



March 2020

ANTIBIOTIC RESISTANCE

Additional Federal Actions Needed to Better Determine Magnitude and Reduce Impact

Accessible Version

GAO Highlights

Highlights of [GAO-20-341](#), a report to congressional requesters

Why GAO Did This Study

Bacterial infections have become more difficult, and sometimes impossible, to treat due to antibiotic resistance, which occurs when bacteria develop the ability to defeat the available drugs designed to kill them. Concerns about rising rates of resistance to available treatment options prompted the federal government to create the 5-year National Action Plan in 2015. The plan called for federal agencies to strengthen surveillance, advance the development of diagnostic tests and new antibiotics, and slow the emergence of resistant bacteria, among other things.

GAO was asked to review federal efforts to address antibiotic resistance. This report examines federal efforts and challenges related to (1) surveillance of antibiotic resistance, (2) the development and use of diagnostic testing to identify antibiotic resistance, (3) the development of treatments for resistant infections, and (4) appropriate antibiotic use. GAO reviewed literature and agency documents; interviewed agency officials and health care industry, drug industry, and other stakeholders; and held a meeting of international and U.S. experts to obtain their views.

What GAO Recommends

GAO is making eight recommendations to strengthen the federal response to combating antibiotic resistance. HHS concurred with seven recommendations and did not concur with one. More details are provided on the next page.

View [GAO-20-341](#). For more information, contact Timothy M. Persons at (202) 512-6888 or personst@gao.gov, or Mary Denigan-Macauley at (202) 512-7114 or deniganmacauleym@gao.gov.

March 2020

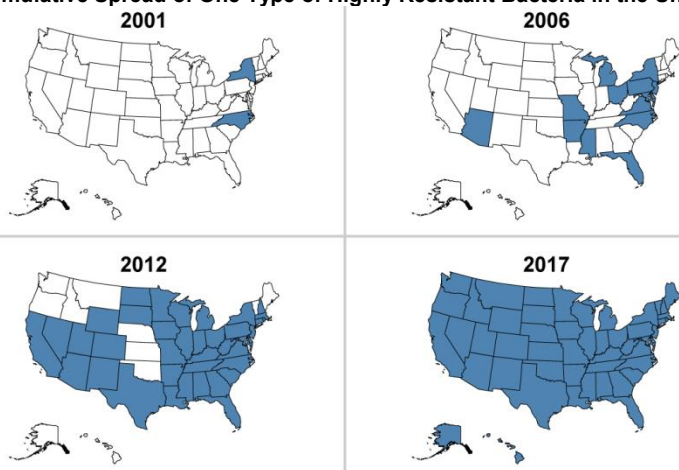
ANTIBIOTIC RESISTANCE

Additional Federal Actions Needed to Better Determine Magnitude and Reduce Impact

What GAO Found

The precise magnitude of the problem of antibiotic resistance is unknown. The Centers for Disease Control and Prevention (CDC) has made progress in expanding surveillance of infections from certain antibiotic-resistant bacteria in the United States and abroad but faces several challenges.

2001-2017 Cumulative Spread of One Type of Highly Resistant Bacteria in the United States



Source: Centers for Disease Control and Prevention (CDC). | GAO-20-341

Note: This figure tracks a type of carbapenem-resistant Enterobacteriaceae (CRE), which, according to CDC, is a "nightmare bacteria" resistant to nearly all available antibiotics. Shading indicates CDC confirmed the presence of these bacteria within that state in that year or a previous one.

CDC faces challenges in conducting surveillance for antibiotic resistance due to the limited data it is able to collect through various surveillance systems. For example, CDC's primary surveillance system for gonorrhea—which CDC classified as an urgent antibiotic resistance threat affecting over half a million patients annually—currently tracks only an estimated 1 to 2 percent of all U.S. cases and only in males. CDC has not fully evaluated the representativeness of the gonorrhea surveillance system's results. However, it could do so, for example, by comparing the trends in their limited sample population with trends it can establish in the overall U.S. population via additional studies. Such an evaluation could give CDC more confidence that the system's data accurately reflect national trends.

Federal agencies have taken steps to advance the development and use of diagnostic tests to identify antibiotic-resistant bacterial infections, but these efforts have limitations. For example, agencies have conducted some studies to establish whether testing can lead to positive health care outcomes, such as reduced rates of antibiotic-resistant infections. However, more such studies are needed, according to experts and agency officials. Without information to guide test usage, clinicians may not be able to select appropriate treatments for their patients. One reason for the insufficient number of studies is that Department of Health and Human Services (HHS) agencies that are in a position to conduct or fund such studies—such as CDC and the Biomedical Advanced Research and

What GAO Recommends

In response to the findings presented in this Highlights, GAO recommends that:

- CDC ensure that its evaluation of its surveillance system for antibiotic-resistant gonorrhea includes measures of the system's representativeness of the U.S. population;
- HHS identify leadership and clarify roles and responsibilities to assess the clinical outcomes of diagnostic testing;
- HHS develop a strategy to further incentivize the development of new treatments for antibiotic-resistant infections, including through the use of postmarket financial incentives;
- HHS direct the CARB Task Force to include in its annual updates to the President plans for addressing any barriers preventing full implementation of the National Action Plan.

In addition, GAO is making four recommendations to address other CDC efforts in surveillance and reporting and to address FDA efforts in monitoring diagnostic tests.

HHS did not concur with the recommendation that it develop a strategy that includes the use of postmarket financial incentives to encourage the development of new treatments for antibiotic-resistant infections, citing its ongoing analysis to understand whether postmarket incentives should be included in such a strategy. GAO recognizes the complexity of this issue and maintains that this recommendation is warranted given that experts and others have called for additional postmarket incentives and the insufficiency of the current pipeline of new treatments for antibiotic-resistant infections.

Development Authority—disagree about what each agency should do. By clarifying roles and responsibilities, HHS agencies could more effectively address the need for more studies. The resulting studies could help demonstrate the value of diagnostic tests for antibiotic resistance, potentially increasing their use and improving patient care.

Experts warn that the current pipeline of antibiotics in development is insufficient to meet the threat of resistance. Several challenges impede the development of new treatments for resistant infections, notably inadequate return on investment for drug companies largely due to low prices and a limited patient population for whom these treatments would be appropriate. While HHS and Department of Defense agencies have provided financial premarket incentives to support antibiotic research and development, experts, federal officials and antibiotic developers agree that more postmarket incentives are needed to overcome the economic challenges. Advisory groups, including a presidential advisory council, and others have called for new postmarket incentives and identified multiple options for their design, including market entry rewards and reimbursement reform (see figure). However, HHS has not developed a strategy to further incentivize development of new treatments for antibiotic-resistant infections, and it may need to request authority and appropriations to create and implement certain types of incentives. Until such incentives are developed, more drug companies may exit the antibiotic development sector, and the pipeline of new treatments may continue to decrease.

