus). It can cause severe infections and spreads easily between hospitalized patients and nursing home residents.**

WHAT YOU NEED TO KNOW

- *C. auris,* first identified in 2009 in Asia, has quickly become a cause of severe infections around the world.
- *C. auris* is a concerning drug-resistant fungus:
  - Often multidrug-resistant, with some strains (types) resistant to all three available classes of antifungals
  - Can cause outbreaks in healthcare facilities
  - Some common healthcare disinfectants are less effective at eliminating it
  - Can be carried on patients' skin without causing infection, allowing spread to others

Data represents U.S. cases only. Isolates are pure samples of a germ.

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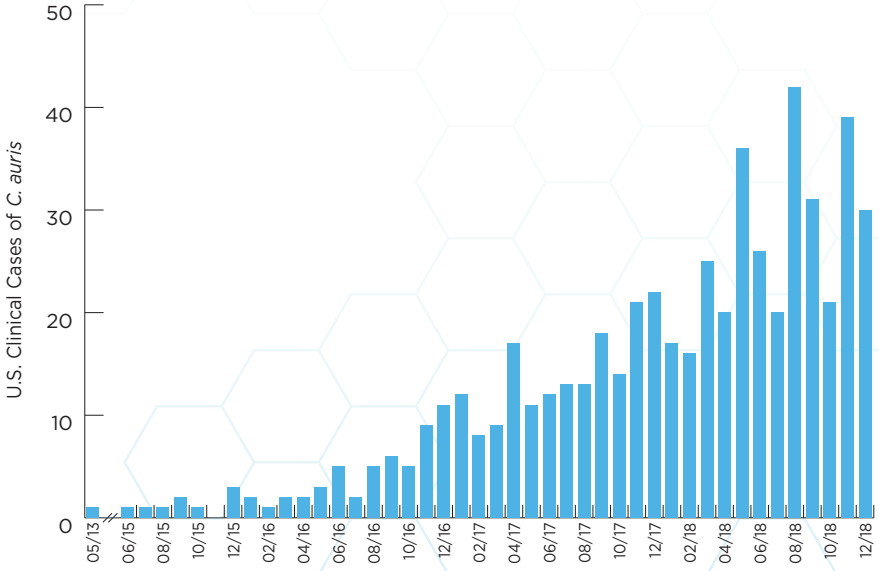
CASES OVER TIME

C. auris began spreading in the United States in 2015. Reported cases increased 318% in 2018 when compared to the average number of cases reported in 2015 to 2017.



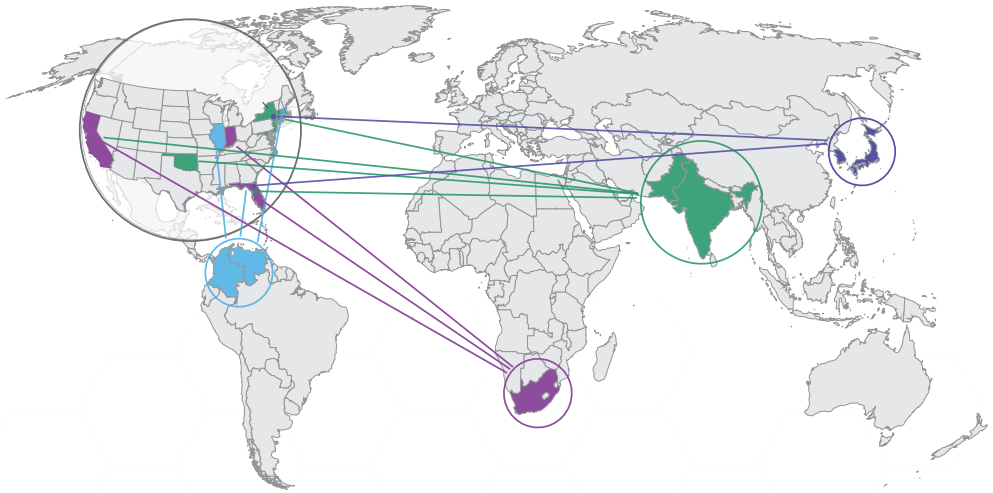
CONTAINING *C. AURIS*

It seemed hard to believe. CDC fungal experts had never received a report describing a *Candida* infection resistant to all antifungal medications, let alone *Candida* that spreads easily between patients. After hearing the news that infections like this were identified by international colleagues in 2016, CDC sounded the alarm in the United States about *C. auris,* a life-threatening *Candida* species.

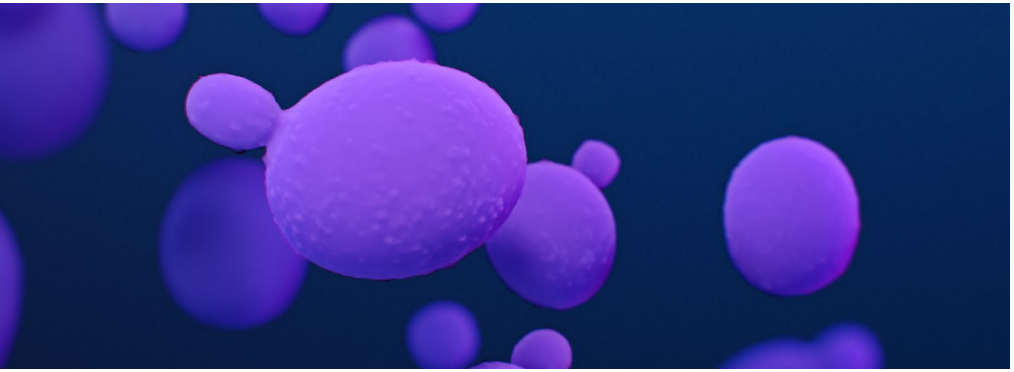
Disease detectives from CDC and state and local health departments soon investigated some of the first U.S. *C. auris* infections. They learned more about how the fungus spreads, and how CDC, health departments, and healthcare facilities can contain it. A key finding was that *C. auris* spreads mostly in long-term healthcare facilities among patients with severe medical problems. CDC and partners developed new tests to rapidly identify it, and continue to work with healthcare facilities to control spread.

A GLOBAL THREAT

Investigators still do not know why four different strains of *C. auris* emerged around the same time across the globe. All four strains have been found in the United States, likely introduced through international travel and subsequent spread in U.S. healthcare facilities.



- South American strain—Florida, Illinois, Massachusetts
- African strain—California, Florida, Indiana
- South Asian strain—California, Connecticut, Florida, Maryland, New York, New Jersey, Oklahoma
- East Asian strain—Florida, New York



ONLINE RESOURCES

About *C. auris*
www.cdc.gov/fungal/Candida-auris/index.html

Information for Laboratorians and Healthcare Professionals
www.cdc.gov/fungal/candida-auris/health-professionals.html

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
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CS298822-A

CLOSTRIDIOIDES DIFFICILE

THREAT LEVEL **URGENT**

223,900 Estimated cases in hospitalized patients in 2017

12,800 Estimated deaths in 2017

$1B Estimated attributable healthcare costs in 2017

Clostridioides difficile (C. difficile) **bacteria can cause life-threatening diarrhea. Infections occur most often in people who have taken antibiotics for other conditions. It is the most common healthcare-associated infection.**

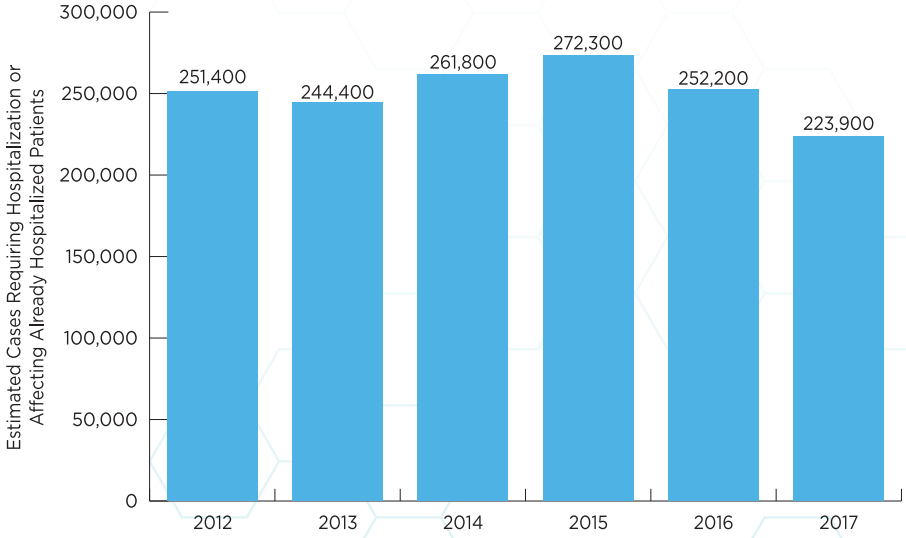
WHAT YOU NEED TO KNOW

- While healthcare-associated *C. difficile* cases are decreasing, community-associated cases are not.
- Strategies to reduce *C. difficile* infections include improving antibiotic use, infection control, and healthcare facility cleaning and disinfection.
- *C. difficile* infections are more common and tend to be more severe in older patients.

Previously *Clostridium difficile.* Also called *C. diff.* Cost includes hospital-onset cases only.

CASES OVER TIME

Continued appropriate infection control, antibiotic use, and diagnostic testing are important to maintain decreases in *C. difficile* cases.



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Centers for Disease Control and Prevention

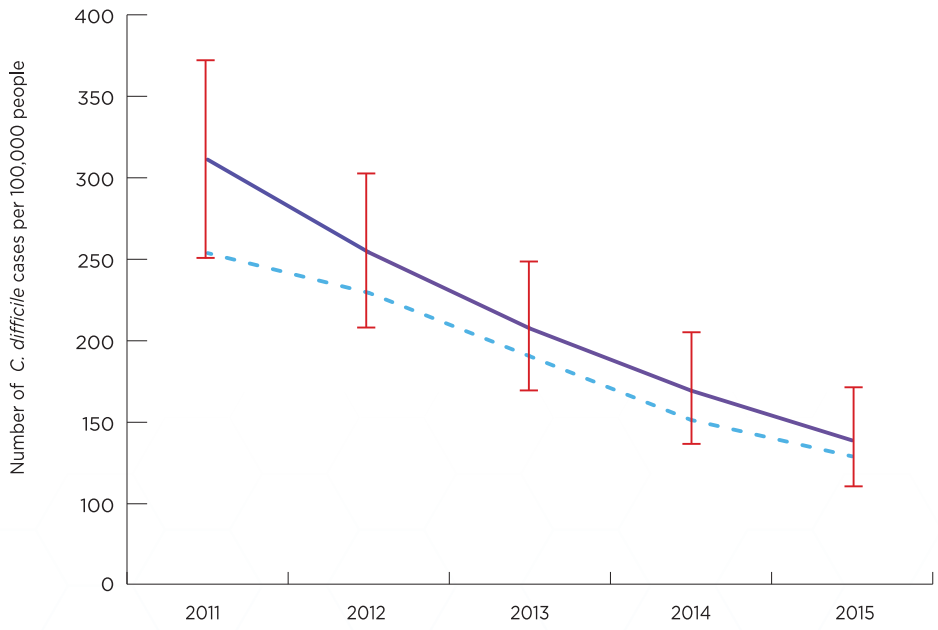
WHERE INFECTIONS HAPPEN

C. difficile infection affects thousands of people every year. It is rarely resistant to antibiotics; however, *C. difficile* usually occurs in people who have taken antibiotics. Improving antibiotic use is an important strategy to reduce these infections. Antibiotics disrupt (unbalance) our microbiome (a community of germs). A common strain of *C. difficile* (ribotype 027) that can cause more serious disease can be associated with use of certain antibiotics, such as fluoroquinolones.

More than half of *C. difficile* cases among long-term care facility residents happen in those who were recently hospitalized. However, from 2011 to 2015, sites within CDC's Emerging Infections Program saw a decrease in *C. difficile* cases in people 65 years or older in long-term care facilities. During this same time, there were declines in hospital fluoroquinolone antibiotic use and *C. difficile* ribotype 027 among people 65 years or older. Improving antibiotic use may have contributed to the decrease in *C. difficile* cases.

C. DIFFICILE CASES

Improving antibiotic use may have contributed to the decrease in long-term care facility-onset *C. difficile* cases in 10 U.S. sites.



Adjusted cases for sex, race, and the percent of cases diagnosed by nucleic acid amplification test.

ONLINE RESOURCES

About *C. difficile* Infections
www.cdc.gov/cdiff/index.html

Tracking *C. difficile* Infections
www.cdc.gov/hai/eip/cdiff-tracking.html

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
The full report, including data sources, is available at www.cdc.gov/DrugResistance/Biggest-Threats.html.

CS298822-A

CARBAPENEM-RESISTANT **ENTEROBACTERIACEAE**

THREAT LEVEL **URGENT**

13,100 Estimated cases in hospitalized patients in 2017

1,100 Estimated deaths in 2017

$130M Estimated attributable healthcare costs in 2017

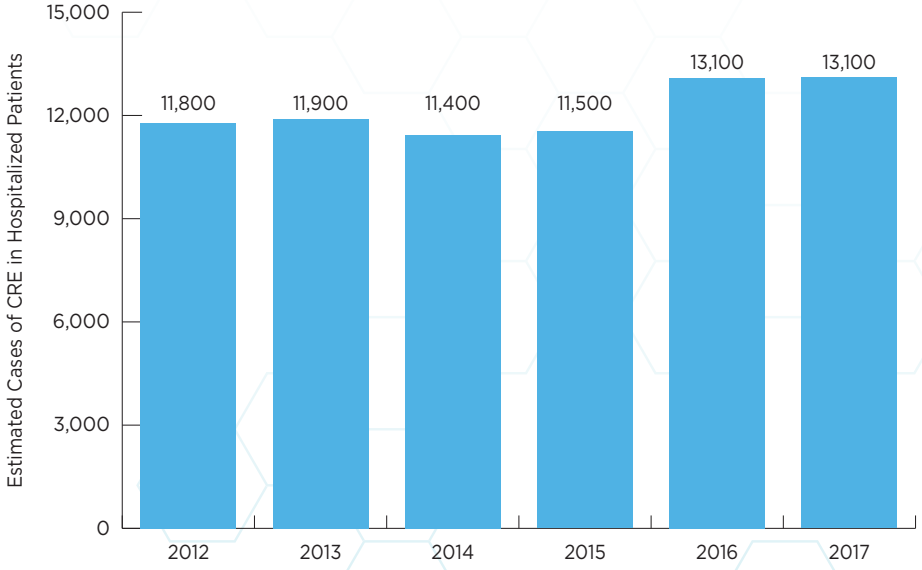
Carbapenem-resistant Enterobacteriaceae (CRE) are a major concern for patients in healthcare facilities. Some bacteria in this family are resistant to nearly all antibiotics, leaving more toxic or less effective treatment options.

WHAT YOU NEED TO KNOW

- Patients who require devices (e.g., catheters) and patients taking long courses of some antibiotics are most at risk for CRE infections.
- CRE can carry mobile genetic elements that are easily shared between bacteria. Approximately 30% of CRE carry a mobile genetic element that can make an enzyme, which makes carbapenem antibiotics ineffective and rapidly spreads resistance that destroys these important drugs.
- Preventing CRE infections and containing the spread of carbapenem resistance is important to protect people.

CASES OVER TIME

Containment strategies have prevented further spread of some types of CRE in the United States, but continued action is needed.



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STOPPING CRE

CDC developed a robust system for detecting and responding to carbapenemase-producing CRE (CP-CRE) in the United States. In 2016, CDC established the Antibiotic Resistance Laboratory Network (AR Lab Network). Through the network, labs in 50 states, many major cities, and Puerto Rico provide clinical laboratories access to advanced detection capacities to identify patients with CP-CRE infections. The AR Lab Network also provides testing to screen people at risk for CP-CRE to help slow or stop its spread.

Patients with CP-CRE may have gone unrecognized before the AR Lab Network. When CP-CRE is identified now, health departments and healthcare facilities can take action to contain its spread, such as having healthcare providers wear gowns and gloves when providing care. This new national public health infrastructure means rapid action is taken to stop spread when even one CP-CRE case is identified.

CDC'S AR LAB NETWORK

To avoid spread seen in the past, CDC funded infrastructure to rapidly detect and respond to future unusual resistance threats. Laboratories nationwide work together to fight antibiotic resistance.

CLINICAL LABS
Collect and submit patient samples for testing at public health department and regional labs

PUBLIC HEALTH DEPARTMENT LABS
Characterize patient samples for species type, carbapenemase production, and resistance profiles

7 REGIONAL LABS AND NATIONAL TB CENTER
Detect antibiotic resistance, track changes in resistance, and identify outbreaks

CDC
Coordinates the network, provides technical expertise, and supports outbreak responses

ONLINE RESOURCES

About CRE in Healthcare Settings
www.cdc.gov/hai/organisms/cre

CDC Vital Signs: Containing Unusual Resistance
www.cdc.gov/vitalsigns/containing-unusual-resistance

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
The full report, including data sources, is available at www.cdc.gov/DrugResistance/Biggest-Threats.html.

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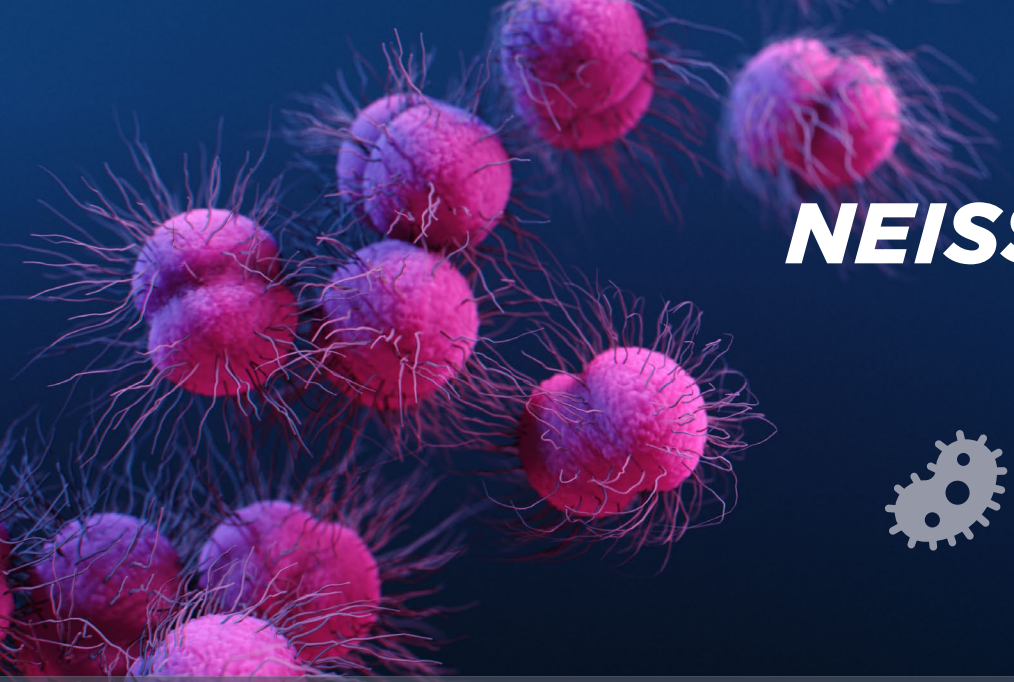


DRUG-RESISTANT *NEISSERIA GONORRHOEAE*

THREAT LEVEL **URGENT**

550,000
Estimated drug-resistant infections each year

1.14M
Total new infections each year

$133.4M
Annual discounted lifetime direct medical costs

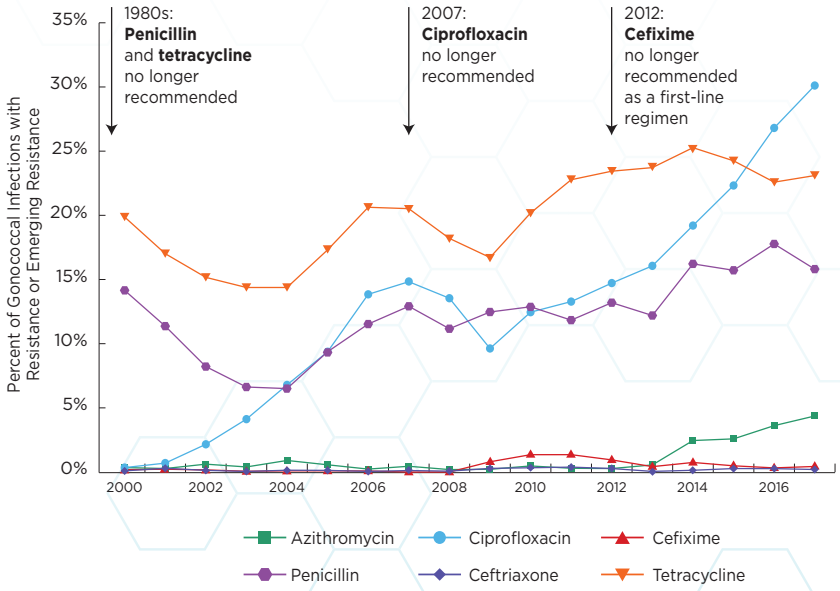
Neisseria gonorrhoeae **causes gonorrhea, a sexually transmitted disease (STD) that can result in life-threatening ectopic pregnancy and infertility, and can increase the risk of getting and giving HIV.**

WHAT YOU NEED TO KNOW

- Gonorrhea has quickly developed resistance to all but one class of antibiotics, and half of all infections are resistant to at least one antibiotic. Tests to detect resistance are not available at time of treatment.
- Gonorrhea spreads easily. Some men and most women do not have symptoms and may not know they are infected, increasing spread.
- Untreated gonorrhea can cause serious and permanent health problems in women and men, including ectopic pregnancy and infertility, and can spread to the blood resulting in cardiovascular and neurological problems.