Examples of Possible Postmarket Incentive Options to Encourage the Development of Antibiotics Identified by Advisory Groups and Others

Market entry reward		Reimbursement reform	
A market entry reward could be awarded in addition to, or in replacement of, sales revenues			
Lump sum payment	Transferable voucher	Licensing arrangement	Add-on payment
<ul style="list-style-type: none"> • Monetary reward paid to developers of new antibiotics • Could be paid over multiple years 	<ul style="list-style-type: none"> • Voucher that could be sold or auctioned and would confer additional market exclusivity for a different pharmaceutical drug 	<ul style="list-style-type: none"> • Antibiotic purchasing arrangement in which hospitals would pay a fixed fee to access the drug, which would allow them to use a certain number of doses 	<ul style="list-style-type: none"> • Payments to hospitals for use of certain antibiotics that are made in addition to the bundled payment the hospital already receives for a patient's inpatient stay

Source: GAO summary of publicly available proposals. | GAO-20-341

Data for Highlight Examples of Possible Postmarket Incentive Options to Encourage the Development of Antibiotics Identified by Advisory Groups and Others

Market entry reward

A market entry reward could be awarded in addition to, or in replacement of, sales revenues

Lump sum payment

- Monetary reward paid to developers of new antibiotics
- Could be paid over multiple years

Transferable voucher

- Voucher that could be sold or auctioned and would confer additional market exclusivity for a different pharmaceutical drug

Reimbursement reform

Licensing arrangement

- Antibiotic purchasing arrangement in which hospitals would pay a fixed fee to access the drug, which would allow them to use a certain number of doses

Add-On payment

Payments to hospitals for use of certain antibiotics that are made in addition to the bundled payment the hospital already receives for a patient's inpatient stay

Federal agencies have made several efforts to promote the appropriate use of antibiotics across health care settings through antibiotic stewardship—giving patients the right antibiotic at the right time, in the right dose, and for the right duration. However, key challenges remain. For example, federal agencies require only certain types of health care facilities to implement stewardship programs. In addition, CDC is limited in its ability to monitor and improve appropriate antibiotic use, in part because providers are not generally required to report antibiotic use data to a centralized database. The 5-year *National Action Plan for Combating Antibiotic-Resistant Bacteria* (National Action Plan) calls for strengthening antibiotic stewardship and for the timely reporting of antibiotic use data across health care settings. An executive order directs an interagency task force—the Combating Antibiotic-Resistant Bacteria (CARB) Task Force, coordinated by HHS—to provide annual updates to the President on, among other things, plans for addressing any barriers to full implementation of the National Action Plan. However, in its progress reports covering the first 4 years of the National Action Plan’s implementation, the task force did not identify plans to address barriers to expanding antibiotic stewardship programs or the collection of antibiotic use data. Until it does so, the government will not have reasonable assurance that it is fully implementing the National Action Plan and addressing antibiotic resistance.

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Antimicrobial Susceptibility Test Devices 137

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AR Option	Antimicrobial Resistance Option
AU Option	Antimicrobial Use Option
AUR Module	Antimicrobial Use and Resistance Module
BARDA	Biomedical Advanced Research and Development Authority
CARB	Combating Antibiotic-Resistant Bacteria
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
CMS	Centers for Medicare & Medicaid Services
DOD	Department of Defense
eGISP	Enhanced Gonococcal Isolate Surveillance Project
EIP	Emerging Infections Program
FDA	Food and Drug Administration
GISP	Gonococcal Isolate Surveillance Program
GLASS	Global Antimicrobial Resistance Surveillance System
GPRA	Government Performance and Results Act
HHS	Department of Health and Human Services
LPAD	Limited Population Pathway for Antibacterial and Antifungal Drugs
MIPS	Merit-based Incentive Payment System
MRSA	Methicillin-resistant Staphylococcus aureus
NARMS	National Antimicrobial Resistance Monitoring System
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
QIDP	Qualified Infectious Disease Product
R&D	research and development
SURRG	Strengthening the United States Response to Resistant Gonorrhea
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance

VA
WHO

Department of Veterans Affairs
World Health Organization

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March 30, 2020

The Honorable Lamar Alexander
Chairman
The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Frank Pallone, Jr.
Chairman
The Honorable Greg Walden
Republican Leader
Committee on Energy and Commerce
House of Representatives

The Honorable Diana DeGette
Chair
The Honorable Brett Guthrie
Republican Leader
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

Since the discovery of penicillin in 1928, many life-saving antibiotics have been developed that have allowed previously incurable infections to be easily treated. However, many types of infections have become more difficult or impossible to treat as bacteria have developed resistance to most—or, in some cases, all—currently available antibiotics. The Centers for Disease Control and Prevention (CDC) considers antibiotic resistance

to be one of the greatest global public health threats of our time.¹ In 2019, CDC estimated that at least 2.8 million people get sick and at least 35,900 die each year from antibiotic-resistant infections in the United States.²

While bacteria naturally develop resistance to antibiotics over time, this problem has been accelerated by the overuse and misuse of antibiotics in

¹Antimicrobial resistance refers broadly to drug-resistant bacterial, fungal, viral, and other types of microbial infections. For the purpose of this report, we focused on antibiotic resistance. CDC uses the term “antibiotics” to refer to drugs that can kill bacteria or fungi. See Department of Health and Human Services, Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2019* (Atlanta, Ga.: Nov. 13, 2019), p. 7. Our review focused on resistance of bacteria against antibiotic drugs and did not focus on resistance of fungi against drugs. In contrast, under the Food, Drug and Cosmetic Act, the term “antibiotic drug” means “any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.” 42 U.S.C. § 321(jj). Note that under the definition under the 21st Century Cures Act, which amended Section 319E of the Public Health Service Act, that for certain purposes of the law, the term “antimicrobial” includes “any antibacterial or antifungal drugs, and may include drugs that eliminate or inhibit the growth of other microorganisms, as appropriate.” 42 U.S.C. § 247d-5(k).

²Centers for Disease Control and Prevention, *Antibiotic Resistance Threats, 2019*. In 2013, CDC had estimated at least 2 million people got sick and 23,000 people died each year from antibiotic-resistant infections; however, in its 2019 report, CDC revised its 2013 estimates by using new data sources and stated that the annual number of antibiotic-resistant infections in 2013 was at least 2.6 million, with 44,000 deaths. See Department of Health and Human Services, Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2013* (Atlanta, Ga.: Apr. 23, 2013).

A study funded by the European Centre for Disease Prevention and Control estimated 671,689 antibiotic-resistant infections and 33,110 deaths caused by antibiotic-resistant infections in 2015 throughout the European Union and the European Economic Area. In addition, the study estimated the health burden of five types of infections with antibiotic-resistant bacteria using a metric called disability-adjusted life-years. A. Cassini et al., “Attributable Deaths and Disability-Adjusted Life-Years Caused By Infections with Antibiotic-Resistant Bacteria in the EU and the European Economic Area in 2015: a Population-Level Modelling Analysis,” *Lancet Infectious Disease*, vol. 19, no. 1 (2019), pp. 56-66.