EMERGING ANTIBIOTIC RESISTANCE

Gonorrhea rapidly develops resistance to antibiotics—ceftriaxone is the last recommended treatment.



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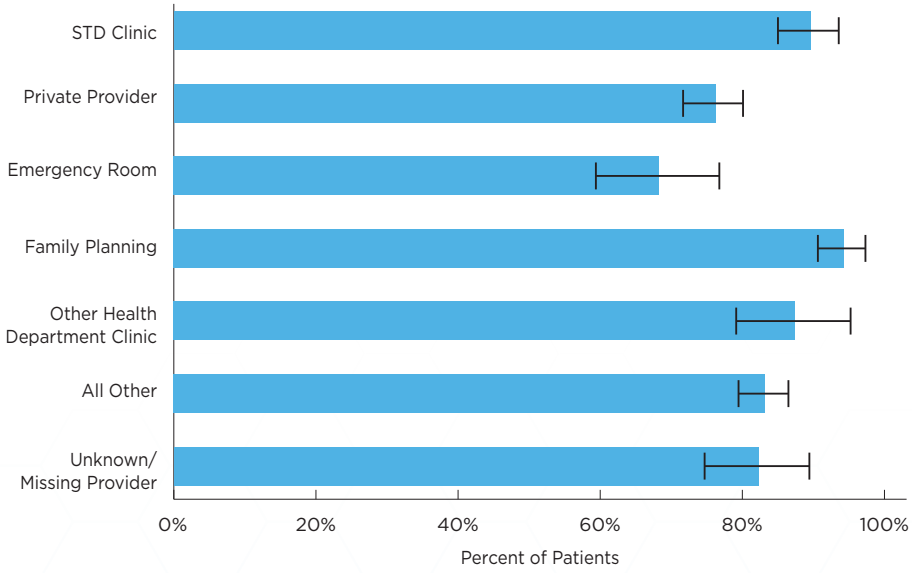
CDC RESPONSE: DRUG-RESISTANT GONORRHEA

Many people who have gonorrhea may not have symptoms, so timely diagnosis through routine screening, with prompt and effective treatment, is needed. CDC develops evidence-based STD Treatment Guidelines, which are the cornerstone of STD prevention and control. It is essential for healthcare providers to follow the guidance to treat their patients with the correct antibiotic, which also slows the threat of emerging antibiotic resistance and helps to reduce gonorrhea in the United States.

A recent CDC analysis found that healthcare providers treated most patients with gonorrhea (82%) in 2017 using CDC's recommended regimen, just two years after CDC published the updated guidelines in 2015. Through the efforts of CDC, partners, and healthcare providers, the uptake of gonorrhea guideline changes by providers was impressively swift. These data highlight the value of robust partnerships to ensure that patients receive the highest quality STD care.

STD TREATMENT ACROSS SETTINGS

Across all U.S. clinical settings, data suggest clinicians treated most patients with CDC's recommended gonorrhea treatment in 2017.



ONLINE RESOURCES

About Gonorrhea
www.cdc.gov/STD/Gonorrhea/Default.htm

Battling Antibiotic-resistant Gonorrhea: A Timeline of Coordinated Teamwork
www.cdc.gov/STD/Products/Success/Hawaii-Success-Stories.pdf

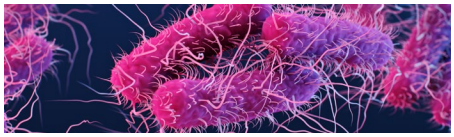
This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
The full report, including data sources, is available at www.cdc.gov/DrugResistance/Biggest-Threats.html.

Serious Threats

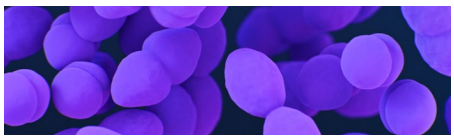
These germs are public health threats that require prompt and sustained action:

DRUG-RESISTANT
CAMPYLOBACTER

DRUG-RESISTANT
CANDIDA



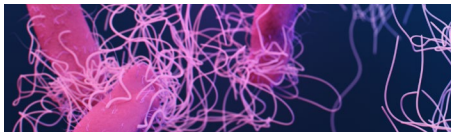
ESBL-PRODUCING
ENTEROBACTERIACEAE



VANCOMYCIN-RESISTANT
ENTEROCOCCI

MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA

DRUG-RESISTANT
NONTYPHOIDAL *SALMONELLA*



DRUG-RESISTANT
***SALMONELLA* SEROTYPE TYPHI**

DRUG-RESISTANT
SHIGELLA

METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS

DRUG-RESISTANT
STREPTOCOCCUS PNEUMONIAE

DRUG-RESISTANT
TUBERCULOSIS

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DRUG-RESISTANT *CAMPYLOBACTER*

THREAT LEVEL **SERIOUS**

448,400 Estimated infections each year

70 Estimated deaths each year

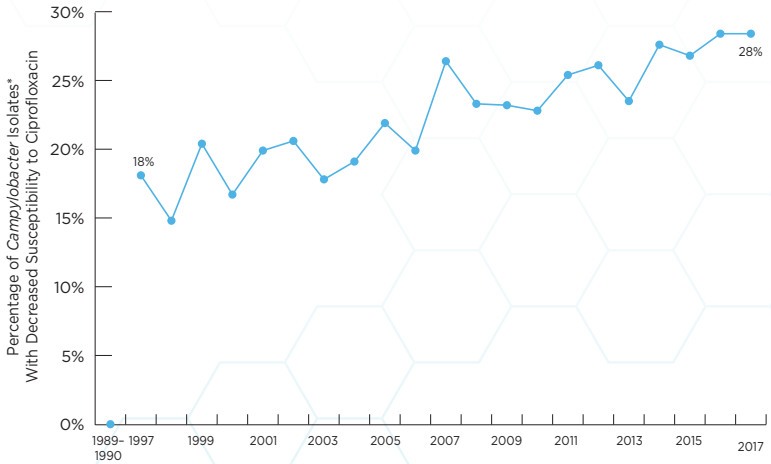
Campylobacter **are bacteria that usually cause diarrhea (often bloody), fever, abdominal cramps, and sometimes complications such as irritable bowel syndrome, temporary paralysis, and arthritis.**

WHAT YOU NEED TO KNOW

- *Campylobacter* causes an estimated 1.5 million infections and $270 million in direct medical costs every year. Of those infections, 29% have decreased susceptibility to fluoroquinolones (e.g., ciprofloxacin) or macrolides (e.g., azithromycin), the antibiotics used to treat severe *Campylobacter* infections.
- *Campylobacter* spreads to people through raw or undercooked chicken, unpasteurized milk, contaminated food and water, and through direct contact with animals.
- *Campylobacter* infections with decreased susceptibility are more common in low- and middle-income countries, putting travelers at risk for infections that may be harder to treat.

RESISTANCE OVER TIME

The percentage of *Campylobacter* with decreased susceptibility to ciprofloxacin has almost doubled in 20 years, limiting treatment options for patients.



*Isolates are pure samples of a germ

Annual national testing began in 1997. Data for 1989–1990 from a sentinel county survey.

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PUPPIES MADE PEOPLE SICK

How could an adorable puppy cause her owner to have a month-long hospital stay, including multiple stays in the intensive care unit? That is what happened to Mike, a 67-year-old retired professor with an existing chronic disease. Within a week of bringing home puppy Mabel from a pet store, Mike experienced diarrhea, fatigue, and lower back pain. The pain became excruciating and he was hospitalized with failing kidneys.

Mike was one of 113 people across 17 states identified as part of an outbreak of multidrug-resistant *Campylobacter* infections linked to pet store puppies. Only one type of antibiotic was able to treat his resistant infection. Due to complications from this infection and his chronic disease, he needed surgery to remove a dead section of stomach. Three months later, Mike finally felt well enough to return to post-retirement work at a bookstore. He still enjoys his pup, but is careful to wash his hands when cleaning up after her.

RESISTANCE SNAPSHOT

As decreased susceptibility in *Campylobacter* increases, the antibiotic options for those who need treatment could disappear.

	PERCENTAGE OF *CAMPYLOBACTER**	ESTIMATED NUMBER OF INFECTIONS PER YEAR	ESTIMATED INFECTIONS PER 100,000 U.S. POPULATION
DECREASED SUSCEPTIBILITY TO CIPROFLOXACIN	28%	429,600	130
DECREASED SUSCEPTIBILITY TO AZITHROMYCIN	4%	55,600	20
DECREASED SUSCEPTIBILITY TO CIPROFLOXACIN **OR** AZITHROMYCIN	29%	448,400	140
DECREASED SUSCEPTIBILITY TO CIPROFLOXACIN **AND** AZITHROMYCIN	2%	36,800	10

Antibiotic susceptibility helps describe how sensitive germs are to particular antibiotics. An antibiotic can stop the growth of or kill a susceptible germ.

*Average (2015–2017), includes *Campylobacter jejuni* and *Campylobacter coli.*

ONLINE RESOURCES

About *Campylobacter*
www.cdc.gov/campylobacter

NARMSNow: Human Data, *Campylobacter* Resistance
wwwn.cdc.gov/NARMSNow

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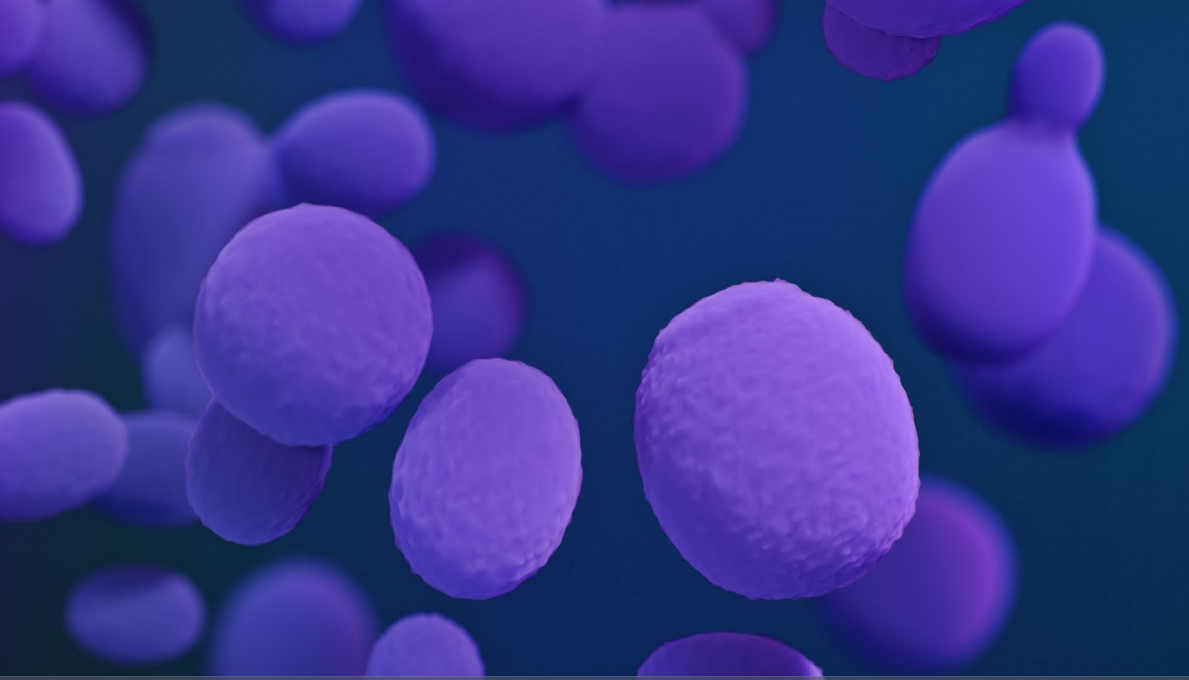


DRUG-RESISTANT *CANDIDA* SPECIES

THREAT LEVEL **SERIOUS**

34,800 Estimated cases in hospitalized patients in 2017

1,700 Estimated deaths in 2017

Dozens of *Candida* species—a group of fungi—cause infections, ranging from mild oral and vaginal yeast infections to severe invasive infections. Many are resistant to the antifungals used to treat them.

WHAT YOU NEED TO KNOW

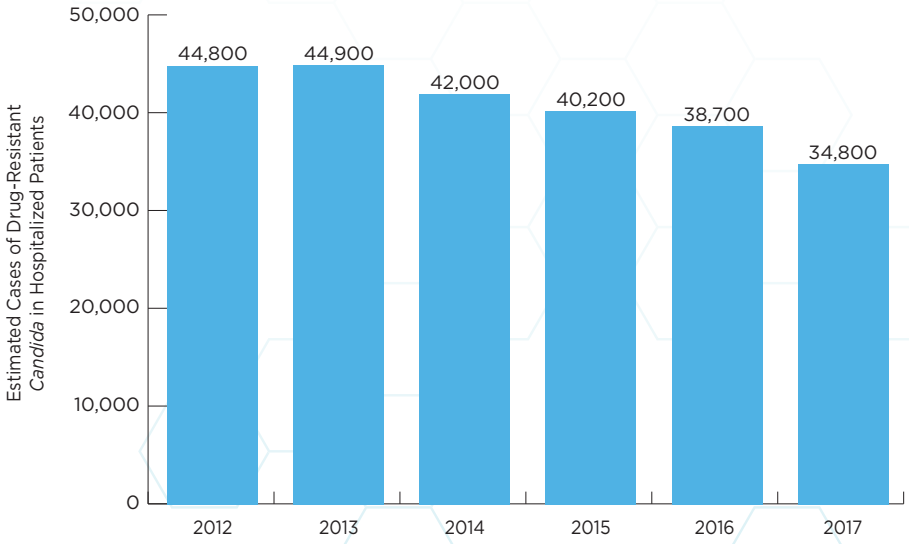
- Only three classes of antifungal drugs are available to treat severe *Candida* infections: azoles, echinocandins, and amphotericin B.
- *Candida* species commonly cause bloodstream infections in hospitalized patients. About one in four of these patients die.
- *Candida* species also cause common yeast infections, which can affect the mouth, skin, and vagina, resulting in more than 3.6 million U.S. healthcare visits each year, and $3 billion estimated direct medical costs.
- Antibiotics used to treat bacterial infections increase the risk of *Candida* infections.

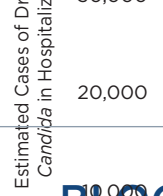
All data represented excludes *C. auris.*

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CASES OVER TIME

Resistant *Candida* are commonly detected in hospitalized patients. About 7% of bloodstream infections are resistant to antifungals.





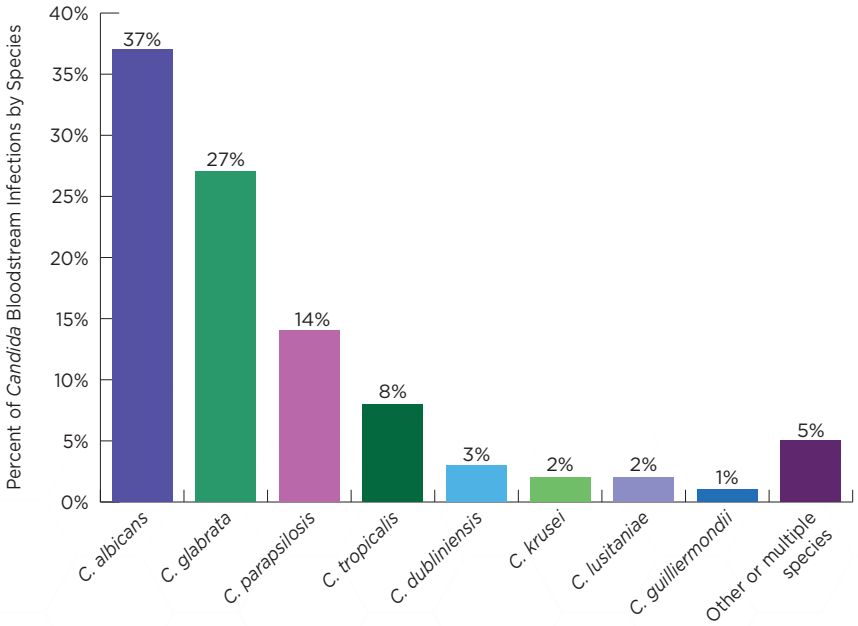
DIFFICULT TO DETECT THREAT

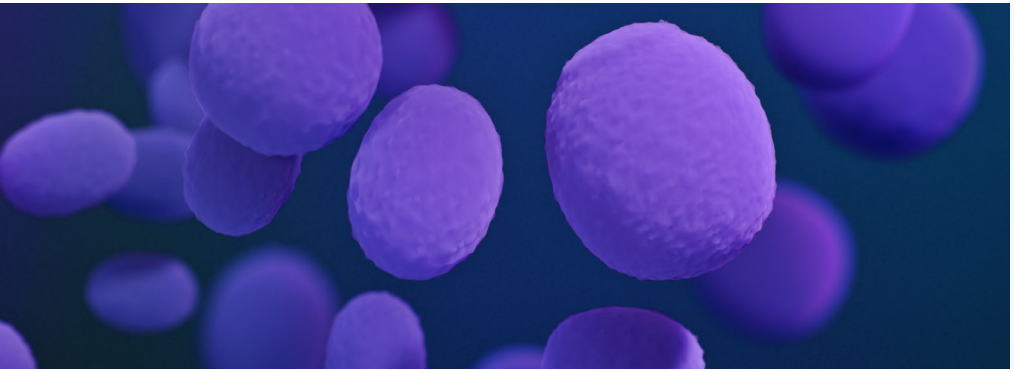
Candida species are well known for causing infections in our mouth, skin, and vagina, but these germs are also a common cause of life-threatening bloodstream infections in hospitals. Most *Candida* infections in people are caused by *Candida albicans,* which has very low levels of drug resistance. However, other types of *Candida,* including *Candida glabrata,* are frequently resistant and more deadly.

Many clinical laboratories do not have the capacity to test *Candida* for drug resistance, limiting the ability to guide treatment and track resistance. Additionally, new, highly resistant species, such as *Candida auris,* are emerging and can also be difficult to identify. CDC's Antibiotic Resistance Laboratory Network helps clinical labs across the United States identify emerging *Candida* species and test for antifungal resistance. This helps lab professionals and healthcare providers rapidly and correctly identify the threat and stop its spread.

BLOODSTREAM INFECTIONS

Candida species are a common cause of bloodstream infections and can be drug-resistant and difficult to treat.