A 2014 study estimated that as many as 10 million people globally could die each year by 2050 if no action is taken to combat antimicrobial resistance. This study examined a limited number of types of bacteria, as well as other pathogens such as malaria, noting that this limitation resulted from a lack of readily available data. The Review on Antimicrobial Resistance, *Tackling a Crisis for the Health and Wealth of Nations*. (December 2014).

human health, food animals, and the environment. The World Health Organization (WHO) has warned that the world urgently needs to change the way antibiotics are prescribed and used, and CDC has highlighted the need for antibiotics to be used more appropriately—a concept called antibiotic stewardship—to preserve their effectiveness and help slow the development of antibiotic resistance.³ CDC officials noted that poor infection control and limited communication between health care facilities also contribute to the spread of antibiotic resistance. Furthermore, WHO and others warned that the pipeline of antibiotics in development is insufficient to tackle the growing threat of antibiotic resistance.⁴ Additionally, diagnostic testing used to identify antibiotic-resistant bacteria is not available for all bacteria of concern. These gaps may hinder the correct diagnosis of antibiotic-resistant infections, which could delay treatment with appropriate antibiotics, contribute to antibiotic overuse, and impede overall surveillance efforts.⁵

Recognizing the growing threat of antibiotic resistance, by Executive Order No. 13676, September 2014, the President established the Task Force for Combating Antibiotic-Resistant Bacteria (CARB Task Force), co-chaired by the Secretaries of the Departments of Health and Human Services (HHS), Defense (DOD), and Agriculture.⁶ In 2015, the CARB Task Force issued the *National Action Plan for Combating Antibiotic-Resistant Bacteria* (hereafter referred to as the National Action Plan), setting forth goals over 5 years to slow the development of resistant bacteria, strengthen national surveillance efforts, advance the development and use of diagnostic tests, and accelerate the development

³World Health Organization, “Antibiotic Resistance,” accessed February 13, 2020, <https://www.who.int/en/news-room/fact-sheets/detail/antibiotic-resistance>. WHO is the Geneva-based coordinating authority on international health within the United Nations system.

CDC defines antibiotic stewardship as the effort to measure and optimize antibiotic use with the goal of optimizing the treatment of infections while reducing the adverse events associated with antibiotic use. Antibiotic stewardship aims to have all patients treated with the right antibiotic at the right time, in the right dose, and for the right duration for a given diagnosis.

⁴World Health Organization, *2019 Antibacterial Agents in Clinical Development: An Analysis of the Antibacterial Clinical Development Pipeline* (Geneva, Switzerland: 2019).

⁵Disease surveillance is the process of reporting, collecting, analyzing, and exchanging information related to cases of infectious diseases.

⁶Exec. Order No. 13676, *Combating Antibiotic-Resistant Bacteria*, 79 Fed. Reg. 56931 (Sept. 23, 2014).

of new treatments, among other things.⁷ Because of the severity of the problem that antibiotic resistance presents for humans and the federal government's commitment to fight it, you asked us to provide information on federal efforts to combat antibiotic resistance. This report examines

1. CDC's efforts to conduct surveillance of antibiotic resistance and any challenges to these efforts;
2. federal efforts to advance the development and use of tests for diagnosing antibiotic-resistant infections;
3. challenges to developing new treatments for antibiotic-resistant infections and federal efforts to address the challenges; and
4. federal efforts to promote the appropriate use of antibiotics and any challenges that remain.

To address all four objectives, we reviewed relevant agency reports and documents; interviewed officials from federal agencies, experts on topics related to antibiotic resistance, and representatives from stakeholder organizations; reviewed relevant laws, regulations, policies, literature, and GAO reports; and attended two national conferences.⁸ We focused our review primarily on agency actions since 2015, when the National Action Plan was published. We also focused our review on human health, as we have reported on federal efforts to address the use of antibiotics in food animals and recommended actions to improve these efforts for more than 20 years.⁹ Additionally, we focused our review on antibiotic-resistant bacteria. Finally, we generally excluded federal efforts related to infection

⁷The White House, *National Action Plan for Combating Antibiotic-Resistant Bacteria* (Washington, D.C.: March 2015).

⁸The two conferences were the World Anti-Microbial Resistance Congress and the Gordon Research Conference on chemical and biological threat defense.

⁹GAO, *Antibiotic Resistance: More Information Needed to Oversee Use of Medically Important Drugs in Food Animals*, [GAO-17-192](#) (Washington, D.C.: Mar. 2, 2017); *Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals*, [GAO-11-801](#) (Washington, D.C.: Sept. 7, 2011); *Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals*, [GAO-04-490](#) (Washington, D.C.: Apr. 22, 2004); and *Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health*, [GAO/RCED-99-74](#) (Washington, D.C.: Apr. 28, 1999).

prevention and control in human health care, on which we have previously reported.¹⁰

We interviewed officials from federal agencies responsible for implementing the aspects of the National Action Plan related to our objectives: HHS's Office of the Assistant Secretary for Planning and Evaluation, the Biomedical Advanced Research and Development Authority (BARDA), CDC, the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Office of Global Affairs; as well as DOD and the Department of Veterans Affairs (VA). We also interviewed experts and representatives from organizations involved in public health and epidemiology, infectious diseases and microbiology, antibiotic research and development (R&D), antibiotic stewardship, and other issues relating to antibiotic resistance. Because antibiotic resistance is a global problem, we also interviewed officials from WHO and other international entities. We identified experts and organizations through literature and other documents we reviewed and through referrals from agency officials and other experts we interviewed. In addition, in September 2018, with the assistance of the National Academy of Sciences, we convened a meeting of experts in antibiotic resistance epidemiology, diagnostic testing, antibiotic development, and antibiotic stewardship. (In this report, we refer to such experts as "experts at our meeting.") For each of our objectives, we identified and reported on actions taken by federal agencies to address antibiotic resistance, and we evaluated these actions against relevant criteria, as applicable, such as Standards for Internal Control in the Federal Government and GAO's leading practices on interagency collaboration.¹¹

To examine CDC's efforts to conduct surveillance for antibiotic resistance and any challenges to these efforts, we reviewed documentation and conducted interviews with agency officials and other key stakeholders on each of the surveillance systems across CDC that collects antibiotic resistance data and reviewed CDC's *Antibiotic Resistance Threats in the*

¹⁰GAO, *Health-Care-Associated Infections in Hospitals: Leadership Needed from HHS to Prioritize Prevention Practices and Improve Data on These Infections*, [GAO-08-283](#) (Washington, D.C.: Mar. 31, 2008).

¹¹GAO, *Standards for Internal Control in the Federal Government*, [GAO-14-704G](#) (Washington, D.C.: Sept. 10, 2014) and *Managing for Results: Key Considerations for Implementing Interagency Collaborative Mechanisms*, [GAO-12-1022](#) (Washington, D.C.: Sept. 27, 2012).

United States, 2013 (2013 Threats Report) and *Antibiotic Resistance Threats in the United States, 2019* (2019 Threats Report) reports.¹² This included a review of health care facility participation data by state and territory in a CDC antibiotic resistance reporting system. We assessed the reliability of these data by reviewing them for any outliers or anomalies and inquiring with agency officials about their source and any known reliability issues. We determined that these data were sufficiently reliable for assessing facility participation rates by U.S. state and territory. We also reviewed documents from WHO's Global Antimicrobial Resistance Surveillance System and interviewed WHO and CDC officials to identify challenges that limit CDC's ability to assess threats from abroad.