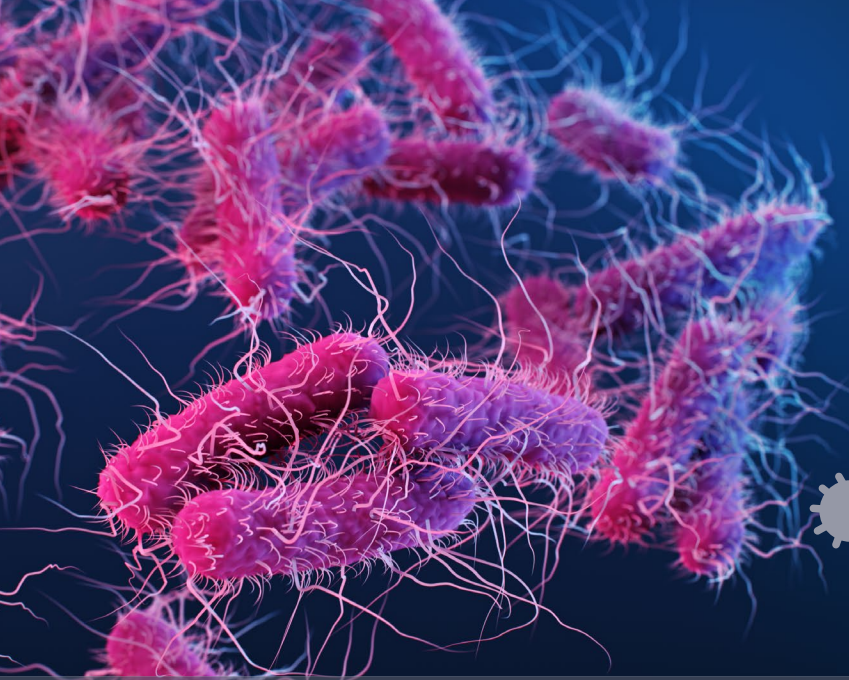




ONLINE RESOURCES

About *Candida* infections
www.cdc.gov/fungal/diseases/candidiasis/index.html

About antifungal resistance
www.cdc.gov/fungal/antifungal-resistance.html



EXTENDED-SPECTRUM BETA-LACTAMASE (ESBL) PRODUCING ENTEROBACTERIACEAE

THREAT LEVEL **SERIOUS**

197,400
Estimated cases in hospitalized patients in 2017

9,100
Estimated deaths in 2017

$1.2B
Estimated attributable healthcare costs in 2017

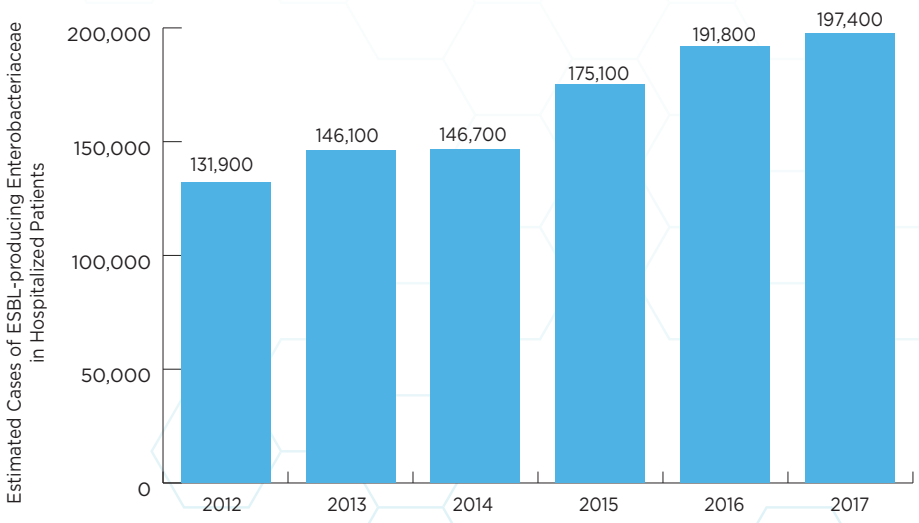
ESBL-producing Enterobacteriaceae (a family of different types of bacteria) are a concern in healthcare settings and the community. They can spread rapidly and cause or complicate infections in healthy people.

WHAT YOU NEED TO KNOW

- ESBLs are enzymes that break down commonly used antibiotics, such as penicillins and cephalosporins, making them ineffective.
- ESBL-producing Enterobacteriaceae often cause infections in otherwise healthy people. About one-quarter of patients with these infections had no known underlying health conditions.
- Antibiotic options to treat ESBL-producing Enterobacteriaceae infections are limited. Healthcare providers often have to use intravenous (IV) carbapenem antibiotics to treat infections that used to be treated with oral antibiotics.

CASES OVER TIME

CDC and partners are working to assess and address why cases of ESBL-producing Enterobacteriaceae have increased since 2012.



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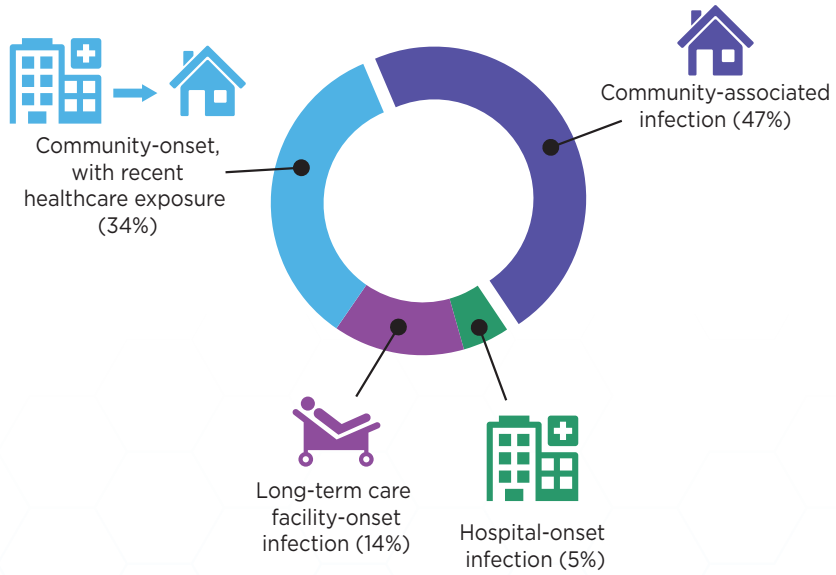
RESISTANCE SPREADS QUICKLY

The Enterobacteriaceae family includes *Escherichia coli (E. coli).* Certain strains (types) of *E. coli,* such as ST131, have quickly spread in the community and among healthcare settings. These strains often cause more severe infections and spread more easily. Additionally, a particular ESBL enzyme, called CTX-M, appears to be spreading in the United States and around the world. The CTX-M enzyme can be shared through DNA (genes) between different Enterobacteriaceae species. When CTX-M and ST131 combine, they are a dangerous combination that can rapidly spread resistance.

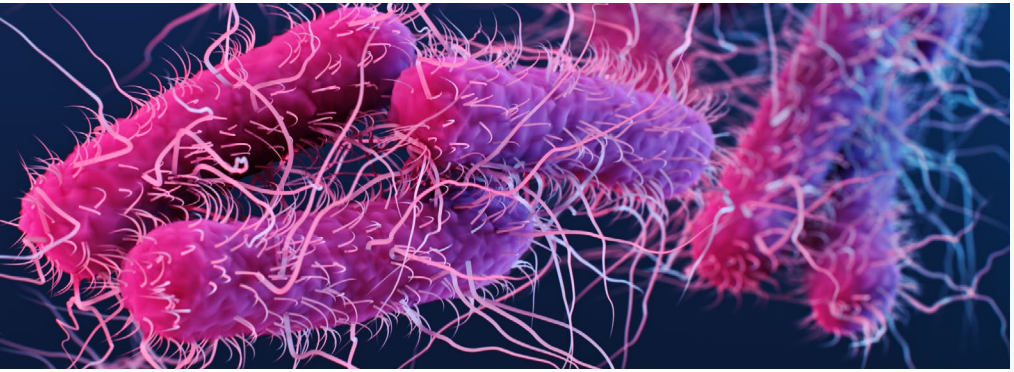
In many cases, even common infections caused by ESBL-producing germs require more complex treatments. Instead of taking oral antibiotics at home, patients with these infections might require hospitalization and IV carbapenem antibiotics. The more we rely on carbapenem antibiotics, the greater the possibility of resistance developing to this important class of antibiotics.

WHERE INFECTIONS CAN HAPPEN

Almost half of ESBL-producing Enterobacteriaceae infections occur in people who have not had recent inpatient healthcare exposure or an invasive medical procedure. These infections are called community-associated infections.



Data shows infections by epidemiological classification (the setting where patients most likely got the infection based on clinical information).



ONLINE RESOURCES

About Healthcare-associated Infections
www.cdc.gov/hai

CDC Healthcare-associated Infections Guidelines and Recommendations
www.cdc.gov/infectioncontrol/guidelines/index.html

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
The full report, including data sources, is available at www.cdc.gov/DrugResistance/Biggest-Threats.html.

VANCOMYCIN-RESISTANT **ENTEROCOCCI** (VRE)

THREAT LEVEL **SERIOUS**

54,500 Estimated cases in hospitalized patients in 2017

5,400 Estimated deaths in 2017

$539M Estimated attributable healthcare costs in 2017

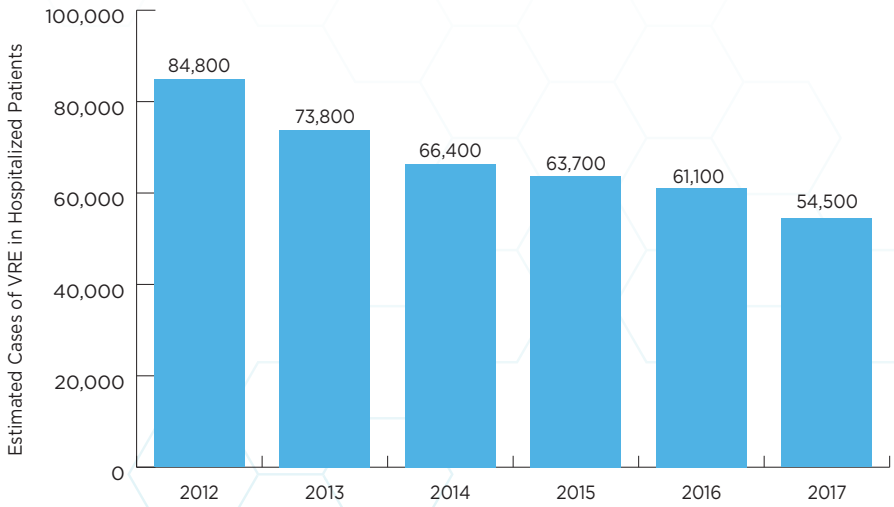
Enterococci, a type of bacteria, can cause serious infections for patients in healthcare settings, including bloodstream, surgical site, and urinary tract infections.

WHAT YOU NEED TO KNOW

- About 30% of all healthcare-associated enterococcal infections are resistant to vancomycin, reducing treatment options.
- Nearly all VRE infections happen in patients with healthcare exposures. Risk factors for VRE infection include stays in long-term care hospitals or intensive care units (ICUs), undergoing organ transplant, or receiving treatment for certain types of cancer.
- VRE is increasingly resistant to additional antibiotics, raising concern that the remaining drugs to treat VRE may become less effective.

CASES OVER TIME

Continued infection control and appropriate antibiotic use are important to maintain decreases in VRE infections.



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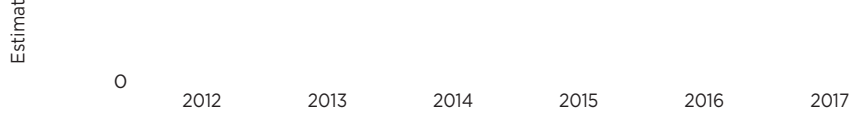


PATIENTS AT RISK

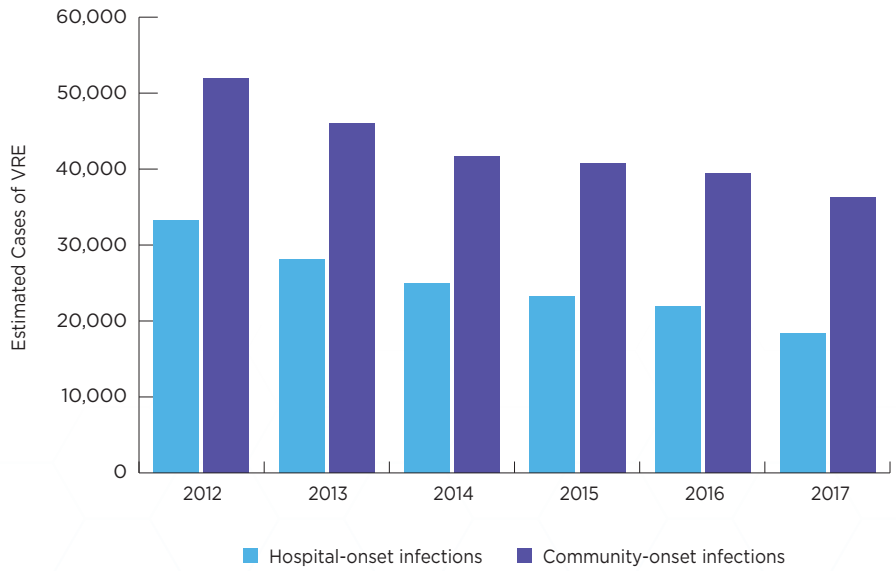
Patients at high risk for VRE infections include those who are undergoing complex or prolonged healthcare (such as patients in long-term acute care hospitals or ICUs) or patients with weakened immune systems (such as patients undergoing cancer treatment or with organ transplants).

In solid organ transplant units, one type of VRE—*Enterococcus faecium (E. faecium)*—is the most common cause of central line-associated bloodstream infections (CLABSIs), according to CDC's National Healthcare Safety Network. More than 70% of these *E. faecium* are resistant to vancomycin, a mainstay for treating these infections. This makes healthcare providers reliant on other antibiotics.

Maintaining and improving infection prevention and control interventions, such as hand hygiene and surface disinfection, is critical to further reduce the number of VRE infections and protect vulnerable patient populations.

COMMUNITY AND HOSPITAL CASES

There were significant decreases in hospital- and community-onset VRE cases—around 30,400 fewer cases in 2017 compared to 2012.



Community-onset infections include infections in patients with recent healthcare exposure and infections in people without prior healthcare exposure.

ONLINE RESOURCES

About VRE in Healthcare Settings
www.cdc.gov/hai/organisms/vre/vre.html

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
The full report, including data sources, is available at www.cdc.gov/DrugResistance/Biggest-Threats.html.

MULTIDRUG-RESISTANT *PSEUDOMONAS AERUGINOSA*

THREAT LEVEL **SERIOUS**

32,600 Estimated cases in hospitalized patients in 2017

2,700 Estimated deaths in 2017

$767M Estimated attributable healthcare costs in 2017

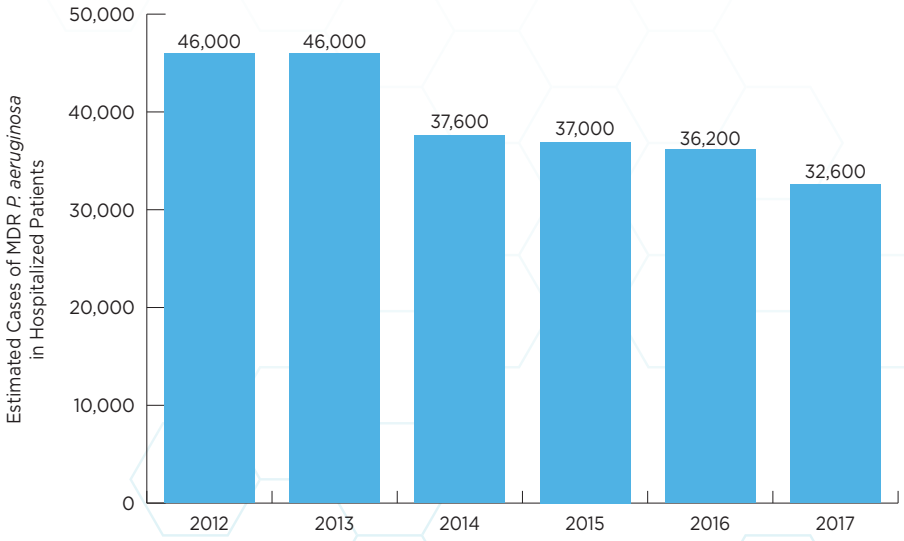
Pseudomonas aeruginosa (P. aeruginosa) **causes many types of healthcare-associated infections, including pneumonia, bloodstream infections, urinary tract infections, and surgical site infections.**

WHAT YOU NEED TO KNOW

- *P. aeruginosa* infections usually occur in people in the hospital or with weakened immune systems. It is particularly dangerous for patients with chronic lung diseases.
- Some types of multidrug-resistant (MDR) *P. aeruginosa* are resistant to nearly all antibiotics, including carbapenems.
- Two to 3% of carbapenem-resistant *P. aeruginosa* carry a mobile genetic element that makes a carbapenemase enzyme. This enzyme makes carbapenem antibiotics ineffective. Mobile genetic elements are easily shared between bacteria, rapidly spreading resistance that destroys these important drugs.

CASES OVER TIME

Continued infection control and appropriate antibiotic use are important to maintain decreases in MDR *P. aeruginosa* infections.



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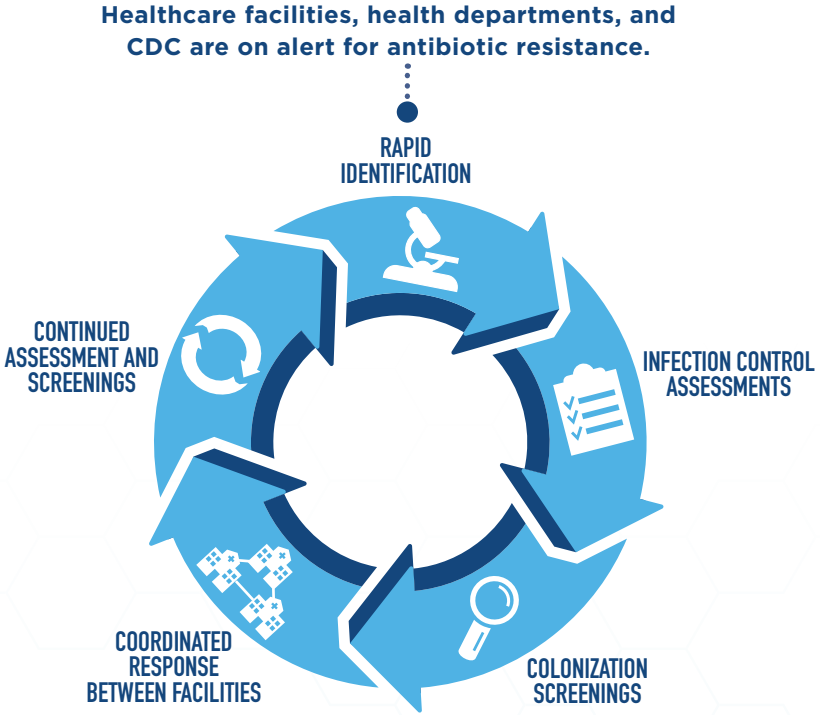
STOPPING SPREAD

In 2018, CDC's Antibiotic Resistance Laboratory Network identified an outbreak of carbapenem-resistant *P. aeruginosa* with an unusual form of resistance. The outbreak included more than 20 people across several states. Health departments reviewed the patients' medical histories, determining that many had undergone surgery at one hospital in Mexico. Most of the patients had surgical site infections and some required prolonged hospitalization in the United States.

CDC and partners took immediate action to implement the Containment Strategy. CDC coordinated a patient notification to U.S. health departments, Canadian and Mexican public health authorities, and the World Health Organization. Hundreds of patients were notified of their risk for possible exposure to carbapenem-resistant *P. aeruginosa,* helping to protect these patients and contain spread.

CDC'S CONTAINMENT STRATEGY

CDC's Containment Strategy helps public health teams launch early, aggressive responses at the first sign of new or unusual resistance.



ONLINE RESOURCES

About *P. aeruginosa* in Healthcare Settings
www.cdc.gov/hai/organisms/pseudomonas.html

Tracking Resistant *P. aeruginosa* in the United States
www.cdc.gov/hai/organisms/pseudomonas/tracking.html

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CS298822-A

DRUG-RESISTANT NONTYPHOIDAL *SALMONELLA*

THREAT LEVEL **SERIOUS**

212,500 Estimated infections each year

70 Estimated deaths each year

Nontyphoidal *Salmonella* can cause diarrhea (sometimes bloody), fever, and abdominal cramps. Some infections spread to blood and can have life-threatening complications.

WHAT YOU NEED TO KNOW

- Nontyphoidal *Salmonella* causes an estimated 1.35 million infections, 26,500 hospitalizations, and 420 deaths each year in the United States, resulting in an estimated $400 million in direct medical costs.
- People can get *Salmonella* from eating contaminated food products or from contact with feces from infected people or animals (including touching animals or their surroundings).
- Antibiotics such as ciprofloxacin, azithromycin, and ceftriaxone are sometimes needed to treat patients with severe *Salmonella* infections. Resistant *Salmonella* infections can be more severe and have higher hospitalization rates.

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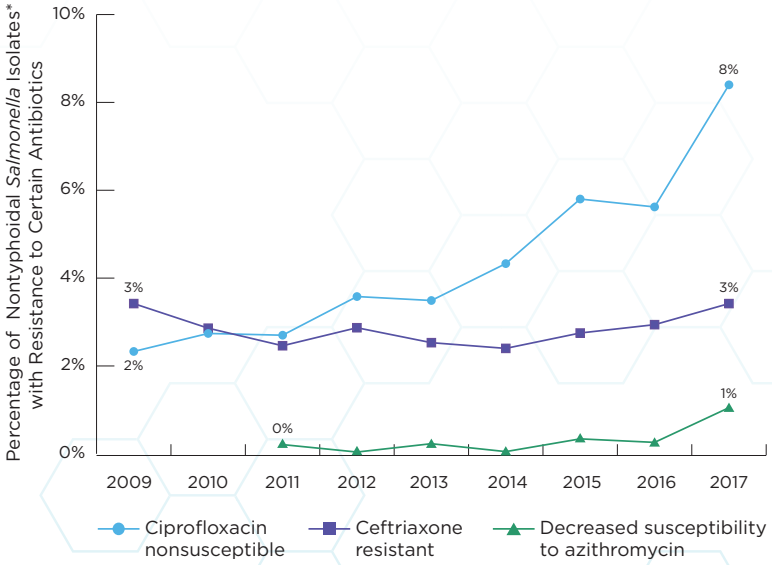
RESISTANCE OVER TIME

Antibiotic-resistant nontyphoidal *Salmonella* infections are on the rise and approaching 10% for ciprofloxacin in 2017.



*Isolates are pure samples of a germ

RESISTANT *SALMONELLA* EMERGES IN THE FOOD CHAIN

Resistance continuously emerges. In 2014, the U.S. Food and Drug Administration (FDA) segment of the National Antimicrobial Resistance Monitoring System (NARMS) collected a chicken breast sample during routine monitoring. The sample was tested using whole genome sequencing—a lab technique that provides genetic information—and identified a multidrug-resistant strain (type) of nontyphoidal *Salmonella* serotype Infantis. This strain included an additional gene that was not common among *Salmonella* from chicken in the United States. However, the CDC segment of NARMS initially identified this strain among ill people returning from travel to South America.

This resistant strain spread rapidly. In 2018, it accounted for 25% of *Salmonella* Infantis infections in people. Most of these infected people had no travel history but had recently eaten chicken. At the same time, the U.S. Department of Agriculture (USDA) segment of NARMS increasingly identified this strain in chicken samples. This strain, along with other types of resistant *Salmonella* linked to foodborne illness from pork, turkey, and beef, leaves healthcare providers with few options to treat patients with severe infections.

RESISTANCE SNAPSHOT

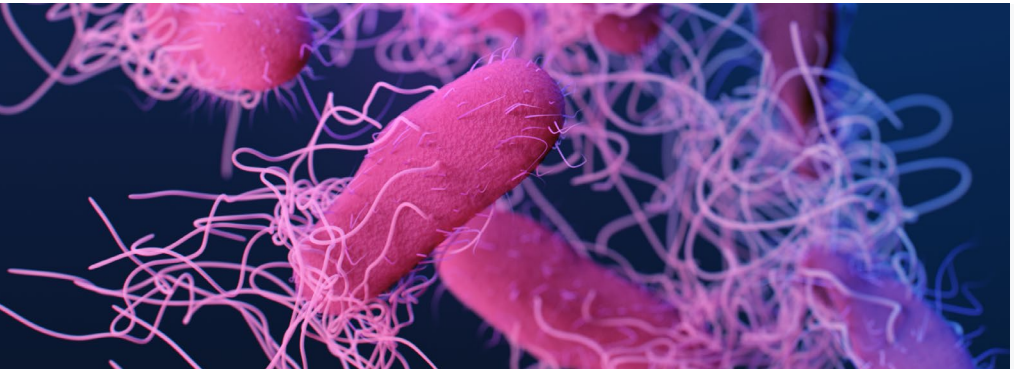
Some nontyphoidal *Salmonella* are becoming less susceptible to essential antibiotics, jeopardizing options to treat severe infections.

	PERCENTAGE OF ALL NONTYPHOIDAL *SALMONELLA**	ESTIMATED NUMBER OF INFECTIONS PER YEAR	ESTIMATED INFECTIONS PER 100,000 U.S. POPULATION
CEFTRIAXONE RESISTANCE	3%	41,000	10
CIPROFLOXACIN NONSUSCEPTIBLE	7%	89,200	30
DECREASED SUSCEPTIBILITY TO AZITHROMYCIN	0.5%	7,400	Less than 5
RESISTANT TO AT LEAST ONE ESSENTIAL ANTIBIOTIC†	16%	212,500	70
RESISTANT TO 3 OR MORE ESSENTIAL ANTIBIOTICS†	2%	20,800	10

Antibiotic susceptibility helps describe how sensitive germs are to particular antibiotics. An antibiotic can stop the growth of or kill a susceptible germ.

*Average (2015–2017)

†Represents the following: ciprofloxacin nonsusceptible, decreased susceptibility to azithromycin, resistance to ceftriaxone, ampicillin, or trimethoprim-sulfamethoxazole.



ONLINE RESOURCES

NARMSNow: Human Data, *Salmonella*
www.cdc.gov/NARMSNow

About *Salmonella*
www.cdc.gov/salmonella

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
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CS298822-A

DRUG-RESISTANT *SALMONELLA* SEROTYPE TYPHI

THREAT LEVEL **SERIOUS**

4,100 Estimated infections each year

Less than 5 Estimated deaths each year

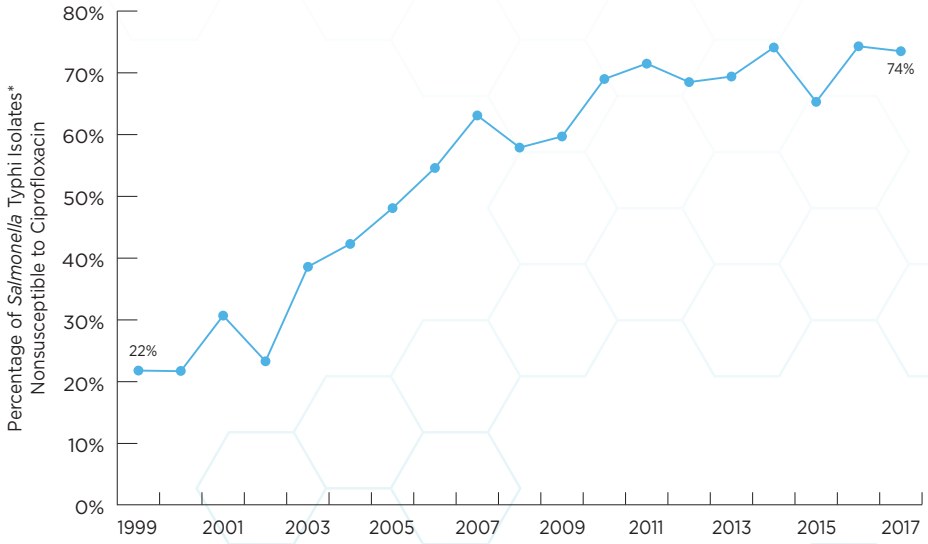
***Salmonella* Typhi bacteria cause typhoid fever, a potentially life-threatening disease. Symptoms include high fever, abdominal pain, and headache. Infection can lead to bowel rupture, shock, and death.**

WHAT YOU NEED TO KNOW

- *Salmonella* Typhi causes an estimated 5,700 infections and 620 hospitalizations each year in the United States. Worldwide, an estimated 11 to 21 million infections occur each year.
- Typhoid fever requires treatment with antibiotics, which is complicated by increasing resistance.
- Most people in the United States become infected while traveling to countries where the disease is common (places with poor sanitation and lack of safe drinking water). Vaccination before travel to countries where the disease is common may prevent typhoid fever.

RESISTANCE OVER TIME

The percent of *Salmonella* Typhi infections nonsusceptible to ciprofloxacin reached 74% in 2017, severely limiting treatment options.



*Isolates are pure samples of a germ

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XDR TYPHOID FEVER IN TRAVELERS

Over the past decade, several strains (types) of *Salmonella* Typhi have become resistant to multiple antibiotics. One recently emerging strain of extensively drug-resistant (XDR) *Salmonella* Typhi is resistant to all but two antibiotic classes recommended for treatment (macrolides and carbapenems). Since 2016, an ongoing outbreak of XDR typhoid fever has sickened more than 5,000 people in Pakistan, and 11 children in the United States who traveled to or from Pakistan.

CDC is working with public health partners across the globe, including Pakistani health authorities, to strengthen prevention efforts, including vaccination. In the United States, healthcare providers, state and local public health officials, and scientists at CDC are closely monitoring emerging resistance among *Salmonella* Typhi strains to identify it quickly and ensure that patients get appropriate antibiotic treatment. Without improved sanitation and access to safe drinking water, this germ and its resistance will continue to pose a risk and spread. U.S. travelers should get vaccinated before going to areas where the disease is common.

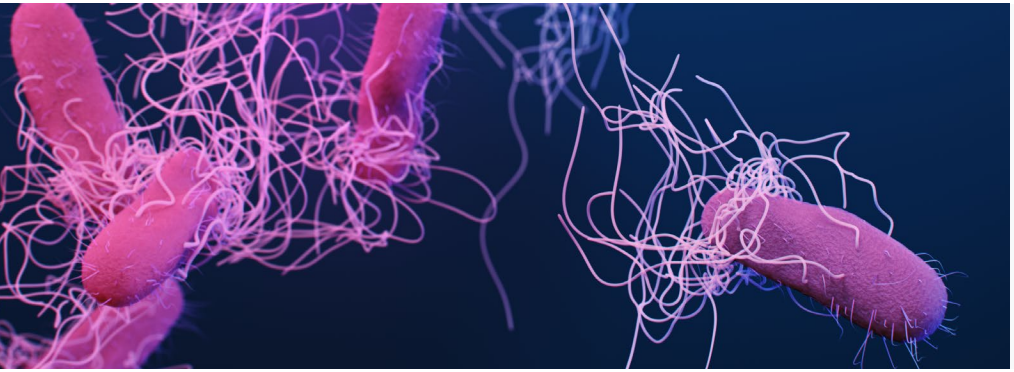
RESISTANCE SNAPSHOT

Salmonella Typhi strains are often nonsusceptible to ciprofloxacin, so antibiotic treatment options are diminishing.

	CIPROFLOXACIN NONSUSCEPTIBLE
PERCENTAGE OF ALL *SALMONELLA* TYPHI*	71%
ESTIMATED NUMBER OF INFECTIONS PER YEAR	4,100
ESTIMATED INFECTIONS PER 100,000 U.S. POPULATION	Less than 5

Antibiotic susceptibility helps describe how sensitive germs are to particular antibiotics. An antibiotic can stop the growth of or kill a susceptible germ.

*Average (2015–2017)



ONLINE RESOURCES

About Typhoid fever
www.cdc.gov/Typhoid-Fever

CDC's MMWR Publication on Emergence of XDR *Salmonella* Typhi Infections Among Travelers
www.cdc.gov/MMWR/Volumes/68/wr/mm6801a3.htm

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
The full report, including data sources, is available at www.cdc.gov/DrugResistance/Biggest-Threats.html.

CS298822-A

DRUG-RESISTANT *SHIGELLA*

THREAT LEVEL **SERIOUS**

77,000 Estimated infections each year

Less than 5 Estimated deaths each year

Shigella **bacteria can cause diarrhea, fever, abdominal pain. These bacteria spread in feces through contact between people, including sexual activity, or through contaminated food, water, or surfaces.**

WHAT YOU NEED TO KNOW

- *Shigella* causes about 450,000 infections each year, and an estimated $93 million in direct medical costs.
- High-risk groups include young children, men who have sex with men, people with weakened immune systems, and travelers to countries with unsafe water and inadequate sanitation.
- Most *Shigella* infections resolve on their own without treatment. Antibiotics such as azithromycin and ciprofloxacin help treat patients with severe infection or weakened immune system, and reduce the spread of germs by decreasing the number of days the patient has diarrhea.

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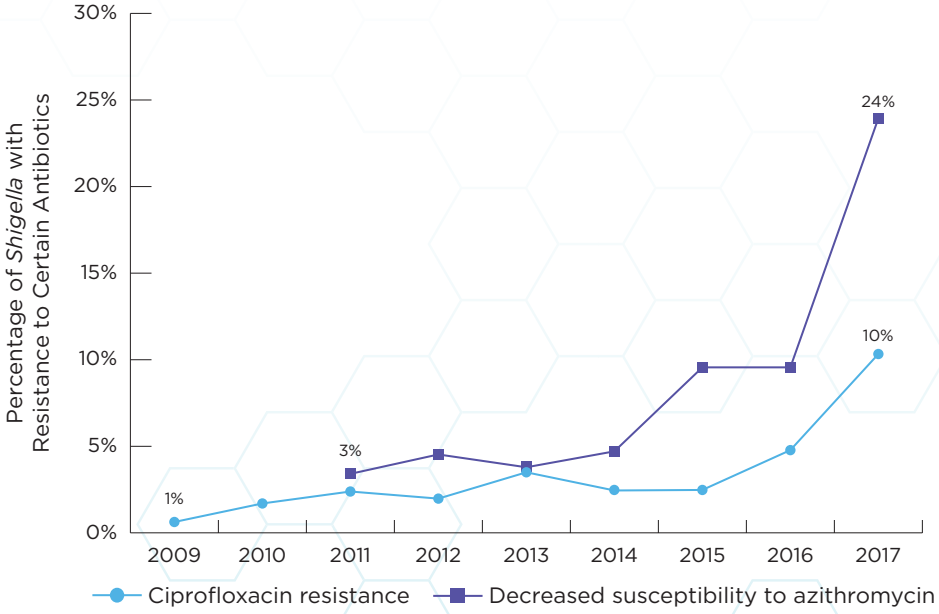
RESISTANCE OVER TIME

Resistant *Shigella* infections have increased notably since 2013.



*Isolates are pure samples of a germ

NEW PREVENTION EFFORTS NEEDED

Shigella infections have become increasingly resistant since 2013. *Shigella* is difficult to control because it spreads easily and rapidly between people, including through sexual activity. Of particular concern are frequently reported outbreaks of multidrug-resistant *Shigella* among men who have sex with men. Most *Shigella* surveillance systems do not routinely collect sexual behavior information.

Routine case investigation and follow-up strategies used for sexually transmitted diseases (STD) could be adapted to strengthen prevention efforts for *Shigella.* Public health experts can work to develop innovative strategies to control and prevent the spread of multidrug-resistant *Shigella* infections by collaborating with STD experts and engaging communities of high-risk groups, including men who have sex with men.

RESISTANCE SNAPSHOT

Among *Shigella,* emerging resistance to important drugs threatens available treatment options.

	PERCENTAGE OF ALL *SHIGELLA**	ESTIMATED NUMBER OF INFECTIONS PER YEAR	ESTIMATED INFECTIONS PER 100,000 U.S. POPULATION
CIPROFLOXACIN RESISTANCE	6%	26,300	10
DECREASED SUSCEPTIBILITY TO CIPROFLOXACIN	17%	74,100	20
DECREASED SUSCEPTIBILITY TO AZITHROMYCIN (DSA)	14%	64,500	20
CIPROFLOXACIN RESISTANCE **OR** DSA	17%	77,000	20
CIPROFLOXACIN RESISTANCE **AND** DSA	3%	13,900	Less than 5

Antibiotic susceptibility helps describe how sensitive germs are to particular antibiotics. An antibiotic can stop the growth of or kill a susceptible germ.

*Average (2015–2017)

ONLINE RESOURCES

NARMSNow: Human Data, *Shigella*
www.cdc.gov/NARMSNow

About *Shigella*
www.cdc.gov/shigella

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
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CS298822-A

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

THREAT LEVEL **SERIOUS**

323,700 Estimated cases in hospitalized patients in 2017

10,600 Estimated deaths in 2017

$1.7B Estimated attributable healthcare costs in 2017

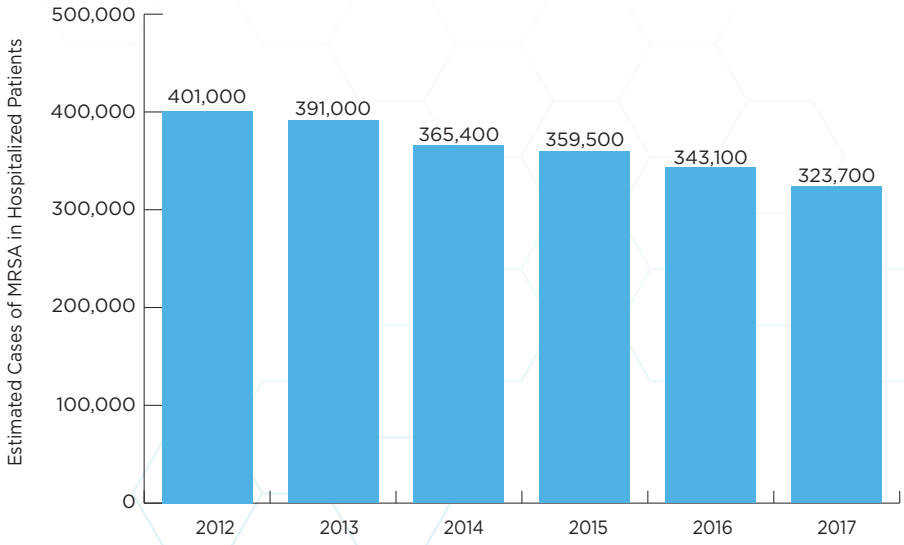
Staphylococcus aureus (S. aureus) **are common bacteria that spread in healthcare facilities and the community. Methicillin-resistant *S. aureus* (MRSA) can cause difficult-to-treat staph infections because of resistance to some antibiotics.**

WHAT YOU NEED TO KNOW

- Although several treatments are still available, MRSA has become resistant to many first-line antibiotics.
- While MRSA infections overall are dropping, progress to prevent MRSA bloodstream infections in healthcare is slowing.
- People who inject drugs are 16 times more likely to develop a serious (invasive) MRSA infection than those who do not.

CASES OVER TIME

Cases represented do not include the many skin infections that happen, but are not cultured and diagnosed.