To examine federal efforts to advance the development and use of diagnostic tests, we also interviewed a nongeneralizable sample of six diagnostic test manufacturers to encompass different types of tests, based a list of manufacturers compiled from our previous work, interviews with select experts, and internet research. We limited our scope to FDA-authorized tests—which we are defining as tests that have been reviewed and cleared or granted authorization by FDA for marketing in the United States—that can identify resistance in at least one type of bacteria categorized as a priority in CDC's 2013 Threats Report.¹³ Some of these tests are called antibiotic susceptibility tests, but we use “tests” to refer to the entire class of such tests. We included in our scope tests that can differentiate between viral and bacterial infections, because these types of tests are included in the National Action Plan.

To identify challenges to developing new treatments for antibiotic-resistant infections and examine federal efforts to address these challenges, we also reviewed literature and reports written by health policy advisory groups on topics related to antibiotic development challenges and incentives for development. Our examination of challenges and related federal actions focused on treatments and, therefore, did not include products designed to prevent infections, such as

¹²We started our audit work in 2018, prior to the issuance of CDC's 2019 Threats Report.

¹³FDA officials told us that the tests under our review are Class II devices and are appropriately referred to as cleared when granted marketing authorization. For a further description of device classes, see our previous report, GAO, *Medical Devices: Challenges and Capabilities to Enable Rapid Diagnoses of Infectious Diseases*, [GAO-17-347](#) (Washington, D.C.: Aug. 14, 2017). Other types of diagnostic tests, such as laboratory-developed tests, are not within the scope of this report. FDA describes laboratory-developed tests as tests designed, manufactured, and used within a single laboratory.

vaccines. We also interviewed 11 randomly selected companies that conduct R&D on new treatments for bacterial infections.¹⁴

To examine federal agency efforts to promote the appropriate use of antibiotics and any challenges that remain, we also analyzed CMS data and related documentation on quality measures and improvement activities related to antibiotics. We reviewed the data for any obvious outliers or anomalies and determined that these data were sufficiently reliable for reporting on the number of clinicians who reported implementing these quality measures and improvement activities. In addition, we reviewed aggregated data from CDC on the total number of eligible U.S. hospitals reporting their antibiotic use data to a CDC system. We assessed the reliability of the aggregated data by reviewing them for any obvious errors or missing data totals and inquiring with agency officials about their source and any known reliability issues. We determined that these data were sufficiently reliable for reporting hospital participation rates in CDC's antibiotic use reporting system. We focused our review on antibiotic use in the United States, rather than global antibiotic use.

Appendix I contains more detailed information on the scope and methodology of our review. Appendixes I and II contain more detailed information about our expert meeting.

We conducted this performance audit from February 2018 to March 2020 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

¹⁴We selected from among companies that are researching or developing antibiotics and alternatives to antibiotics—which we call “nontraditional products” in this report—and we included companies that do and do not have existing FDA-approved drugs on the market.

Background

Antibiotics are drugs that work by killing bacteria or slowing their growth.¹⁵ However, some bacteria have developed ways to resist the effects of antibiotics, for example, by preventing antibiotics from entering the cell or pumping them out after the antibiotic enters. Bacteria that are able to survive in the presence of antibiotics will multiply and pass on their new genetic material that confers resistance to future generations of bacteria and, in some cases, to other types of bacteria.¹⁶ Resistance can arise in bacteria in humans, animals, and the environment, including in health care settings, and can spread through contact with infected people or animals, contact with contaminated water, soil or surfaces, or consumption of contaminated food.¹⁷

The spread of antibiotic resistance threatens not only the ability to fight bacterial infections but also threatens to reverse some significant medical gains. For example, in addition to treating infections, antibiotics have allowed for numerous medical procedures, such as joint replacements, caesarian sections, organ transplants, chemotherapy, and dialysis—all of which would be significantly riskier without effective antibiotics. Antibiotic resistance also poses a significant economic burden resulting from the direct costs of treating those with resistant infections and the loss of economic productivity from those who get sick or die.¹⁸

¹⁵We note that in its 2019 report, consistent with applicable authorities, CDC uses the term “antibiotics” to refer to drugs that can kill bacteria or fungi. CDC’s *Antibiotic Resistance Threats, 2019*, p. 7. See also, 21 U.S.C. § 321(jj); 42 U.S.C. § 247d-5(k). However, as we explained previously, we have only considered those antibiotics that can kill bacteria.

¹⁶Scientists have identified more than 1,600 genes that confer resistance for bacteria. Of significant global scientific concern is the *mcr* gene, which confers resistance to polymyxins, known as the “drugs of last resort” for treating certain types of infections. The *mcr* gene was first discovered in China in 2015 but has since been found in bacteria cultured from humans and animals on at least five continents, including in the United States.

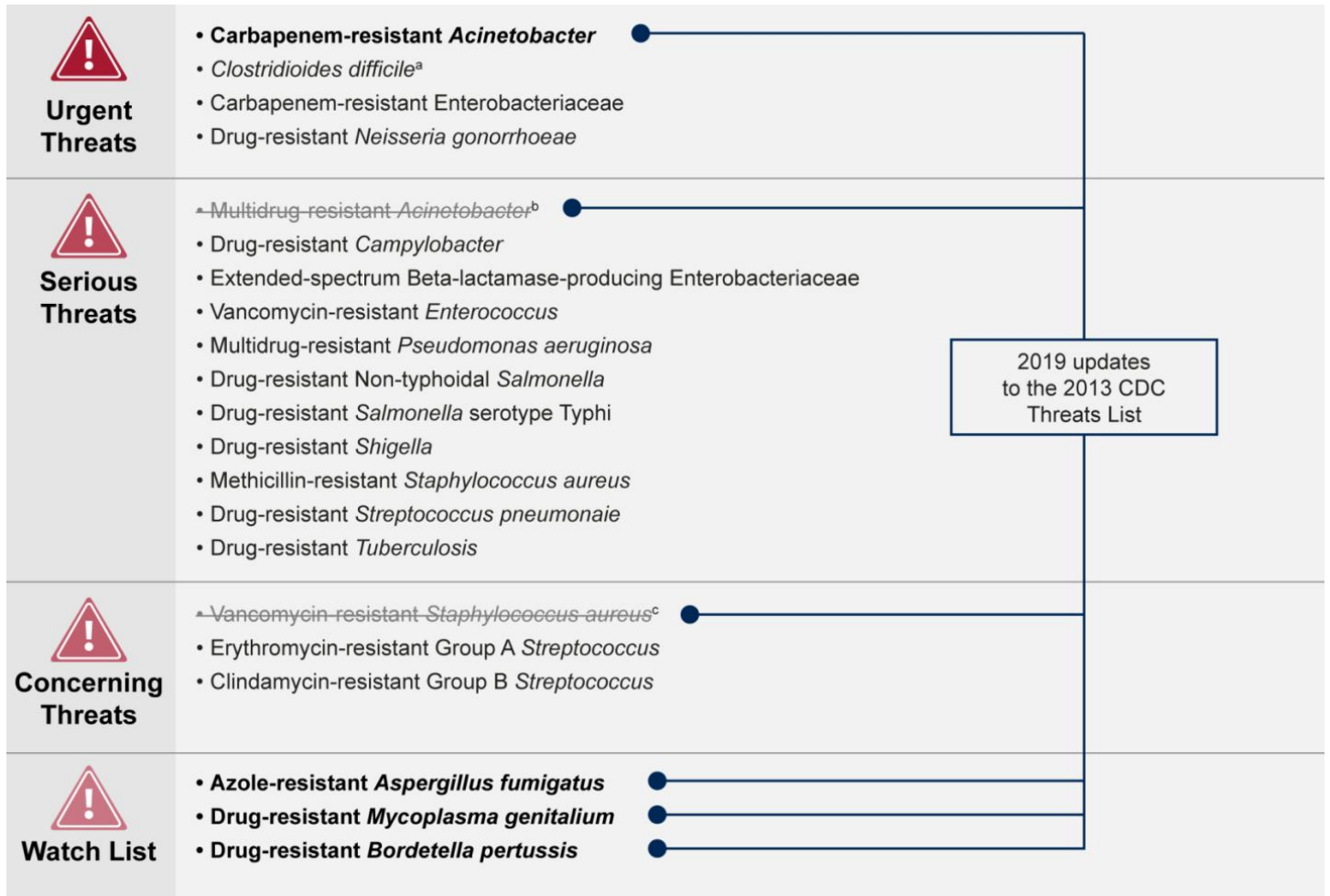
¹⁷The National Action Plan includes a goal to strengthen surveillance of antibiotic resistance using a “One-Health” approach, which recognizes the interaction between humans, animals, and the environment.