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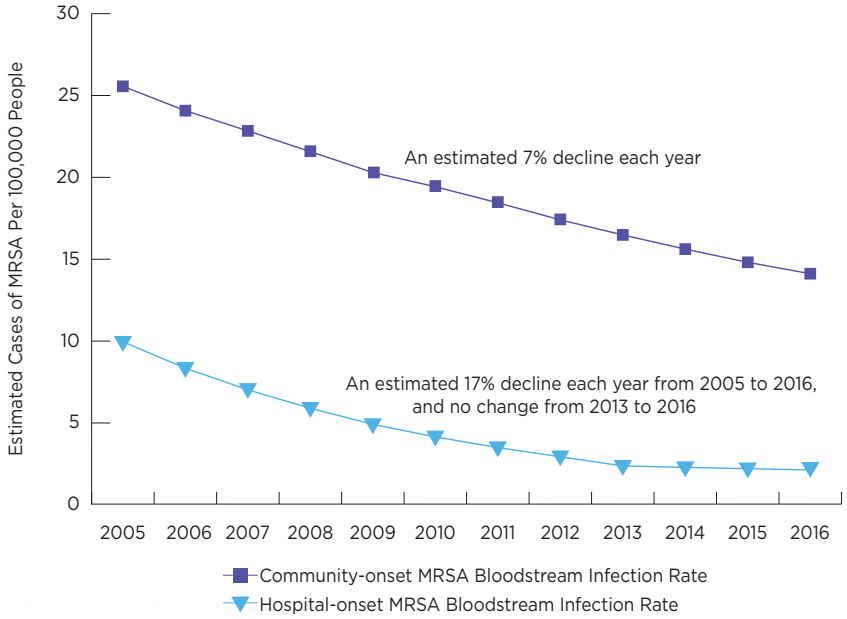
MRSA INFECTIONS CAN BE PREVENTED

MRSA infections are preventable and many lives have been saved through effective infection control interventions. Veterans Affairs (VA) medical centers reduced rates of MRSA by 55% between 2005 and 2017. This success was driven by the implementation of CDC-recommended interventions at 153 VA hospitals across the country. The VA took steps to prevent the spread of MRSA and device- and procedure-associated infections. This included screening all patients for MRSA on admission, tracking MRSA infections, using Contact Precautions (such as gloves and gowns) for people with MRSA, and increasing the emphasis on hand hygiene.

Success was also driven by a change in institutional culture, which made preventing MRSA infections the responsibility of any VA employee taking care of patients. Employee adherence to infection prevention practices was tracked. Many hospitals outside of the VA system have also successfully reduced MRSA rates by assessing facility data and implementing CDC-recommended prevention strategies.

REDUCTIONS IN HOSPITALS HAVE STALLED

New strategies in healthcare, along with current CDC recommendations, could prevent more MRSA infections. MRSA infections in communities may be connected to the opioid crisis.



Adjusted bloodstream infection rates from population-based surveillance in six CDC Emerging Infections Program sites. Community-onset infections include those in people who have not had recent inpatient healthcare exposure or an invasive medical procedure.

ONLINE RESOURCES

About MRSA
www.cdc.gov/mrsa/index.html

CDC Vital Signs: Staph Infections Can Kill
www.cdc.gov/vitalsigns/staph/index.html

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DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

THREAT LEVEL **SERIOUS**

900,000 Estimated infections in 2014

3,600 Estimated deaths in 2014

Streptococcus pneumoniae **(pneumococcus) is a leading cause of bacterial pneumonia and meningitis in the United States. It also is a common cause of bloodstream infections, and ear and sinus infections.**

WHAT YOU NEED TO KNOW

- Overall, there are more than 2 million pneumococcal infections each year in the United States, resulting in more than 6,000 deaths and $4 billion in total costs. In more than 30% of infections, the bacteria are resistant to one or more clinically relevant antibiotics.
- Pneumococcal pneumonia leads to an estimated 150,000 hospitalizations for adults each year and accounts for $1.3 billion in direct medical costs (65% of direct costs for all adult pneumococcal disease treatment).
- Drug-resistant *S. pneumoniae* is one of the only germs listed in this report with an effective vaccine to prevent infections, called pneumococcal conjugate vaccine (PCV).

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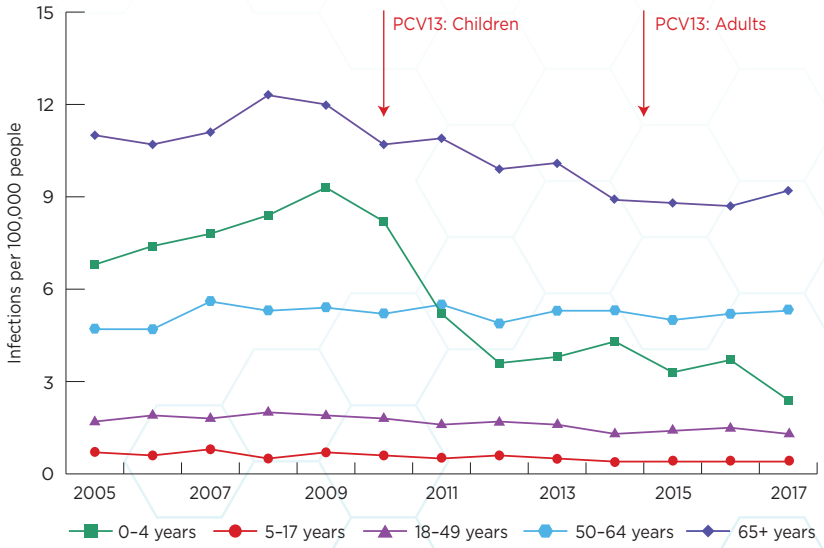
INFECTIONS OVER TIME BY AGE

Rates of antibiotic-resistant invasive pneumococcal infections have decreased across age groups in the United States from 2005 to 2017.



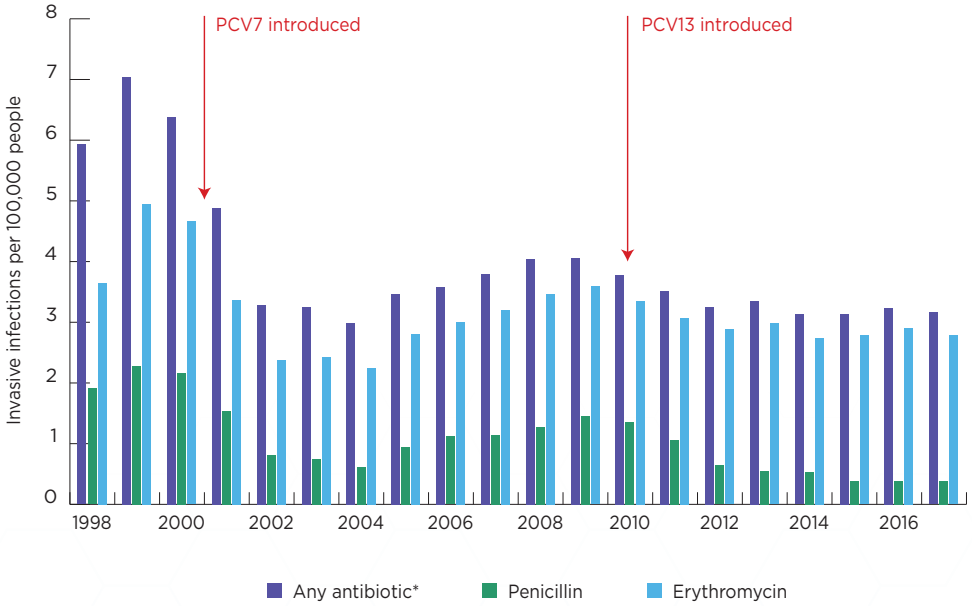
VACCINE: AN EFFECTIVE TOOL

Pneumococcal conjugate vaccine (PCV) helps prevent infections and slow the development of pneumococcal resistance. PCV has reduced pneumococcal infections caused by vaccine strains, most of which were resistant, by more than 90% in children. It has also decreased the spread of resistant *S. pneumoniae* strains, because vaccinated people do not spread the bacteria. Blocking the spread reduces resistant infections among children, as well as adults, through vaccine indirect effects (or "herd immunity"). From 2000 to 2009, PCV7 provided protection against seven pneumococcal strains. These strains caused more than 83% of the antibiotic-resistant invasive infections in children prior to PCV7 introduction.

Beginning in 2010, use of PCV13 expanded that protection to 13 strains, one of which—serotype 19A—accounted for more than 30% of resistant infections prior to PCV13 introduction. Since PCV introduction among U.S. children 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. Achieving high vaccination coverage and encouraging appropriate antibiotic use will slow the spread of pneumococcal resistance.

INFECTIONS OVER TIME BY ANTIBIOTIC

Antibiotic-resistant invasive pneumococcal infections have decreased in the United States since PCVs were introduced.



*Any antibiotic includes germs not susceptible (not sensitive) to at least one of the following antibiotics: penicillin, amoxicillin, erythromycin, cefotaxime, ceftriaxone, cefuroxime, tetracycline, vancomycin, or levofloxacin.

ONLINE RESOURCES

About Drug-resistant Pneumococcal Disease
www.cdc.gov/Pneumococcal/Drug-Resistance.html

Bact Facts Interactive: Data from Active Bacterial Core Surveillance
wwwn.cdc.gov/BactFacts/Index.html

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CS298822-A

DRUG-RESISTANT **TUBERCULOSIS** (TB)

THREAT LEVEL **SERIOUS**

847 Cases in 2017

62 Deaths in 2017

$164,000 Per MDR case

$526,000 Per XDR case

TB is caused by *Mycobacterium tuberculosis,* bacteria that usually attack the lungs. Drug-resistant TB develops when the antibiotics used to treat TB are misused or mismanaged, and it can spread.

WHAT YOU NEED TO KNOW

- TB spreads from person to person through the air. It is one of the world's most deadly infectious diseases.
- In most cases, TB is curable; however, people with TB can die without proper treatment. Treatment for drug-resistant TB is costly, lengthy, disrupts lives, and can have life-threatening side effects.
- MDR TB is resistant to two first-line antibiotics. XDR TB is resistant to some first- and second-line antibiotics.
- The number of drug-resistant TB cases in the United States remain stable due to effective control strategies.

Data represents U.S. cases only. MDR: multidrug-resistant. XDR: extensively drug-resistant.

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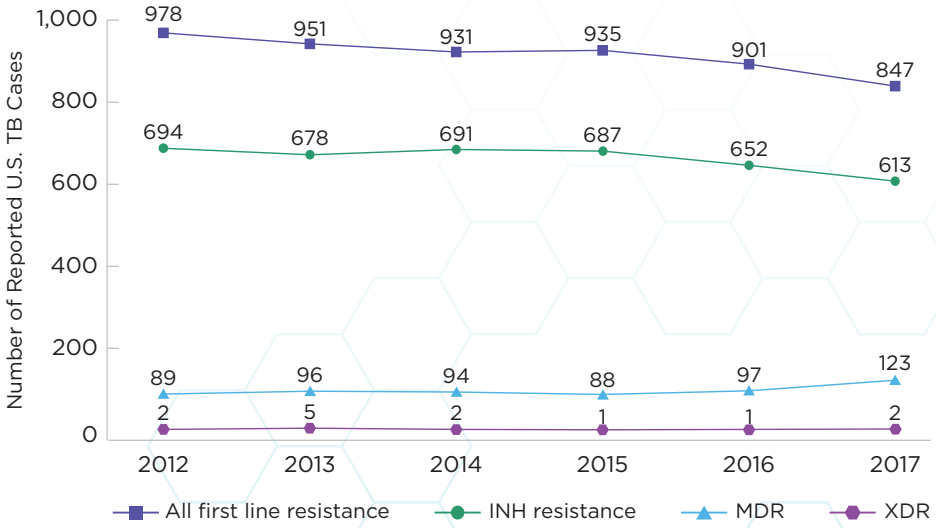
CASES OVER TIME

TB is most commonly resistant to isoniazid, one of the first-line TB antibiotics (called INH resistance).



TOXIC SIDE EFFECTS FROM TB TREATMENT

Dr. Dalene von Delft was a newly qualified doctor in South Africa when her dreams of becoming a pediatric surgeon were shattered. Dalene contracted MDR TB. Treatment took 19 harrowing months.

Dalene had to inject toxic second-line antibiotics that can cause severe side effects. She took 30 pills a day—24 for TB and six for the side effects of TB treatment. The treatment made her so ill that she started to go deaf. Dalene had to make potentially life-threatening decisions to stop treatment to preserve her hearing and career. She often listened to music, worried the songs would be the last she ever heard.

MDR TB affects people in the United States and around the world. Dalene recovered due to a new treatment that was in development. She founded a campaign to help protect healthcare workers and medical students against work hazards. CDC continues to work to stop the spread of TB and protect the health of all people.

TYPES OF RESISTANCE

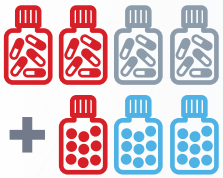
TB treatment requires four first-line antibiotics: rifampin, isoniazid, pyrazinamide, and ethambutol. When TB becomes resistant to any of these drugs, it limits treatment options and puts the patient at risk for untreatable TB.

DRUG-RESISTANT TB

Resistant to 1 of 4 first-line antibiotics used to treat TB. The most common is INH-resistant TB, which is resistant to isoniazid.

MDR TB

Resistant to 2 of 4 first-line antibiotics, isoniazid and rifampin—the most potent drugs to treat TB.



XDR TB

Rare type of MDR TB that is also **resistant to at least 1 of the 3** second-line antibiotics, including fluoroquinolones. Second-line antibiotics can be toxic and cause severe side effects.

First-line antibiotics Second-line antibiotics

ONLINE RESOURCES

About Drug-resistant TB
www.cdc.gov/TB/Topic/DRTB

TB Personal Stories
www.cdc.gov/TB/Topic/Basics/PersonalStories.htm

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
The full report, including data sources, is available at www.cdc.gov/DrugResistance/Biggest-Threats.html.

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Concerning Threats

These germs are public health threats that require careful monitoring and prevention action:

ERYTHROMYCIN-RESISTANT
GROUP A *STREPTOCOCCUS*

CLINDAMYCIN-RESISTANT
GROUP B *STREPTOCOCCUS*

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ERYTHROMYCIN-RESISTANT GROUP A *STREPTOCOCCUS*

THREAT LEVEL **CONCERNING**

5,400 Estimated infections in 2017

450 Estimated deaths in 2017

Group A *Streptococcus* (GAS) bacteria can cause mild infections such as sore throat and impetigo, and severe invasive disease such as cellulitis, pneumonia, flesh-eating infections, and sepsis.

WHAT YOU NEED TO KNOW

- GAS is the most common bacterial cause of sore throats, often referred to as strep throat.
- GAS can also cause severe invasive infections. People who are elderly, have skin breakdown, or have chronic medical conditions (such as diabetes) are at increased risk.
- Each year in the United States, GAS causes approximately 1 to 2.6 million cases of strep throat, 12,500 to 20,000 invasive infections, and 1,250 to 1,900 deaths.
- Increasing resistance to erythromycin and clindamycin complicates treatment of GAS infections.

Data represents only invasive infections.

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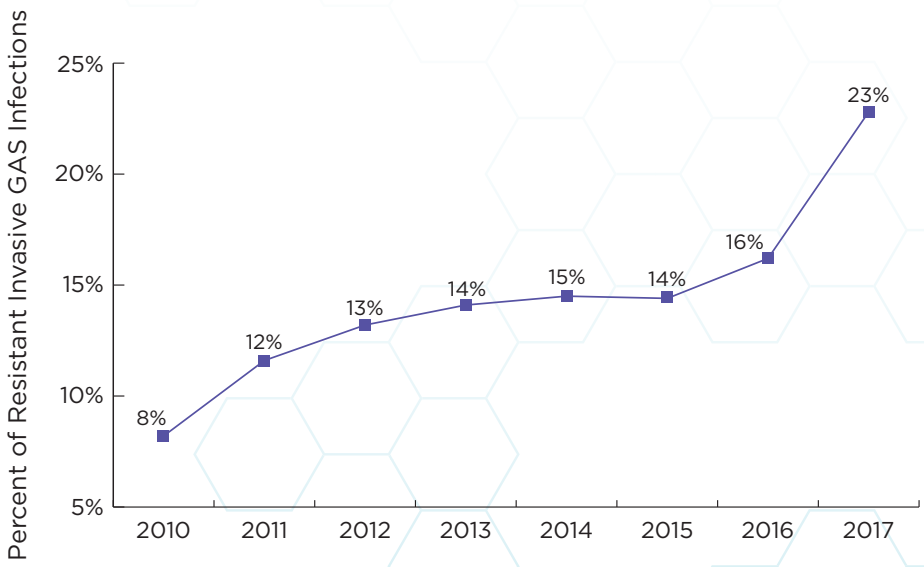
INFECTIONS OVER TIME

ERYTHROMYCIN RESISTANCE

The percent of invasive GAS infections that are resistant to erythromycin has nearly tripled in 8 years.



RESISTANCE COMPLICATES TREATMENT

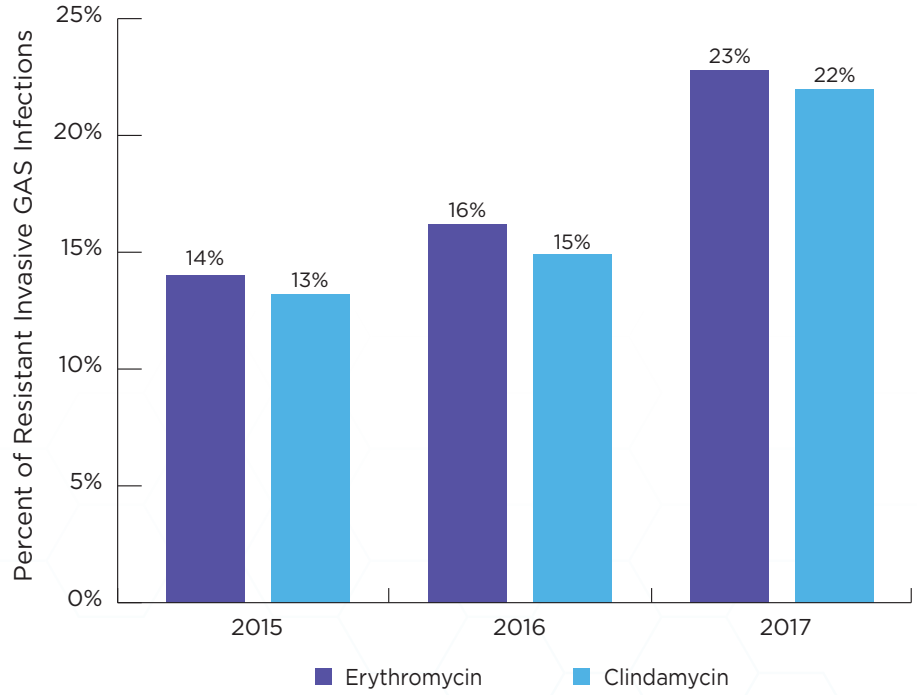
We have all known someone who has had strep throat—imagine if it were untreatable. Germs would spread, more people would get sick, and some might develop rheumatic fever, a complication of strep throat that can damage the heart.

Currently, GAS is not resistant to penicillin or amoxicillin, first-line antibiotics for strep throat. However, doctors often use erythromycin and azithromycin (macrolide antibiotics) to treat strep throat, particularly for people who are allergic to penicillin. Additionally, clindamycin, in combination with penicillin, is the recommended treatment for severe, life-threatening GAS infections such as flesh-eating disease and streptococcal toxic shock syndrome. Increasing resistance to erythromycin and other macrolides, and to clindamycin complicates the treatment of both strep throat and severe invasive infections. Vaccines are in development, but it will be some time before one is available for use.

INFECTIONS OVER TIME

ERYTHROMYCIN AND CLINDAMYCIN RESISTANCE

More than one in five invasive GAS infections are caused by erythromycin- and clindamycin-resistant strains, limiting the patient's treatment options.



ONLINE RESOURCES

About Erythromycin-resistant Group A *Streptococcus*
www.cdc.gov/GroupAStrep/Index.html

Bact Facts Interactive: Data from Active Bacterial Core Surveillance
wwwn.cdc.gov/BactFacts/Index.html

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
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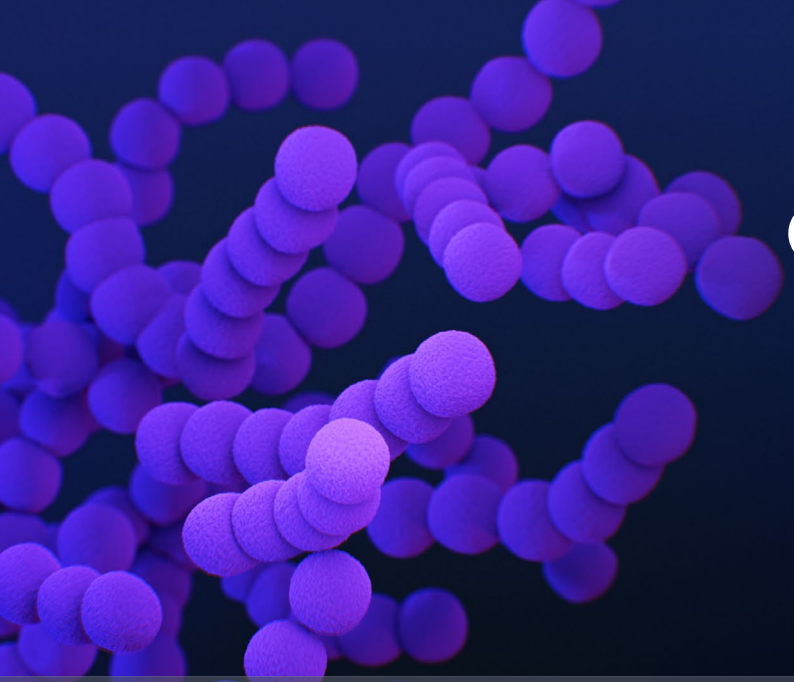

CLINDAMYCIN-RESISTANT GROUP B *STREPTOCOCCUS*

THREAT LEVEL **CONCERNING**

13,000 Estimated infections in 2016

720 Estimated deaths in 2016

Group B *Streptococcus* (GBS) is a type of bacteria that can cause severe illnesses—including bloodstream infections, pneumonia, meningitis, and skin infections—in people of all ages.

WHAT YOU NEED TO KNOW

- Overall, about 31,000 severe GBS infections occurred in 2016, causing 1,700 deaths.
- In adults, GBS causes infections among pregnant women, older adults, and people with certain medical conditions, such as diabetes.
- Mothers can pass GBS to their infants during labor, threatening newborns with sepsis during the first week of life. When indicated, doctors give mothers antibiotics during labor to protect their newborns from GBS disease.
- Resistance to clindamycin limits treatment and prevention options for adults with severe penicillin allergy.

Data represents only invasive infections, including bloodstream infections and meningitis.

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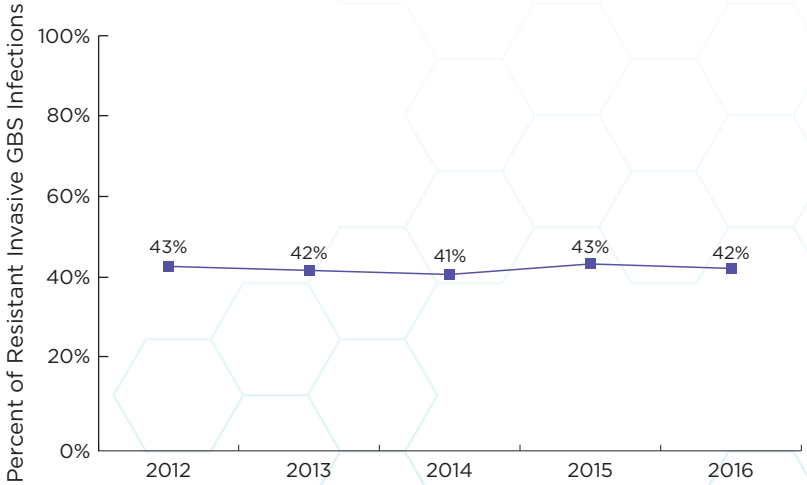
INFECTIONS OVER TIME

CLINDAMYCIN RESISTANCE

Clindamycin-resistant strains have caused more than 40% of GBS infections, limiting prevention and treatment options for people with severe penicillin allergy.



ANTIBIOTICS CRITICAL FOR GBS

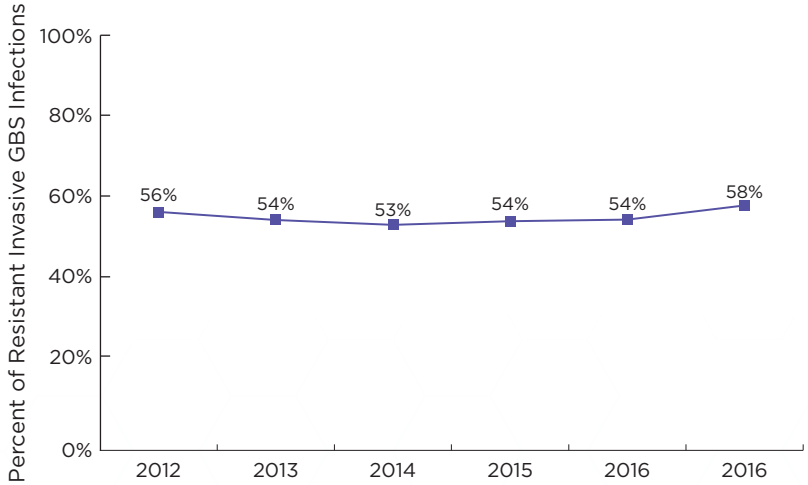
About one in every four pregnant women carry GBS bacteria in their body. Mothers who test positive for GBS during pregnancy can pass GBS to their newborns. Healthcare providers give these mothers penicillin or ampicillin during labor to prevent the spread of GBS to newborns during birth. Clindamycin is recommended when a mother has a severe penicillin allergy. Clindamycin can also be used to treat adult GBS infections if the patient has a severe penicillin allergy.

However, clindamycin-resistant germs cause more than 40% of GBS infections. Resistance to a related antibiotic called erythromycin is even more common—more than 50%. This seriously limits options for GBS disease prevention and treatment. Vaccines are in development for mothers-to-be to prevent GBS disease in their newborns. Until available, improving the way antibiotics are prescribed and taken helps fight the spread and development of antibiotic resistance, and ensures that these life-saving drugs will be available for future generations.

INFECTIONS OVER TIME

ERYTHROMYCIN RESISTANCE

Erythromycin-resistant strains have caused more than half of GBS infections.



ONLINE RESOURCES

About Clindamycin-resistant Group B *Streptococcus*
www.cdc.gov/GroupBStrep/Index.html

Bact Facts Interactive: Data from Active Bacterial Core Surveillance
wwwn.cdc.gov/BactFacts/Index.html

This fact sheet is part of CDC's 2019 Antibiotic Resistance Threats Report.
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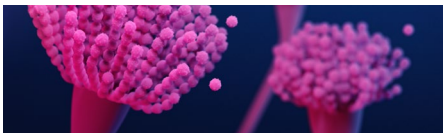
Watch List

CDC's Watch List includes three threats that are uncommon, or the full burden of these germs is not yet understood in the United States. There is the potential for these resistant germs to spread across borders and cause significant morbidity and mortality. CDC and other public health experts are closely monitoring these germs, which have the potential to be included as listed threats in the future. Early detection of resistant germs within the United States, followed by implementation of prevention strategies, could reduce spread and public health impact.



AZOLE-RESISTANT ***ASPERGILLUS FUMIGATUS***

Aspergillus fumigatus is a fungus that can cause life-threatening infections in people with weakened immune systems. These infections are treated with antifungals called azoles. Azoles are also increasingly used in agriculture to prevent and treat fungal diseases in crops. Azole use in human medicine and agriculture can contribute to resistance to antifungal medicines. Although few infections caused by azole-resistant *A. fumigatus* have been identified in the United States, many more infections have been reported in other countries. *A. fumigatus* is challenging to detect because symptoms are similar to many other respiratory infections. When *A. fumigatus* is identified as the cause of an infection, most U.S. laboratories do not have the capability to test for resistance. CDC currently has limited tracking for *A. fumigatus* infections, but CDC is working to better understand how common these infections are and identify the best prevention strategies.

DRUG-RESISTANT ***MYCOPLASMA GENITALIUM***

M. genitalium bacteria are sexually transmitted and can cause urethritis in men (inflammation of the urethra) and may cause cervicitis in women (inflammation of the cervix). If left untreated, *M. genitalium* may also cause pelvic inflammatory disease in women, leading to chronic pelvic pain, ectopic pregnancy, and infertility. Few antibiotics are available to treat *M. genitalium* infections. Resistance to azithromycin, which has been recommended for treatment, is high across the globe. CDC is collaborating with partners, including STD clinics and other Federal agencies, on research to better understand the prevalence of *M. genitalium* in the United States and how resistance develops in this germ.

DRUG-RESISTANT ***BORDETELLA PERTUSSIS***

Pertussis, a respiratory illness commonly known as whooping cough, is a very contagious disease caused by a type of bacteria called *Bordetella pertussis*. It can cause serious and sometimes deadly complications, especially in babies. The best way to prevent this infection is to get vaccinated. Azithromycin and erythromycin are the recommended antibiotics to treat whooping cough. While antibiotic-resistant pertussis is rarely reported in the United States, resistance has been documented in other countries. CDC is monitoring resistance in the United States by testing isolates received through CDC's Emerging Infections Program.

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SUPPLEMENTARY MATERIAL

CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE
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Acknowledgments

Special thanks to **CDC's Antibiotic Resistance Coordination and Strategy Unit** within the **Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases,** for leading the development of the *Antibiotic Resistance Threats in the United States, 2019:*

Lacey Avery
Kathryn Ayres
Katy Capers
Michael Craig
Stephanie Gumbis
Tara Henning
Sarah Jones
Liz McClune
Brittany Barnett Moskowitz
Jean Patel
Dawn Sievert
Eric Ransom
Tessa Revolinski
Kaytna Thaker

Additional thanks to the following CDC Centers and Divisions, and external organizations:

National Center for Emerging and Zoonotic Infectious Diseases

Grace Appiah
James Baggs
Michael Beach
Karlyn Beer
Casey Barton Behravesh
Allison Brown
Beau Bruce
Sandra N. Bulens
Stefanie Bumpus
Denise Cardo
Heather Carleton
Danielle Carter
Tom Chiller
Nicole Coffin
Sarah Collier
Alison Cooper
Nadezhda Duffy
Anthony Fiore
Jason P. Folster
Kaitlin Forsberg
Cindy R. Friedman
Amanda Garcia-Williams
Nicole Gladden
Runa Gokhale
Julian Grass
Elizabeth Greene
Patricia M. Griffin
Alice Guh
Alison Laufer Halpin
Kelly Hatfield
Brendan Jackson
Kelly Jackson
John A. Jernigan
Alex Kallen
Beth Karp
Amy E. Kirby
Lauren Korhonen
Seth Kroop
Shawn Lockhart
Caitlyn Lutfy
Joseph Lutgring
Meghan Lyman
Shelley Magill
Zachary Marsh
Natalie L. McCarthy
Cliff McDonald
Felcita Medalla
Eric Mintz
Laura Murrell
Megin Nichols
Heather Ewing Ogle
Babatunde Olubajo
Prabasaj Paul
Kamile Rasheed
Sujan Reddy
Hannah E. Reses
Jared Reynolds
Jessica Schindelar
R. Douglas Scott II
Isaac See
Rachel B. Slayton
Arjun Srinivasan
Robert V. Tauxe
Snigdha Vallabhaneni
Louise Francois Watkins
Jean M. Whichard
Kate Wiedeman
Sabrina Williams
Hannah Wolford
Sarah H. Yi
Foodborne Outbreak Response Team
Enteric Zoonoses Activity

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

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Jennifer Ludovic
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Raul Romaguera
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Clarisse Tsang

National Center for Immunization and Respiratory Diseases

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Barbara Mahon
Lesley McGee
Benjamin Metcalf
Srinivas Nanduri
Tamara Pilishvili
Stephanie Schrag
Tami Skoff
Lucia Tondella
Chris Van Beneden
Xin Wang

Division of Communication Services

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Keith Bailey
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Alissa Eckert
Dan Higgins
Bob Hobbs
Anita Jones
Betsy Lescosky
Debra Lowery
Meredith Newlove
Jennifer Oosthuizen
Stephanie Rossow
Belinda Ware

External Organizations

Becton, Dickinson and Company
Cerner
Deloitte Digital + Heat
Premier
VA Salt Lake City Healthcare System & University of Utah School of Medicine

Glossary

Adverse drug event: Harms resulting from the use of medication and include allergic reactions, side effects, overmedication, and medication errors.

Amplification: An increase in the number of resistant germs in a person, animal, or the environment.

Animal husbandry: The practice of breeding and caring for farm animals.

Antibiotic stewardship: Improving the way antibiotics are prescribed and used.

Antibiotic susceptibility testing: A way to describe how sensitive germs are to particular antibiotics. An antibiotic can stop the growth of or kill a susceptible germ.

Antibiotic resistance: When germs develop the ability to defeat the drugs designed to kill them. That means the germs are not killed and continue to grow.

Antibodies: Naturally occurring proteins produced by the body in response to invading germs.

Antimicrobials: Drugs that treat infections by killing or slowing the growth of germs causing infection.

- **Antibiotics:** Drugs that treat infections caused by bacteria (e.g., strep throat, foodborne illness).
- **Antifungals:** Drugs that treat infections caused by fungi (e.g., athlete's foot, yeast infections).

Beta-lactam antibiotics: A class of antibiotics that have been critically important to modern medicine. They kill bacteria by binding to proteins and thereby stop the germ from creating or properly forming a cell wall.

Biosecurity: Practices intended to reduce the risk of diseases being carried onto the farm, spread to the animals across the farm, and transmitted off the farm. This includes the property the animals are housed on and in, the people who interact with the animals, and the equipment and vehicles that come onto the property.

Carbapenems: A class of beta-lactam antibiotics active against many Gram-positive and Gram-negative organisms, usually reserved for treatment of the most resistant infections.

Carbapenemase: An enzyme produced by certain bacteria, including some Enterobacteriaceae, that makes carbapenems, celphalosporins and penicillins ineffective.

Cephalosporins: Antibiotics that kill bacteria by preventing the cell wall from properly forming.

Colonization: The presence of germs on or in the body without symptoms of an infection.

First-line antibiotics: Antibiotics recommended as the first treatment for infections because they maximize the chance of curing the infection while minimizing the chance of experiencing harms from antibiotics, including antibiotic resistance and side effects.

Germ: Very small living organisms including bacteria, fungi, parasites, and viruses. In this report, CDC uses "germ" to describe bacteria and fungi, including pathogens.

Gram-negative bacteria: A group of germs, characterized by having relatively thin cell walls, that are increasingly resistant to many available antibiotics. They often find new ways to develop resistance and can sometimes share these abilities with other bacteria, increasing the spread of resistance. Examples of Gram-negative bacteria include *Acinetobacter* species, *P. aeruginosa,* and *E. coli.*

Gram-positive bacteria: A group of germs, characterized by having thick cell walls, that are increasingly resistant to many available antibiotics. They often find new ways to develop resistance and can sometimes share these abilities with other bacteria, increasing the spread of resistance. Examples of Gram-positive bacteria include Streptococci, Staphylococci, and Enterococci.

Healthcare-associated germ: A germ patients can get while receiving medical treatment in hospitals, outpatient clinics, nursing homes, and other facilities where people receive care.

Infection control: Preventing or stopping the spread of infections.

Isolate: Pure samples of a germ.

Medically important antibiotics: Antibiotics that are commonly needed to treat infections in people.

Microbiome: The community of naturally-occurring microbes that live in or on the body (for example, stomach, intestines, skin).

Mobile genetic elements: Genetic material that can move from germ to germ and share resistance traits. This means that some germs can share their DNA and make other germs become resistant.

Multidrug-resistant germs: Germs that are resistant to multiple antibiotics available for treatment.

Non-susceptible infections: Infections that cannot be treated effectively with certain antibiotics.

One Health: A collaborative, multisectoral, and trans-disciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment.

Pan-resistant infections: Infections that are caused by germs resistant to all antibiotics available for treatment.

Pathogen: Harmful germs that can cause infection.

Penicillins: Antibiotics that kill bacteria by binding to proteins and thereby stop the germ from creating or properly forming a cell wall.

Phages (bacteriophages): Viruses that infect and replicate within bacteria. In some cases, phages can kill bacteria.

Resistance mechanisms: Defense strategies that germs develop to help them survive and avoid the effects of antibiotics.

Susceptible infections: Infections that can be treated effectively with antibiotics.

Toxicity: Poisonous or harmful.

Virulence factors: Characteristics that help a germ cause disease.

Acronyms

The following list includes acronyms used in the report. They are defined upon first use in the report.

ABCs	Active Bacterial Core Surveillance System
ADE	Adverse drug event
AR (AMR)	Antibiotic resistance (antimicrobial resistance)
AR Lab Network	Antibiotic Resistance Laboratory Network
CARB	*National Action Plan for Combating Antibiotic Resistant Bacteria*
CDC	Centers for Disease Control and Prevention
CRE	Carbapenem-resistant Enterobacteriaceae
DNA	Deoxyribonucleic acid
ESBL	Extended-spectrum beta-lacatamase
FDA	U.S. Food & Drug Administration
FMT	Fecal matter transplant
GAS	Group A *Streptococcus*
GBS	Group B *Streptococcus*
HHS	U.S. Department of Health and Human Services
KPC	*Klebsiella pneumoniae* carbapenemase
LB	Live biotherapeutics
LVAD	Left ventricular assist devices
NARMS	National Antimicrobial Resistance Monitoring System
NAAT	Nucleic acid amplification tests
NDM	New Delhi Metallo-beta-lactamase
OXA-48	Oxacillinase-48
STD	Sexually transmitted disease
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
VIM	Verona integron-encoded metallo-beta-lactamase
WGS	Whole Genome Sequencing
WHO	World Health Organization

TECHNICAL APPENDIX

ERYTHROMYCIN-RESISTANT
GROUP A *STREPTOCOCCUS*

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Data Methods

Drug-resistant *Campylobacter*

Estimates of the annual number of infections and deaths from *Campylobacter* with decreased susceptibility to ciprofloxacin or azithromycin are reported. They were derived by multiplying an estimate of the annual number of *Campylobacter* infections or deaths in the United States[1] by the average prevalence of resistance among *Campylobacter jejuni* and *Campylobacter coli* isolates collected during 2015–2017 and tested by the National Antimicrobial Resistance Monitoring System (NARMS). Isolates were tested by broth microdilution to determine minimum inhibitory concentrations (MICs) for ciprofloxacin, azithromycin, and other antibiotics.[2] Epidemiological cutoff values (ECOFFs) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were used to interpret MICs for *C. jejuni* and *C. coli.*[3] EUCAST uses the term "non-wild-type" to describe bacteria with MICs above the ECOFFs and to distinguish them from "wild-type" bacteria without resistance mechanisms. Non-wild-type isolates are referred to as having "decreased susceptibility" in this report. For *C. jejuni,* decreased susceptibility to ciprofloxacin was defined as MIC ≥1 µg/mL and decreased susceptibility to azithromycin as MIC ≥0.5 µg/mL. For *C. coli,* decreased susceptibility to ciprofloxacin and decreased susceptibility to azithromycin were both defined as MIC ≥1 µg/mL.

Many assumptions were made in deriving the estimates. Since ECOFFs are only available for *Campylobacter jejuni* and *Campylobacter coli* (which accounted for ~98% of *Campylobacter* species tested by NARMS during 2015–2017), the average prevalence of resistance was assumed to be the same for other species when calculating the estimated number of infections and deaths from resistant *Campylobacter.* The estimated number of infections from resistant *Campylobacter* was divided by the U.S. population and multiplied by 100,000 to calculate the estimated number of resistant infections per 100,000 people. The U.S. population in 2014 (approximately 318.6 million people) was used for the calculation because the estimated number of *Campylobacter* infections in the United States was based on this population.[1] The estimated direct medical costs were based on the estimated cost of hospitalization and estimated cost of emergency department visits for all *Campylobacter* infections, in 2014 U.S. dollars.[1] The sentinel county survey data displayed in *Campylobacter: Resistance Over Time* was previously reported.[4]

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Candida auris

National *Candida auris (C. auris)* case counts were obtained through monthly CDC outreach to state health departments, which tracked cases individually as this fungus emerged but before formal public health surveillance could be established. CDC began collecting data on *C. auris* cases in 2016 following a clinical alert, but some cases were identified retrospectively through laboratory data review. The earliest known U.S. case was identified retrospectively from a specimen collected in 2013. Cases were defined using the standardized case definitions for *C. auris.*[1] A clinical case is defined as a person with culture of *C. auris* from any body site when the specimen was collected for the purposes of diagnosing or treating disease in the normal course of care.