¹⁸According to CDC, antibiotic-resistant infections require extended hospital stays, additional follow-up visits to health care providers, and the use of treatments that may be more costly and potentially more toxic.

In the 2013 Threats Report, CDC identified 17 bacterial pathogens that the agency considers to be “urgent,” “serious,” or “concerning” because they have developed enough resistance to antibiotics to be considered a threat to human health. (See fig. 1.) According to CDC, certain types of bacteria, called gram-negative bacteria, are particularly worrisome because they are becoming resistant to nearly all drugs that would be considered for treatment.¹⁹

¹⁹Gram-negative bacteria are characterized by a double cell membrane, which can pose as a barrier to antibiotics trying to enter the cell, and pumps that can expel antibiotics from the cell.

Figure 1: Bacteria CDC Considered to Be Threats in 2013 and 2019



Source: Centers for Disease Control and Prevention (CDC). | GAO-20-341

Data table for Figure 1: Bacteria CDC Considered to Be Threats in 2013 and 2019

Threat level	Bacteria
Urgent Threats	Carbapenem-resistant <i>Acinetobacter</i> (2019 update to the 2013 CDC Threats List) <i>Clostridioides difficile</i> ^a Carbapenem-resistant Enterobacteriaceae Drug-resistant <i>Neisseria gonorrhoeae</i>
Serious Threats	Multidrug-resistant <i>Acinetobacter</i> ^b (removed from serious threat level in 2019 update to the 2013 CDC Threats List) Drug-resistant <i>Campylobacter</i> Extended-spectrum Beta-lactamase-producing Enterobacteriaceae Vancomycin-resistant <i>Enterococcus</i> Multidrug-resistant <i>Pseudomonas aeruginosa</i> Drug-resistant Non-typhoidal <i>Salmonella</i> Drug-resistant <i>Salmonella</i> serotype Typhi Drug-resistant <i>Shigella</i> Methicillin-resistant <i>Staphylococcus aureus</i> Drug-resistant <i>Streptococcus pneumoniae</i> Drug-resistant <i>Tuberculosis</i>
Concerning Threats	Vancomycin-resistant <i>Staphylococcus aureus</i> ^c (removed from concerning threat level in 2019 update to the 2013 CDC Threats List) Erythromycin-resistant Group A <i>Streptococcus</i> Clindamycin-resistant Group B <i>Streptococcus</i>
Watch List (2019 updates to the 3013 CDC Threats List)	Azole-resistant <i>Aspergillus fumigatus</i> Drug-resistant <i>Mycoplasma genitalium</i> Drug-resistant <i>Bordetella pertussis</i>

Note: In 2013, CDC also considered fluconazole-resistant *Candida*, which is a fungus, to be a serious threat. In 2019, CDC added *Candida auris* as an urgent threat and focused on drug-resistant *Candida* as a serious threat.

^a*Clostridioides difficile* was formerly known as *Clostridium difficile*.

^bIn 2019, CDC shifted *Acinetobacter* from its list of serious threats to its list of urgent threats because of the emergence of easily spread resistance and the lack of antibiotics currently available or in development to treat these infections. CDC also reported that, in 2019, they focused on “carbapenem-resistant” *Acinetobacter*, instead of “multidrug-resistant” *Acinetobacter*.

^cCDC dropped Vancomycin-resistant *Staphylococcus aureus* from its threats list in 2019, noting that the 14 identified cases of infection with this bacteria were considered isolated cases, and spread from patient to patient has never been documented.

The most serious gram-negative infections can be acquired in hospitals or other health care settings and can cause pneumonia, bloodstream infections, wound or surgical site infections, and meningitis. Nine of the 17 bacterial threats on CDC’s threat list are gram-negative. One of the bacteria CDC considers to be an urgent threat—*Clostridioides difficile* (*C. difficile*)—is classified as a threat not because it is resistant to antibiotics, but because it is caused by the same factors that drive antibiotic

resistance, such as antibiotic use. CDC estimates that *C. difficile* alone accounted for 12,800 deaths in U.S. hospitals in 2017.²⁰ CDC's 2013 Threats Report also identified one type of fungus—*Candida auris*—that it considered to be a serious threat (see text box).

***Candida auris* Is a Resistant Fungal Threat**

Candida auris (*C. auris*) is an emerging infectious fungus that, according to the Centers for Disease Control and Prevention (CDC), presents a global health threat in part because it is highly resistant to anti-fungal drugs and is challenging to address. *C. auris* was first identified in Japan in 2009. CDC reported 806 confirmed cases in the United States, as of August 31, 2019. According to CDC, *C. auris* is highly transmissible and some commonly used hospital surface disinfectants appear to be less effective against *C. auris*. A CDC official told us *C. auris* is a good example of an emerging threat that requires more research and associated efforts to properly address.

Addressing *C. auris* is challenging for reasons including the rise of resistance and limitations in diagnostic tests. According to CDC, there are three classes of antifungals available to treat *C. auris*. However, CDC has identified strains that are resistant to all three classes. A CDC official noted that getting new antifungals to market is challenging because, among other things, the demand for antifungals, relative to antibiotics, is low. Additionally, according to FDA, although reliable tests for identifying *C. auris* exist, commonly used laboratory tests may misidentify this fungus, posing a barrier to correct diagnosis. In 2018, the Food and Drug Administration (FDA) cleared a test based on mass spectrometry to identify *C. auris*, but this test cannot characterize resistance. FDA officials told us there are three FDA-cleared tests available for testing for other *Candida* species' resistance to fluconazole. However, none of these tests can provide rapid results, such as within an hour. Finally, interpretation of culture-based diagnostic tests, which examine how well bacteria grow in the presence of an antibiotic, is challenging due to the lack of established interpretive criteria for *C. auris*, by both the Clinical and Laboratory Standards Institute, which promotes the development and use of voluntary laboratory consensus standards and guidelines within the health care community, and by FDA.