Confirmatory species identification and antifungal susceptibility testing were performed at CDC or public health laboratories that are part of the Antibiotic Resistance Laboratory Network.[2] Resistance rates were calculated using all *C. auris* isolates for which the AR Lab Network conducted antifungal susceptibility testing. CDC performed whole-genome sequencing on *C. auris* to evaluate relatedness of strains in the United States and around the world.[3,4]

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Carbapenem-resistant *Acinetobacter baumanii* (CRAB)*

Data for this analysis are from CDC's Emerging Infections Program (EIP) active laboratory- and population-based surveillance. Data from 2013 is from sites in Colorado (5 counties), Georgia (8 counties), Maryland (3 counties), Minnesota (2 counties), New Mexico (1 county), New York (1 county) and Oregon (3 counties). Data from 2014-2017 is from Colorado (5 counties), Georgia (8 counties), Maryland (3 counties), Minnesota (2 counties), New Mexico (1 county), New York (1 county), Oregon (3 counties) and Tennessee (8 counties). A case was defined as the first positive CRAB test in a 30-day period taken from a normally sterile site (e.g., blood, pleural fluid) or urine that occurred in a surveillance area resident whose test was identified to have an MIC of >=2 µg/mL for meropenem or imipenem or >1µg/mL for doripenem (Bulens et al). Local clinical laboratories in each surveillance area performed antimicrobial susceptibility testing and reported the method used. Most clinical laboratories used automated testing instruments (Reno et al.). Additional antimicrobial susceptibility information from patient medical records was collected and used for analysis. All reported interpretations were combined for completeness for the antibiotics presented.

Select Antibiotics	2013	2014	2015	2016	2017
Any fluoroquinolone	98%	93%	97%	92%	89%
Any extended-spectrum β-lactam	80%	75%	81%	79%	75%
Ampicillin/ sulbactam	62%	62%	59%	64%	61%
Trimethoprim/ sulfamethoxazole	84%	74%	81%	77%	66%

[1]Aminoglycosides are not included in this table as they are not typically recommended as single agent therapies for serious CRAB infections.

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*These methods refer to page 2 of the carbapenem-resistant *Acinetobacter* pathogen page. See page 134 for additional methods.

Clostridioides difficile

National estimates of the number of *Clostridioides difficile* infections *(C. difficile,* CDI) requiring hospitalization or in already hospitalized patients were obtained from data submitted to CDC's Emerging Infections Program (EIP)'s *C. difficile* surveillance program. As of 2017, 35 counties in 10 states participated in EIP CDI surveillance. A case of CDI was defined as a positive stool test (toxin or molecular assay) in a person aged ≥1 who did not have a positive test during the previous 8 weeks. Medical record review was performed on all CDI cases in 8 of 10 EIP sites and on a random sample of 33% of cases from the remaining 2 EIP sites. CDI cases were classified as community-associated if there was no documentation of an overnight stay in a healthcare facility in the 12 weeks before the patient's *C. difficile*-positive stool specimen; all other CDI cases were classified as healthcare-associated. Multiple imputation analysis was performed for missing race and epidemiologic class (community-associated versus healthcare-associated) based on the distribution of known race and epidemiologic class by age, sex, and EIP site. For the 2 EIP sites that performed sampling, we used the distribution of known race, age, sex, epidemiologic class, and hospitalization data among sampled cases to estimate these data for the non-sampled cases using domain analysis. The population estimates from the U.S. Census Bureau, stratified by age, sex, and race distribution of the U.S. and EIP population, were used to calculate the sampled weights to estimate the 2012–2017 national burden of CDI requiring hospitalization or in already hospitalized patients. To account for the increasing diagnostic use of nucleic acid amplification test (NAAT) since 2011, we built two logistic regression models, one for community-associated CDI and another for healthcare-associated CDI, adjusting for age, sex, race, and diagnostic methods (i.e., NAAT vs other test types). To assess the change in national estimates of CDI hospitalizations from 2012 to 2017, we used the NAAT coefficient from the logistic regression models to hold NAAT usage rate constant at the same rate as it was in 2011 (55%), while accounting for age, sex, and race of the U.S. population.

The estimated number of CDI deaths in 2017 was calculated by multiplying the national estimate of the number of CDIs requiring hospitalization by an estimate of CDI-attributable mortality (expressed as a percentage) obtained from the literature. Although estimates of CDI-attributable mortality published since 2000 range from 4.5% to 16.7%, the attributable mortality of CDI appears higher during epidemic periods; estimates of attributable mortality range from 4.5% to 5.7% during endemic periods.[1] Because it was derived from a patient population most similar to patients with CDI requiring hospitalization, an estimate of attributable mortality of 5.7% at 180 days was used.[2]

In order to derive a nationally representative estimate of the attributable costs of hospital-onset CDI, we used information from four published studies that developed estimates of cost using studies that included large study populations or studies that conducted a meta-analysis on costs based on multiple studies.[3–6] Table 1 presents the estimates from the four studies of the attributable per infection CDI costs. Adjusting these estimates to 2017 dollars using the Producer Price index,[7] the costs ranged from just over $10,000 to approximately $18,000 per infection. Using the average of these estimates, our estimate for the attributable cost per hospital-onset CDI is $12,675. This cost does not include any downstream healthcare costs that may occur after the index hospitalization, nor does it include any economic impacts to the patient from lost work time, diminished productivity, pain and suffering, or any long-term morbidities resulting from the infection. To determine the estimated national attributable cost of hospital-onset CDI in 2017, we first determined the estimated national burden of hospital-onset CDI based on the proportion of hospitalized CDI cases reported to EIP that were hospital-onset CDI. We then multiplied the estimated national burden of hospital-onset CDI by $12,675.

Table 1: Attributable CDI Hospital Costs

First Author (year)	Type of Study	Estimation of Costs	$ year	Mean of Estimates	Adjustment to 2017 $ (*PPI)	Attributable Cost (2017 $)
[3]McGlone et al. (2010)	cost simulation model	Graves method**	2010	$9,177	1.132	$10,385
[4]Bysshe et al. (2017)	systematic literature review	meta-analysis (9 studies)	2015	$17,260	1.039	$17,933
[5]Stewart & Hollenbeak (2007)	Retrospective cohort NIS data	propensity-matching	2007	$8,426	1.219	$10,275
6Zimlichman et al. (2012)	systematic literature review	meta-analysis (2 studies)	2012	$11,285	1.073	$12,105
					Mean of estimates	$12,675

**Lost revenue for each case was determined by the cost of a bed-day for each CDI-attributable additional length of stay for each episode.

We determined the incidence rate (defined as the number of cases per 100,000 population) of long-term care facility (LTCF)-onset CDI using data from CDC's Emerging Infections Program (EIP). Thirty-five counties in 10 states participated in EIP CDI surveillance. A case of CDI was defined as a positive stool test (toxin or molecular assay) in a person aged ≥1 without a positive test during the prior 8 weeks. Cases were categorized as LTCF-onset if the *C. difficile*-positive stool was collected in a LTCF or from a LTCF resident who had a positive stool test within 3 days of hospital admission. We limited this analysis to persons aged ≥65 years. Multiple imputation analysis was performed for missing race and epidemiologic class. Medical record review was performed on all CDI cases in 8 of 10 EIP sites and on a random sample of cases from 2 EIP sites. For the 2 EIP sites where only a sample of cases underwent medical record review, domain analysis was used to estimate race and epidemiologic class using a weighted frequency based on 33% random sampling. The LTCF-onset CDI incidence rates from 2011 to 2015 were calculated using the US Census data. We assessed the change in LTCF-onset CDI incidence rates from 2011 to 2015 by using a generalized linear mixed model with negative binomial distribution, adjusting for sex, race, and the percent of cases diagnosed by nucleic acid amplification test.

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Extended-spectrum beta-lactamase (ESBL-) producing Enterobacteriaceae†

ESBL infections data were obtained from a pilot surveillance project carried out from October 1, 2017 through December 31, 2017. Active laboratory- and population-based surveillance took place in selected counties in New Mexico (1 country), New York (1 county), and Tennessee (4 counties), and at sentinel facilities in Colorado (1 county) and Georgia (1 county). A case was defined as the first positive test from a sterile site (e.g., blood, pleural fluid, etc.) in a 30-day period for *Escherichia coli, Klebsiella pneumoniae,* or *Klebsiella oxytoca* resistant to ≥1 extended-spectrum cephalosporin (ceftazidime, cefotaxime, ceftriaxone) and non-resistant to all carbapenem antibiotics that occurred in a surveillance area resident. Information about potential risk factors was abstracted from medical records. Cases were categorized using medical record review as 1) hospital-onset if the positive test occurred on or after the fourth day of a hospital stay; 2) long-term care facility onset if the patient was in a long-term care facility three days before the positive test, 3) community-onset, with recent healthcare exposure, otherwise if the patient had one of several significant prior health care exposures such as a recent inpatient health care facility stay, surgery, chronic dialysis or indwelling devices; or, 4) community-associated, if the patient had none of the care exposures listed above.

†These methods refer to page 2 of the extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae pathogen page. See page 134 for additional methods.

Erythromycin-resistant Group A *Streptococcus* (GAS)

Estimates of the proportion of GAS isolates resistant to erythromycin and clindamycin are from isolates collected through Active Bacterial Core surveillance (ABCs), which is part of CDC's Emerging Infections Program (EIP) network.[1] ABCs conducts surveillance for invasive bacterial infections, including GAS, at 10 sites located throughout the United States. In 2017, the surveillance population for GAS was approximately 34 million people. Isolates are collected on an estimated 80% of all cases (approximately 1200-1900 isolates per year) and sent to reference laboratories for susceptibility testing to 14 different antibiotics (ampicillin, cefazolin, cefotaxime, cefoxitin, ceftizoxime, ciprofloxacin, clindamycin, daptomycin, erythromycin, levofloxacin, linezolid, penicillin, tetracycline, and vancomycin) using Clinical and Laboratory Standards Institute (CLSI) methods until 2015.[2] Beginning in 2016, susceptibility to antibiotics was predicted from whole-genome sequencing data.[3]

Cases and deaths were estimated by applying the 2017 resistant rate to erythromycin (22.8%) to total cases (23,650) and total deaths (1,980) reported in the 2017 report of ABCs.[4] Erythomycin and clindamycin resistance rates from 2015–2017 are based on data collected through ABCs.

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Clindamycin-resistant Group B *Streptococcus*

Estimates of the proportion of GBS isolates resistant to erythromycin and clindamycin are from isolates collected through Active Bacterial Core surveillance (ABCs), which is part of CDC's Emerging Infections Program (EIP) network. ABCs conducts surveillance for invasive bacterial infections, including GBS, at 10 sites located throughout the United States representing a population of approximately 37 million persons.[1] Surveillance isolates were collected from 7 ABCs sites until 2013; an 8th site began collecting isolates in 2014. In 2016, isolates were collected from ~80% (approximately 2200) of cases from these 8 sites. Reference laboratories performed susceptibility testing to 14 different antibiotics (ampicillin, cefazolin, cefotaxime, cefoxitin, ceftizoxime, ciprofloxacin, clindamycin, daptomycin, erythromycin, levofloxacin, linezolid, penicillin, tetracycline, and vancomycin) using Clinical and Laboratory Standards Institute (CLSI) methods until 2015.[2] Beginning in 2016, susceptibility to antibiotics were predicted from whole-genome sequencing data.[3,4] Estimates of severe disease are also from ABCs.

Cases and deaths were estimated by applying the 2016 overall resistance rate to clindamycin (42%) from the ABCs antimicrobial susceptibilities report to total cases (30,800) and total deaths (1,700) reported in the 2016 ABCs GBS surveillance report.[5]

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Methicillin-resistant *Staphylococcus aureus* (MRSA)[‡]

MRSA bloodstream infection data are from CDC's Emerging Infections Program (EIP) active laboratory- and population-based surveillance, which collected data from California (3 counties), Connecticut (statewide), Georgia (8 counties), Minnesota (1 county), New York (1 county) and Tennessee (1 county). These sites reported surveillance data from 2005–2016. In 2016, the total number of people living in areas covered by EIP surveillance was 13 million people. A case of MRSA bloodstream infection was defined as a positive blood culture for MRSA from a surveillance area resident who had not previously tested positive for MRSA in a normally sterile site (e.g., blood, pleural fluid) during the previous 30 days. The number of new cases per year was calculated per 100,000 people counted in the US Census and stratified according to when each person tested positive for MRSA, which was determined through medical record review as 1) hospital-onset if the positive culture occurred on or after the fourth day of a hospital stay; 2) healthcare–associated community-onset if the positive culture occurred in an outpatient or during the first 3 days of hospitalization in a patient with one of several significant prior healthcare exposures; and 3) community-associated. Community-onset infections include health care–associated community-onset and community-associated infections in people without prior health care exposure. Adjusted annual decreases were modeled using Poisson regression and accounting for changes in the overall population and dialysis population demographics. Postcensus bridged-race census files were used for EIP analyses.

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[‡]These methods refer to page 2 of the methicillin-resistant *Staphylococcus aureus* pathogen page. See page 134 for additional methods.

Drug-resistant *Neisseria gonorrhoeae*

Estimates of the number of gonococcal infections with any resistance pattern, including reduced susceptibility to cephalosporins or azithromycin, are included in this report. They are derived by multiplying an estimate of the annual number of gonococcal infections in the United States[1] by the prevalence of reduced susceptibility or resistance among urethral *Neisseria gonorrhoeae* isolates collected and tested by the Gonococcal Isolate Surveillance Project (GISP) during 2017.[2]

Many assumptions were made in deriving the estimates. Data from the National Health and Nutrition Examination Survey (NHANES) provided gonorrhea prevalence estimates; NHANES only measures urogenital infections and does not include oropharyngeal or rectal infections. The average duration of infection, used to calculate incidence, was based on expert opinion due to an absence of published data. Also, estimates of resistance in GISP are from a sentinel surveillance system. Compared to the regional distribution of reported gonococcal infections, GISP relatively over-samples patients from the West Coast, where resistance traditionally first emerges in the United States. The Clinical Laboratory Standards Institute (CLSI) categorizes susceptibility to cefixime and ceftriaxone as minimum inhibitory concentrations (MICs) ≤0.25 μg/ml.[3] For this analysis, isolates with cefixime MICs ≥0.25 μg/ml were considered to have reduced cefixime susceptibility, and isolates with ceftriaxone MICs ≥0.125 μg/ml were considered to have reduced ceftriaxone susceptibility. An azithromycin MIC ≥2.0 μg/ml was considered to have reduced azithromycin susceptibility. Resistance to any antimicrobial includes resistance to penicillin (MIC ≥ 2.0 μg/ml), tetracycline (MIC ≥2.0 μg/ml), ciprofloxacin (MIC ≥ 1.0 μg/ml), or reduced susceptibility to the cephalosporins or azithromycin.

GISP, established in 1986, is a sentinel antibiotic-resistant gonorrhea surveillance system with partners that include CDC, sexually transmitted disease clinics, and local public health labs at 20–35 sentinel sites, and regional laboratories in the United States.[4] Gonococcal isolates are collected for culture from up to the first 25 men diagnosed with gonococcal urethritis at each sentinel site each month. Antimicrobial susceptibility testing is performed using agar dilution for a panel of antimicrobials at regional labs that includes penicillin, tetracycline, ciprofloxacin, cefixime, ceftriaxone, and azithromycin.

To estimate the actual cost of antibiotic-resistant gonorrhea in the United States, the calculation includes the estimated discounted lifetime direct medical cost of the 550,000 antibiotic-resistant gonococcal infections each year, including cost of care for acute infections and sequelae, using methods published previously (adjusted to 2018 dollars).[5] Because costs are different for men and women due to higher sequelae costs in women, the sex ratio of diagnosed and reported infections in 2017[2] was applied to the 2017 number of estimated antibiotic-resistant gonococcal infections to calculate the total cost of antibiotic-resistant gonorrhea (as noted above, GISP collects isolates from men only for susceptibility testing). The emergence of antibiotic-resistant gonorrhea can result in notable increases in gonorrhea incidence and adverse health outcomes, and in the number of new HIV infections attributable to the facilitative effects of gonorrhea on HIV transmission and acquisition.[6,7] Even without incorporating potential increases in gonorrhea incidence or HIV attributable to antibiotic-resistant gonorrhea, the estimated discounted lifetime direct medical cost of resistant gonorrhea is $133.[4] million annually.

Neisseria gonorrhoeae: Emerging Antibiotic Resistance

Notes: Data from Gonococcal Isolate Surveillance Project (GISP). Prevalence of fluoroquinolone, penicillin, or tetracycline resistance [fluoroquinolone (ciprofloxacin) = MIC ≥1.0 μg/mL; penicillin = MIC ≥2.0 μg/mL or β-lactamase positive; tetracycline = MIC ≥2.0 μg/mL] or elevated azithromycin, cefixime, or ceftriaxone MICs [azithromycin = MIC ≥1.0 μg/mL (2000–2004); ≥2.0 μg/mL (2005–2017); cefixime = MIC ≥0.25 μg/mL); ceftriaxone = MIC ≥0.125 μg/mL]. Cefixime susceptibility was not tested in 2007 and 2008.

Neisseria gonorrhoeae: STD Treatment Across Settings

Notes: Includes 10 jurisdictions participating in the STD Surveillance Network (SSuN); proportions and 95% confidence intervals reflect weighted estimates for all diagnosed and reported gonococcal infections in participating jurisdictions where patients received recommended gonorrhea treatment by provider type.

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Drug-resistant nontyphoidal *Salmonella*

Estimates of the annual number of infections from nontyphoidal *Salmonella* that were resistant to ceftriaxone, were ciprofloxacin nonsusceptible, had decreased susceptibility to azithromycin, were resistant to at least one essential antibiotic, or were resistant to three or more essential antibiotics are reported. The estimated number of deaths from nontyphoidal *Salmonella* with resistance to at least one essential antibiotic is also reported. These estimates were derived by multiplying the estimate of the annual number of nontyphoidal *Salmonella* infections or deaths in the United States[1] by the average prevalence of resistance among nontyphoidal *Salmonella* isolates collected during 2015–2017 and tested by the National Antimicrobial Resistance Monitoring System (NARMS). Isolates were tested by broth microdilution to determine minimum inhibitory concentrations (MICs) for ceftriaxone, ciprofloxacin, azithromycin, ampicillin, trimethoprim-sulfamethoxazole, and other antibiotics.[2] Breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI) were used to categorize MICs when available.[3] Isolates with ciprofloxacin MICs categorized by CLSI as intermediate (MIC = 0.12–0.5 µg/ml) or resistant (MIC ≥1 µg/ml) were considered ciprofloxacin nonsusceptible. For azithromycin, CLSI breakpoints are only established for *Salmonella* serotype Typhi, with MIC ≥32 µg/ml categorized as resistant based on MIC distribution data and limited clinical data.[3] In this report, nontyphoidal Salmonella isolates with an azithromycin MIC ≥32 µg/ml were considered to have decreased susceptibility to azithromycin. Isolates were defined as resistant to at least one essential antibiotic if they met at least one of the following criteria: resistant to ceftriaxone, nonsusceptible to ciprofloxacin, decreased susceptibility to azithromycin, resistant to ampicillin, or resistant to trimethoprim-sulfamethoxazole. Isolates were defined as resistant to three or more essential antibiotics if they met at least three of those criteria.

Many assumptions were made in deriving the estimates. The estimated number of infections from resistant nontyphoidal *Salmonella* was divided by the U.S. population and multiplied by 100,000 to calculate the estimated number of infections from resistant *Salmonella* per 100,000 population. The U.S. population in 2014 (approximately 318.6 million people) was used for the calculations because the estimated number of nontyphoidal *Salmonella* infections in the United States was based on this population.[1] The estimated direct medical costs were based on estimated cost of hospitalization and estimated cost of emergency department visits for nontyphoidal *Salmonella* infections, in 2014 US dollars.[1]

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Revised Dec. 2019

Drug-resistant *Salmonella* Serotype Typhi

Estimates of the annual number of infections and deaths from *Salmonella* serotype Typhi that were ciprofloxacin nonsusceptible are reported. They were derived by multiplying the estimated annual number of Typhi infections or deaths in the United States[1] by the average prevalence of ciprofloxacin nonsusceptible Typhi isolates collected during 2015–2017 and tested by the National Antimicrobial Resistance Monitoring System (NARMS). Isolates were tested by broth microdilution to determine the minimum inhibitory concentrations (MICs) for ciprofloxacin and other antibiotics.[2] Breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI) were used to categorize ciprofloxacin MICs.[3] Isolates with ciprofloxacin MICs categorized by CLSI as intermediate (MIC = 0.12–0.5 µg/ml) or resistant (MIC ≥1 µg/ml) were considered ciprofloxacin nonsusceptible.