Source: GAO summary of CDC interviews and website and FDA interviews. | GAO-20-341

U.S. spending on antibiotics in health care from 2010 through 2015 was estimated in one study to be nearly \$56 billion, ranging from \$8.4 billion to \$10.6 billion annually.²¹ While CDC states that antibiotic prescribing improved nationally with a 5 percent decrease from 2011 to 2016, the agency estimated in 2017 that at least 30 percent of antibiotics used across both outpatient and inpatient settings are still prescribed unnecessarily or incorrectly and, therefore, are considered

²⁰The deaths caused by *C. difficile* are not included in the 35,000 deaths that CDC attributed to antibiotic-resistant infections in CDC's *Antibiotic Resistance Threats, 2019*. *Clostridioides difficile* was formerly known as *Clostridium difficile*.

²¹Spending estimates were based on an analysis of data on purchases by health care settings and public services in the United States. See K. J. Suda et al., "Antibiotic Expenditures by Medication, Class, and Healthcare Setting in the United States, 2010-2015," *Clinical Infectious Diseases*, vol. 66, no. 2 (2018): pp. 185-90.

inappropriate.²² According to CDC, approximately 85 to 95 percent of the nation’s antibiotic use, by volume, occurred in outpatient settings from 2010 through 2015; and roughly 270 million antibiotic prescriptions—equivalent to 836 per 1,000 persons in the United States—were written in these settings in 2016. (For more information on antibiotic use in the United States, see text box.)

Antibiotic Use in the United States

A 2017 Centers for Disease Control and Prevention (CDC) report estimates that about 30 percent of antibiotics used in U.S. hospitals are inappropriate (unnecessary or prescribed incorrectly), and as much as 50 percent of antibiotics prescribed in outpatient settings—such as physicians’ offices, emergency departments, urgent care centers, and retail clinics—may be inappropriate. For example, CDC reports that each year, an estimated 47 million unnecessary antibiotic prescriptions are written in physicians’ offices and emergency departments. Most of these unnecessary prescriptions are for respiratory conditions most commonly caused by viruses—including common colds, viral sore throats, and bronchitis—that do not respond to antibiotics, or for bacterial infections that do not always need antibiotics, like many sinus and ear infections. Furthermore, CDC reports that even when antibiotics are needed, prescribers often favor drugs that may be less effective and may carry more risk over more targeted, “first-line” drugs recommended by nationally recognized antibiotic prescribing guidelines. (First-line drugs are the drugs generally recommended for initial treatment for a given diagnosis, often combining the best efficacy with the best safety profile or the lowest cost.) According to CDC, antibiotics are among the most frequently prescribed medications in nursing homes, with up to 70 percent of residents receiving one or more courses of systemic (non-topical) antibiotics in a year; CDC also cites studies showing that 40 to 75 percent of antibiotics prescribed in nursing homes may be inappropriate. CDC further reports that harms from antibiotic overuse include the risk of serious diarrheal infections from *C. difficile*, increased adverse drug events and drug interactions, and increased risk of infection with antibiotic-resistant organisms.

Source: CDC, *Antibiotic Use in the United States, 2017: Progress and Opportunities* (Atlanta, Ga.: 2017), *The Core Elements of Antibiotic Stewardship for Nursing Homes* (Atlanta, Ga.: 2015), and “Measuring Outpatient Antibiotic Prescribing,” accessed August 27, 2019, <https://www.cdc.gov/antibiotic-use/community/programs-measurement/measuring-antibiotic-prescribing.html>. | GAO-20-341

²²Department of Health and Human Services, Centers for Disease Control and Prevention, *Antibiotic Use in the United States, 2017: Progress and Opportunities* (Atlanta, Ga.: 2017) and *Antibiotic Use in the United States, 2018 Update: Progress and Opportunities* (Atlanta, Ga.: 2019).

According to CDC officials, “unnecessary” antibiotic use means the antibiotic was prescribed when no antibiotic was needed, based on clinical practice guidelines. “Inappropriate” antibiotic use includes both unnecessary antibiotic use, as well as inappropriate antibiotic selection, dosing, or duration when antibiotics are indicated. CDC officials also told us they consider “misuse” and “inappropriate use” to be synonymous terms.

The National Action Plan and Federal Agency Responsibilities

Vaccines Can Also Help Prevent Antibiotic Resistance

While we did not include vaccines in the scope of this report, vaccines play a role in helping combat antibiotic resistance because they are designed to prevent infections, including resistant infections. In addition, by preventing infections from occurring, they can reduce the need to use antibiotics, which in turn, can slow the development of antibiotic resistance. For example, according to the Centers for Disease Control and Prevention (CDC), since introduction of the pneumococcal conjugate vaccine among children in 2000, rates of antibiotic-resistant infections caused by certain *Streptococcus pneumoniae* strains decreased by 97 percent among children under 5 and by more than 60 percent among adults. However, few vaccines are available that target antibiotic-resistant bacteria on CDC's threat list.

Source: GAO summary of CDC information. | GAO-20-341

In September 2014, the President signed Executive Order No. 13676 (Executive Order), which directed that several federal actions be initiated related to antibiotic resistance. For example, the Executive Order directed the creation of the National Action Plan, which the White House released in 2015, to provide a roadmap for federal agencies to respond to the threat of antibiotic resistance.²³ The National Action Plan set five major goals over 5 years related to (1) slowing the emergence of resistant bacteria and preventing the spread of resistant infections; (2) strengthening national One-Health surveillance efforts to combat resistance;²⁴ (3) advancing the development and use of rapid and innovative diagnostic tests for the identification and characterization of resistant bacteria; (4) accelerating basic and applied R&D for new antibiotics, other therapeutics, and vaccines; and (5) improving international collaboration and capacities related to the first four goals.²⁵ In addition, the National Action Plan discusses the importance of preventing and controlling infections, such as through rapid detection, to combat antibiotic resistance domestically and globally (see text box). Within each of these five goals, the National Action Plan contains numerous objectives, sub-objectives, agency-specific milestones, and other performance targets called significant outcomes. For example, the National Action Plan set a significant outcome of reducing inappropriate antibiotic use by 50 percent in outpatient settings and by 20 percent in inpatient settings by 2020.

²³Exec. Order No. 13676 (Sept. 23, 2014).

²⁴One-Health recognizes the interaction between humans, animals, and the environment.

²⁵Similarly, the objectives of WHO's *Global Action Plan on Antimicrobial Resistance* are to (1) improve awareness and understanding of antimicrobial resistance through effective communication, education, and training; (2) strengthen the knowledge and evidence base through surveillance and research; (3) reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures; (4) optimize the use of antimicrobial medicines in human and animal health; and (5) develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions. World Health Organization, *Global Action Plan on Antimicrobial Resistance* (Geneva, Switzerland: 2015).

Infection Prevention and Control

According to the World Health Organization (WHO), effective infection prevention and control measures are a practical and scientific approach to reduce health care-associated infections in patients and health care workers, and help combat antibiotic resistance. Infection prevention and control measures serve as the cornerstone of actions needed to address epidemics, pandemics, and antibiotic resistance. Such measures include implementing hand hygiene practices, providing vaccinations, cleaning and disinfecting hospital rooms, isolating patients with infectious diseases, decontaminating and sterilizing medical equipment, and tracking data about emerging infectious diseases. WHO states that health care-associated infections are a global challenge from which no country or health care facility is immune. The Centers for Disease Control and Prevention (CDC) has taken actions to address and track health care-associated infections, including antibiotic-resistant infections. For example, in 2009, CDC issued guidance for infection control targeting Enterobacteriaceae that may be resistant to carbapenem, a class of antibiotics. In 2018, CDC published a study suggesting that a tracked decline in the proportion of resistant bacteria, including carbapenem-resistant Enterobacteriaceae, observed in some health care settings, could be attributable—at least in part—to actions such as those outlined in its 2009 guidance. In addition, CDC has reported that U.S. hospitals have made major progress since 2005 in declining rates of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia because of infection prevention measures.