Many assumptions were made in deriving the estimates. The estimated number of illnesses from ciprofloxacin nonsusceptible *Salmonella* Typhi was divided by the US population and multiplied by 100,000 to calculate the estimated number of ciprofloxacin nonsusceptible infections per 100,000 people. The US population in 2006 (approximately 299 million people) was used for the calculations because the estimated number of Typhi infections in the United States was based on this population. Worldwide case estimates are from published sources.[4]

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Drug-Resistant *Shigella*

Estimates of the annual number of infections from *Shigella* that were resistant to ciprofloxacin, had decreased susceptibility to ciprofloxacin (DSC), had decreased susceptibility to azithromycin (DSA), were either ciprofloxacin resistant *or* had DSA, or were ciprofloxacin resistant *and* had DSA are reported. The estimated number of deaths from *Shigella* that were either ciprofloxacin resistant *or* had DSA is also reported. These estimates were derived by multiplying an estimate of the annual number of *Shigella* infections or deaths in the United States[1] by the prevalence of *Shigella* isolates with resistance or decreased susceptibility collected during 2015–2017 and tested by the National Antimicrobial Resistance Monitoring System (NARMS). Isolates were tested by broth microdilution to determine minimum inhibitory concentrations (MICs) for ciprofloxacin, azithromycin, and other antibiotics.[2] Clinical breakpoints and epidemiological cutoff values (ECVs) defined by the Clinical and Laboratory Standards Institute (CLSI) were used to categorize MICs when available.[3] Isolates with a ciprofloxacin MIC ≥1 µg/ml were categorized as resistant per CLSI's clinical breakpoint. Isolates with a ciprofloxacin MIC ≥0.12 µg/ml and <1 µg/ml may often carry resistance genes and were defined as having DSC in this report. This definition includes MICs categorized as "susceptible" (MIC ≤0.25 µg/ml) and "intermediate" (MIC=0.5 µg/ml) by CLSI. Clinical breakpoints for azithromycin have not been established for *Shigella;* instead ECVs established by CLSI were used to interpret azithromycin MICs and define DSA. CLSI uses the term "non-wild-type" to describe bacteria with MICs above the ECV and to distinguish them from "wild-type" bacteria without resistance mechanisms. Azithromycin ECVs have been established by CLSI for *Shigella sonnei* (MIC ≥32 µg/ml) and *Shigella flexneri* (MIC ≥16 µg/ml) but not for other species. In this report, *Shigella flexneri* isolates with MIC ≥16 µg/ml were defined as having DSA; all other species of *Shigella* (including *sonnei)* with MIC ≥32 µg/ml were defined as having DSA.

Many assumptions were made in deriving these estimates. The estimated number of infections from resistant *Shigella* was divided by the U.S. population and multiplied by 100,000 to calculate the estimated number of infections from resistant *Shigella* per 100,000 population. The U.S. population in 2014 (approximately 318.6 million people) was used for the calculations because the estimated number of *Shigella* infections in the United States was based on this population.[1] The estimated direct medical costs were based on the estimated cost of hospitalization combined with the estimated cost of emergency department visits for *Shigella* infections, in 2014 U.S. dollars.[1]

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Drug-Resistant *Streptococcus pneumoniae*

Trends in the incidence of antibiotic-resistant invasive pneumococcal disease per 100,000 people are from Active Bacterial Core surveillance (ABCs), which is part of CDC's Emerging Infections Program (EIP) network.[1] ABCs conducts surveillance for invasive bacterial infections, including *Streptococcus pneumoniae*, at 10 sites located throughout the United States representing a population of approximately 30 million persons. Isolates are collected on ≥90% of all cases (approximately 3,200 isolates per year) and sent to reference laboratories for susceptibility testing to 17 different antibiotics (amoxicillin, cefotaxime, ceftriaxone, cefuroxime, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, levofloxacin, linezolid, meropenem, penicillin, rifampin, synercid, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin). Minimum inhibitory concentrations were determined using conventional testing (broth microdilution) or, starting in 2015, predicted from whole-genome sequencing of isolates. Clinical and Laboratory Standards Institute (CLSI) breakpoints were applied to define resistance or susceptibility.[2]

The burden of antibiotic-resistant pneumococcal disease is estimated using multiple methods. We estimated the total number of all *S. pneumoniae* infections (2 million) by updating the analysis from Huang and colleagues.[2] We then applied the proportion of infections non-susceptible to clinically relevant drugs (i.e., penicillin, ceftriaxone, cefotaxime, erythromycin, levofloxacin, tetracycline, trimethoprim/sulfamethoxazole) in 2014 (ranging by age group and clinical syndrome from 36 to 50%) to the total number of all *S. pneumoniae* infections in order to estimate the number of resistant cases. Numbers of deaths were estimated by applying the proportion of infections non-susceptible to a clinically relevant drug to the total number of deaths from pneumococcal disease.[3]

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Drug-resistant Tuberculosis (TB)

Tuberculosis (TB) is a nationally notifiable disease; CDC receives TB case reports from all 50 states, the District of Columbia, New York City, five U.S. territories, and three freely associated states. Incidence of TB cases that are first-line drug resistant, isoniazid-resistant, multidrug-resistant (MDR), and extensively drug-resistant (XDR) were derived from the National Tuberculosis Surveillance System (NTSS), which CDC uses to collect TB case reports. Drug-resistant TB is resistant to 1 of 4 first-line antibiotics used to treat TB. The most common is INH-resistant TB, which is resistant to isoniazid. MDR TB is resistant to 2 of 4 first-line antibiotics, isoniazid and rifampin—the most potent drugs to treat TB. XDR TB is a rare type of MDR TB that is also resistant to at least 1 of the 3 second-line antibiotics, including fluoroquinolones. Reported cases are verified according to the TB Case Definition for Public Health Surveillance and are reported and counted according to the Recommendations for Reporting and Counting TB Cases.[1]

The number of deaths associated with drug-resistant TB was obtained from the CDC's National Center for Health Statistics, Multiple Cause of Death Files, available from CDC's WONDER online database.[2] Data were compiled from the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.

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Carbapenem-resistant *Acinetobacter,* Drug-resistant *Candida,* Carbapenem-resistant Enterobacteriaceae (CRE), Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, Multidrug-resistant *Pseudomonas aeruginosa,* Vancomycin-resistant *Enterococcus* (VRE), Methicillin-resistant *Staphylococcus aureus* (MRSA)

This section describes methods used to calculate national burden estimates for the following pathogens: carbapenem-resistant *Acinetobacter* spp (CRAsp), drug-resistant *Candida,* carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, multidrug-resistant *Pseudomonas aeruginosa,* vancomycin-resistant *Enterococcus* (VRE) and Methicillin-resistant *Staphylococcus aureus* (MRSA).

Data Sources

Three electronic health databases were used to calculate national burden estimates: Premier Healthcare Database,[1] Cerner Health Facts[2] and BD Insights Research Database.[3–6] Data from any inpatient visit in an included acute care hospital that took place between January 1, 2012–December 31, 2017 were analyzed. Because data use agreements prohibited any access to identifiers by the investigators this analysis did not constitute human-subjects research.

Hospital Cohort

A dynamic cohort of short-term acute care hospitals was created from each of the databases from 2012–2017. A hospital's data was included in the cohort for any month during which it reported at least one positive result from a microbiology culture with associated antimicrobial susceptibility testing data.

The hospital cohort for this analysis comprised 722 hospitals accounting for 7.4 million discharges annually (over 20% of United States hospital discharges/admissions annually). Cohort hospital characteristics are similar in distribution to those of all U.S. acute care hospitals (Table 1).

Case Cohort Definition

From the hospital cohort, we identified a cohort of patients who had any clinical culture that yielded an isolate of an organism of interest, and that had accompanying susceptibility testing results sufficient for determining whether that isolate had the resistance phenotype of interest (Table 2). We categorized clinical culture specimen types as either sterile, non-sterile, or surveillance based on body site. Specimens that were categorized as surveillance (i.e., cultures labeled as rectal, perirectal, or nasal) were excluded. Among clinical isolates with sufficient susceptibility testing results, those with the resistance phenotype of interest were eligible to be considered as an incident case. Only isolates from patients having no culture yielding the same resistance phenotype of interest in the previous 14 days were counted as an incident case. For patients with isolates with the resistance phenotype of interest from both a sterile and non-sterile positive culture taken within 14 days of each other, only the sterile culture was counted as an incident case. For both CRE and ESBL-producing Enterobacteriaceae reporting, denominator definitions account for potential antimicrobial susceptibility cascade reporting by hospitals (Table 2).

Cases were defined as community-onset (CO) when the culture was obtained immediately preceding admission or within the first three days of hospitalization, and hospital-onset (HO) when the culture was obtained on day four or later.

National Estimate of Cases

For each year, we used a raking-procedure to determine weights for extrapolating the number of discharges included in our sample to match the distribution of discharges, stratified by bed size, U.S. census division, urban/rural designation, and teaching status, for all U.S. hospitals included in the American Hospital Association survey for that respective year.[7] We applied a weighted means survey procedure to calculate pathogen-specific national case estimates for each year.

Rates and Trends

Pooled rates were calculated using the weighted number of cases and discharges in each month. We examined temporal trends using a multivariable logistic model incorporating a survey design with the corresponding weights and hospital designation as the specific cluster.[8,9] Using monthly hospital level data from 2012–2017, we modeled cases per discharge or admission, controlling for hospital characteristics, month of discharge, proportion of patients in specific age, and database. The parameter year, representing the trend, was modelled in two ways: as a log-linear trend (i.e., continuous variable) and as a linear combination of five independent parameters representing each year (i.e., as a categorical variable). Because results were similar, linear trends are reported throughout. For pathogens with notable differences in HO and CO trends, results were stratified. Trends in proportion of isolates exhibiting a resistant phenotype were calculated using the same methodology.

Attributable Mortality

Estimates of 90-day attributable mortality, including in-hospital and post-discharge deaths, were derived from a retrospective cohort study of patients with an inpatient admission in the U.S. Veterans Health Administration (VHA) system between January 2007 and October 2015. We adapted previously published methodologies[10] using the phenotype definitions established for this report to identify cases. Using multivariable Poisson regression models with standard errors clustered at the individual level, we calculated the excess risk of mortality for cases compared to a matched cohort (selected using exposure density sampling matched on the day of culture[11]); we reported the adjusted excess risk of mortality (i.e., risk difference) for cases compared to controls as the attributable mortality.[12–14] Due to limitations in sample size, three pathogens (CRE, CRAsp and MDR- *Pseudomonas)* were combined to create a pooled estimate for MDR Gram negative pathogens. Using the VHA cohort, we calculated 90-day estimates for attributable mortality separately for community-onset and hospital-onset cases.

Attributable Costs

Attributable costs for each pathogen were similarly derived from a retrospective cohort study of patients with an inpatient admission in the VHA system between October 2007 and December 2015, according to previously published methodology.[15] To provide cost estimates generalizable to non-VHA populations, the VHA Health Economics Resource Center (HERC) Average Cost data was used.[16–18] Absolute differences in costs were estimated individually for hospital-onset sterile, community-onset sterile, hospital-onset non-sterile, community-onset non-sterile cases using multivariable generalized linear models (GLM) with a gamma distribution and log link[19] adjusted for multiple patient characteristics. Models had clustered standard errors at the patient level. Our attributable cost estimates represent the excess direct medical costs of a positive clinical culture, from the perspective of the healthcare provider. Our estimates do not include any other downstream health care costs that may take place after the index hospitalization, nor any economic impacts to the patient from lost work time, diminished productivity, pain or suffering, mortality, or any long-term morbidities resulting from the infection.

We applied attributable mortality and costs estimates to the corresponding burden estimates projected above to calculate the estimated annual deaths and costs.

Candida species

For *Candida* spp., there were several differences in the methodology used. Some hospitals contributing data used in calculating estimates for bacterial pathogens did not routinely report culture results for *Candida,* and therefore estimates for *Candida* spp. were generated using only the subset of the hospitals that consistently reported fungal pathogen results (n=507 in 2017 representing 20% of all U.S. discharges). Weights for the extrapolation of *Candida* spp. infections were recalculated using the new cohort.

Only a small subset of hospitals reporting to the electronic health databases routinely submitted antifungal susceptibility results for *Candida* spp., therefore we could not use these databases to estimate the proportion of *Candida* spp. that were resistant to antifungal agents. Instead, after generating an estimate of the burden of all *Candida* spp. (regardless of antifungal susceptibility), we multiplied by an estimate of the percent of *Candida* spp. resistant to any antifungal agent (8.1%) among blood isolates collected through CDC's Emerging Infections Program (EIP).

Attributable mortality for *Candida*-positive cultures was estimated using the Premier Healthcare Database. Adjusted risk differences from logistic regression models comparing *Candida*-positive cases with matched

controls were calculated using an outcome of in-hospital deaths or discharge to hospice. Up to five matched controls were selected from the same hospital using exposure density sampling by day of an inpatient stay (i.e., the selected control must have been in the hospital with no positive *Candida* culture on the day of hospitalization that the matched case had a positive culture). Models were adjusted for patient and hospitalization characteristics. No estimate of attributable cost for *Candida*-positive cultures was calculated.

Table 1a. Demographics for all included hospitals, stratified by Electronic Health Database, compared with the distribution of U.S. hospitals as provided by the American Hospital Association (AHA)

Characteristics	Cerner Number (%)	Premier Number (%)	BD Number (%)	Combined (C+P+BD)* Number (%)	AHA(9) Number (%)
Total	178 (100%)	189 (100%)	355 (100%)	722 (100%)	4847 (100%)
Urban	127 (71.3%)	135 (71.4%)	266 (74.9%)	528 (73.1%)	2965 (61.2%)
Rural	51 (28.7%)	54 (28.6%)	89 (25.1%)	194 (26.9%)	1882 (38.8%)
Teaching	55 (30.9%)	50 (26.5%)	128 (36.1%)	233 (32.3%)	1768 (36.5%)
Non-Teaching	123 (69.1%)	139 (73.5%)	227 (63.9%)	489 (67.7%)	3079 (63.5%)
No. of beds, <300	144 (80.9%)	127 (67.2%)	227 (63.9%)	498 (69.0%)	4025 (83.0%)
No. of beds, ≥300	34 (19.1%)	62 (32.8%)	128 (36.1%)	224 (31.0%)	822 (17.0%)
Annual Discharges/ Admissions	1,727,265 (5.0%)	1,153,040 (3.3%)	4,508,717 (13.1%)	7,389,022 (21.4%)	34,554,279

*For *Candida* estimates, a subset of these hospitals (n=507) were used to generate the estimates representing 6,906,862 discharges (20.0%).

Table 1b. U.S. Census Division location for all included hospitals, stratified by Electronic Health Database, compared with the distribution of U.S. hospitals as provided by the American Hospital Association (AHA)

Characteristics	Cerner Number (%)	Premier Number (%)	BD Number (%)	Combined (C+P+BD)* Number (%)	AHA(9) Number (%)
1-New England	7 (3.9%)	9 (4.8%)	7 (2.0%)	23 (3.2%)	181 (3.7%)
2-Mid-Atlantic	7 (3.9%)	22 (11.6%)	48 (13.5%)	77 (10.7%)	412 (8.5%)
3-South Atlantic	37 (20.8%)	53 (28.0%)	43 (12.1%)	133 (18.4%)	714 (14.7%)
4-Northeast Central	19 (10.7%)	51 (27.0%)	84 (23.7%)	154 (21.3%)	735 (15.2%)
5-Southeast Central	14 (7.9%)	9 (4.8%)	46 (13.0%)	69 (9.6%)	392 (8.1%)
6-Northwest Central	18 (10.1%)	6 (3.2%)	13 (3.7%)	37 (5.1%)	700 (14.4%)
7-Southwest Central	19 (10.7%)	21 (11.1%)	61 (17.2%)	101 (14.0%)	738 (15.2%)
8-Mountain	26 (14.6%)	1 (0.5%)	17 (4.8%)	44 (6.1%)	418 (8.6%)
9-Pacific	31 (17.4%)	17 (9.0%)	36 (10.1%)	84 (11.6%)	557 (11.5%)

Table 2. Detailed Pathogen Phenotype Definitions

Pathogen	Organisms	Medications	Numerator	Denominator
Methicillin-resistant *Staphylococcus aureus* (MRSA)	*Staphylococcus aureus*	Methicillin, oxacillin, cefoxitin	Any isolate that tested (R) to at least 1 of these: methicillin, oxacillin, cefoxitin	Any isolate with at least 1 susceptible (S) or non-susceptible result (I, R) to: methicillin, oxacillin, cefoxitin
Vancomycin-resistant Enterococcus (VRE)	Enterococcus spp.	Vancomycin	Any isolate that tested (R) to vancomycin	Any isolate that tested (S, I, R) to vancomycin
Carbapenem-resistant Enterobacteriaceae (CRE)	*E. coli, Klebsiella* spp., *Enterobacter* spp.	Imipenem, meropenem, doripenem, ertapenem, ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, cefotetan	Any isolate with at least 1 resistant result (R) to imipenem, meropenem, doripenem, ertapnem	*Any isolate with at least 1 non-susceptible or susceptible result (S, I, R) to imipenem, meropenem, doripenem, ertapnem OR same isolate with at least 2 reported susceptible (S) results to: ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, cefotetan
Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae	*E. coli, Klebsiella* spp. (not *Klebsiella aerogenes)*	Cefotaxime, ceftriaxone, ceftazidime, cefepime, ampicillin, piperacillin, aztreonam, cefazolin	Any isolate with at least 1 non-susceptible, result (I or R) to: cefotaxime, ceftriaxone, ceftazidime, cefepime	**Any isolate with at least 1 susceptible (S) or non-susceptible result (I, R) to: cefotaxime, ceftriaxone, ceftazidime, cefepime OR same isolate with at least 2 reported susceptible (S) results to: ampicillin, piperacillin, aztreonam, or cefazolin
Carbapenem-resistant *Acinetobacter* (CRAsp)	*Acinetobacter* spp.	Imipenem, meropenem, doripenem	Any isolate with at least 1 non-susceptible result (I or R) to: imipenem, meropenem, doripenem	Any isolate with at least 1 susceptible (S) or non-susceptible result (I, R) to at least 1 drug in the medication categories
Multidrug-resistant (MDR) *Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	1. Extended-spectrum cephalosporins (cefepime, ceftazidime), 2. Fluoroquinolones (ciprofloaxacin, levofloxacin), 3. Aminoglycosides (amikacin, gentamicin, tobramycin), 4. Carbapenems (imipenem, meropenem, doripenem), 5. Piperacillin Group (piperacillin, piperacillin/tazobactam)	Any isolate that tested either (I) or (R) to at least 1 drug in at least 3 of the medication categories	Any with at least 1 susceptible (S) or non-susceptible result (I, R) to at least 1 drug in the medication categories
Drug-Resistant *Candida*	*Candida* spp.	N/A	*Candida*-positive results are any isolate identified as *Candida* in the microbiology tables regardless of sensitivity testing; *Candida* positives are multiplied by %R from Emerging Infections Program (EIP) data	Any isolate identified as *Candida* in the microbiology tables regardless of sensitivity testing

*Accounted for cascade reporting by assuming isolates of Enterobacteriaceae to be carbapenem-susceptible if no carbapenem susceptibility result was reported but the isolate was reported to be susceptible to >1 of the following: ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, or cefotetan

**Accounted for cascade reporting by assuming isolates of Enterobacteriaceae to be susceptible to third and fourth generation cephalosporins if no susceptibility test results to these agents were reported but the isolate was reported to be susceptible to >1 of the following: ampicillin, piperacillin, aztreonam, or cefazolin.

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Publication Date: November 2019

Revised Dec. 2019
CS298821-C