Source: GAO summary of WHO and CDC documents. | GAO-20-341

The interagency CARB Task Force, which was created by the Executive Order to issue and monitor the implementation of the National Action Plan, is co-chaired by the Secretaries of Defense, Agriculture, and HHS, and is additionally comprised of representatives from VA and several other agencies. Representatives from HHS agencies—including BARDA, CDC, CMS, FDA, and NIH—make up nearly two-thirds of the task force's participants (see table 1). According to the HHS Assistant Secretary for Planning and Evaluation officials who coordinate it, the task force is developing a new National Action Plan that will span the years 2020 through 2025. To provide additional advice to the CARB Task Force and the Secretary of HHS, the Executive Order also created the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), which is composed of 15 non-governmental members.²⁶

²⁶Exec. Order No. 13676, § 4 Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, 79 Fed. Reg. 56931 (Sept. 23, 2014); continued by Exec. Order No. 13708 § 1(jj), 80 Fed. Reg. 60271 (Sept. 30, 2015), and Exec. Order No. 13811 § 1(z), 82 Fed. Reg. 46363 (Sept. 29, 2017). In June 2019, Congress passed the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019, which transitioned authority for the PACCARB from Executive Order to law. Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019, Pub. L. No. 116-22, § 505, 133 Stat. 905 (June 24, 2019), 42 U.S.C. § 247d-5, note.

PACCARB has produced four reports, including one published in July 2019 with recommendations for the next National Action Plan.

Table 1: Examples of Key Roles and Responsibilities of Select Department of Health and Human Services Agencies Related to Combating Antibiotic Resistance

Agency	Examples of key roles and responsibilities
Agency for Healthcare Research and Quality (AHRQ)	AHRQ’s mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable. AHRQ funds research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship. AHRQ also conducts nationwide projects that work with front-line clinicians to promote the implementation of evidence-based methods for infection prevention and antibiotic stewardship in hospitals, long-term care, and ambulatory care settings.
Biomedical Advanced Research and Development Authority (BARDA)	BARDA’s mission is to help secure the nation from chemical, biological, radiological, and nuclear threats, as well as from pandemic influenza and emerging infectious diseases. Through public-private partnerships, BARDA invests in products, such as antibiotics and diagnostic tests, which can be used to fight the threat of antibiotic resistance. BARDA, along with the National Institutes of Health, helped launch the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) in 2016, which is a public-private international partnership that funds research and development of new antibiotics, diagnostic tests, vaccines, and other treatments to combat antibiotic resistance. ^a
Centers for Disease Control and Prevention (CDC)	CDC has a primary responsibility to protect the public health through the prevention of disease and health promotion. CDC monitors the emergence of antibiotic-resistant infections and the use of antibiotics. CDC provides state and local health departments with resources to detect and track antibiotic-resistant pathogens, support antibiotic-resistance experts to implement infection control activities, and respond to outbreaks to stop the spread, in addition to promoting appropriate use of antibiotics in human health care to prevent the emergence of new resistance. CDC also supports research on and implements prevention strategies, such as educational programs targeting the public and health care providers that are designed to provide information on the appropriate use of antibiotics.
Centers for Medicare & Medicaid Services (CMS)	CMS is responsible for administering the Medicare and Medicaid programs. Medicare provides federally financed health insurance coverage to people age 65 and older and certain other individuals. Medicaid is a joint federal-state program that finances health care coverage for low-income and medically needy individuals. CMS sets payment rates for Medicare beneficiaries receiving treatment in hospitals, including those with antibiotic-resistant infections. In addition, CMS determines patient health and safety requirements for certain types of health care facilities (such as hospitals and nursing homes) participating in the Medicare and Medicaid programs. ^b CMS also administers other programs designed to improve the quality of health care provided to Medicare and Medicaid beneficiaries as well as other patients.
Food and Drug Administration (FDA)	Part of FDA’s responsibility for protecting the public health involves ensuring the safety and efficacy of human drugs and medical devices marketed in the United States, including antibiotics and diagnostic tests. FDA reviews and approves drugs, reviews and authorizes marketing for diagnostic devices, and provides educational information to consumers and health care providers about the appropriate use of antibiotics. FDA also approves, regulates, and collects data on antibiotics used in food animals, and monitors antibiotic-resistant bacteria in retail meat and poultry.
National Institutes of Health (NIH)	NIH’s mission is to apply fundamental knowledge about living systems to enhance health, lengthen life, and reduce illness and disability. According to NIH officials, NIH and its National Institute of Allergy and Infectious Diseases (NIAID) fund and conduct research to better understand how antibiotic resistance develops, and supports the research and development of new diagnostic tests, treatments, and vaccines for antibiotic-resistant infections. For example, NIAID’s Antibacterial Resistance Leadership Group provides extramural funding to a global consortium of scientific experts leading clinical research on important scientific questions related to antibiotic resistance.
Office of Global Affairs	The Office of Global Affairs represents the United States in international negotiations that set the worldwide agenda to address antibiotic resistance and coordinates across federal agencies to inform policies and programs. The office co-chairs the Transatlantic Task Force on Antimicrobial Resistance on behalf of the Department of Health and Human Services.

Source: Department of Health and Human Services documentation and prior GAO reports. | GAO-20-341

^aCARB-X restricts its funding to projects that target drug-resistant bacteria identified by CDC as a serious or urgent threat in its 2013 Threats Report, or by the World Health Organization as a critical or high threat.

^bCMS refers to these health and safety requirements as Conditions of Participation or Conditions for Coverage, depending on the type of health care facility.

The Executive Order also charged the CARB Task Force with providing annual updates to the President regarding progress made in implementing the National Action Plan, plans to address any barriers preventing its full implementation, and recommendations for any new or modified actions, taking federal government resources into consideration. Since 2015, the CARB Task Force has produced four progress reports, which summarize agency actions toward meeting the goals and milestones laid out in the National Action Plan; these reports were provided to the President and are publicly available.²⁷

CDC Has Expanded Surveillance of Antibiotic Resistance, but Faces Challenges Determining the Magnitude of the Problem

Since the National Action Plan was released in 2015, CDC has made progress in expanding surveillance for antibiotic resistance in the United States and abroad. However, the magnitude of the problem and its trends over time remain unknown, in part because of challenges in three areas: (1) tracking antibiotic resistance across all health care settings, (2) reporting complete and timely information on magnitude and trends of antibiotic resistance, and (3) tracking and assessing the global antibiotic resistance threat.

CDC Has Expanded Surveillance of Priority Bacteria

To better assess the full extent of antibiotic resistance, CDC has expanded its surveillance of priority bacteria in the United States in order

²⁷United States Taskforce for Combating Antibiotic-Resistant Bacteria (CARB Task Force), *National Action Plan for Combating Antibiotic-Resistant Bacteria: First 180 Days Report* (November 2015), *National Action Plan for Combating Antibiotic-Resistant Bacteria: Progress Report for Years 1 and 2* (October 2017), *National Action Plan for Combating Antibiotic-Resistant Bacteria: Progress Report: Year 3* (October 2018), and *National Action Plan for Combating Antibiotic-Resistant Bacteria: Progress Report: Year 4* (September 2019).

to better assess the full extent of antibiotic resistance since the 2015 National Action Plan was released.

CDC tracks antibiotic resistance through several infectious disease surveillance systems in collaboration with state and local health officials, health care providers and facilities, and laboratories.²⁸ Rather than establishing a single surveillance system for antibiotic resistance, CDC generally incorporates tracking of antibiotic resistance into broader surveillance systems, according to agency officials. The surveillance systems are spread across various divisions within CDC that specialize in specific types of infection or certain settings. (See table 2 for a description of each system and the resistant bacteria it tracks.)

Table 2: Description of Centers for Disease Control and Prevention (CDC) Surveillance Systems and Priority Bacteria Tracked

Surveillance system	Description of system	Priority bacteria tracked
Antibiotic Resistance Laboratory Network (AR Lab Network)	The AR Lab Network provides nationwide lab capacity to rapidly detect antibiotic resistance in health care, food, and the community, and inform local responses to prevent spread and protect people. It includes labs in 50 states, several large cities, and Puerto Rico, including seven regional labs and the National Tuberculosis Molecular Surveillance Center.	Testing for: <i>Neisseria gonorrhoeae</i> <i>Acinetobacter</i> Carbapenem-resistant Enterobacteriaceae <i>Salmonella</i> , and more

²⁸Public health surveillance is the ongoing, systematic collection, analysis, and interpretation of health-related data essential to planning, implementation, and evaluation of public health practice.

Letter

Surveillance system	Description of system	Priority bacteria tracked
Emerging Infections Program (EIP)	<p>A network of public health-academic hospital collaborations in 10 states. It provides access to bacterial and fungal samples for testing and detailed clinical case data.^a EIP has population level data, and does not focus on infections occurring in health care facilities as does the National Healthcare Safety Network. The three main programs within EIP collect different types of resistance data:</p> <ul style="list-style-type: none"> • Active Bacterial Core provides clinical information and resistance data for bacteria that cause infections predominately in the community • The Healthcare-Associated Infections-Community Interface provides clinical information and resistance data for bacteria and fungi that cause infections at the intersection of health care and the general community • Foodborne Diseases Active Surveillance Network (FoodNet) supplies clinical and epidemiologic data on the human enteric isolates followed in the National Antimicrobial Resistance Monitoring System (NARMS) 	<p>Active Bacterial Core: <i>Streptococcus pneumoniae</i> Groups A and B <i>Streptococcus</i> Healthcare-Associated Infections-Community Interface: <i>Clostridioides difficile</i> (<i>C. difficile</i>) Carbapenem-resistant Enterobacteriaceae Extended-spectrum Beta-lactamase-producing Enterobacteriaceae Carbapenem-resistant <i>Acinetobacter</i> Carbapenem-resistant <i>Pseudomonas aeruginosa</i> (2016-2018) Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)^b FoodNet: (see NARMS list)</p>
Gonococcal Isolate Surveillance Program (GISP)	A program to track antibiotic resistance data for gonococcal isolates. Isolates are collected from sexually-transmitted disease clinics in approximately 28 cities.	<i>Neisseria gonorrhoeae</i>
National Antimicrobial Resistance Monitoring System (NARMS)	<p>A national public health surveillance system that tracks changes in the susceptibility of foodborne and other enteric bacteria to antibiotics of human and veterinary medical importance. NARMS is a collaborative effort among CDC, the Food and Drug Administration (FDA), the U.S. Department of Agriculture, and state and local health departments. CDC tests bacteria isolated from human samples, while FDA and the U.S. Department of Agriculture test bacteria isolated from samples taken from retail meats and food animals at slaughter, respectively.</p>	<p><i>Salmonella</i> <i>Campylobacter</i> <i>Shigella</i> <i>Escherichia coli</i> O157</p>
National Healthcare Safety Network (NHSN)	A system that collects and provides data on infections and drug resistance in health care settings. Since NHSN collects data directly from health care facilities, it can provide facility-level information on health care-associated infections and antibiotic resistance to those facilities and to CDC.	<p><i>Staphylococcus aureus</i> <i>Enterococcus</i> Enterobacteriaceae <i>Acinetobacter</i> <i>Pseudomonas aeruginosa</i> <i>C. difficile</i> MRSA</p>

Surveillance system	Description of system	Priority bacteria tracked
National Notifiable Diseases Surveillance System	CDC receives data on diseases that are deemed “nationally notifiable” by the Council of State and Territorial Epidemiologists. Notifiable disease surveillance begins at the level of local, state, and territorial public health departments (also known as jurisdictions). Jurisdictional laws and regulations mandate reporting of cases of specified infectious and non-infectious conditions to health departments.	Carbapenemase-producing Carbapenem-resistant Enterobacteriaceae Vancomycin-resistant <i>Staphylococcus aureus</i>
National Tuberculosis Surveillance System	Collects data on tuberculosis cases, including resistance data. Public health departments from 50 states and the U.S. territories contribute data.	<i>Mycobacterium tuberculosis</i>

Source: GAO summary of information from CDC websites. | GAO-20-341

^aCDC also tracks a fungal infection, fluconazole-resistant *Candida*, in the Emerging Infections Program.

^bAccording to CDC, MRSA was formerly a part of the Active Bacterial Core.

According to CDC and other officials and documents we reviewed, including the National Action Plan Year 3 Progress Report, CDC has taken the following actions, among others, to expand surveillance in order to better assess the scope of antibiotic resistance:

- Established the Antibiotic Resistance Laboratory Network in 2016 to improve testing capacity to better identify antibiotic resistance in the United States. The network consists of 55 state and local (including Puerto Rico), and seven regional, public health laboratories and the National Tuberculosis Molecular Surveillance Center.²⁹ The network is improving and expanding laboratory capacity response at public health laboratories around the country, as well as at regional centers, according to representatives from two national professional organizations of state and local health officials and epidemiologists.
- Expanded antibiotic resistance-related efforts in its Emerging Infections Program (EIP), a network that seeks to monitor, prevent, and control emerging infectious diseases. For example, since 2015, more of the existing 10 EIP sites are conducting surveillance for invasive *Staphylococcus aureus* infections, carbapenem-resistant Enterobacteriaceae, and *C. difficile*, among others. Separately, the National Action Plan had included a goal for CDC to expand EIP by adding up to 10 sites within 3 years. However, CDC officials told us

²⁹The seven regional laboratories in the network are located in Maryland, Minnesota, New York, Tennessee, Utah, Washington, and Wisconsin. The laboratories were established under CDC’s new efforts through the Antibiotic Resistance Solutions Initiative in 2016 to help health departments nationwide tackle antibiotic resistance and other patient safety threats, including through the Epidemiology and Laboratory Capacity for Infectious Diseases Cooperative Agreement.

that in light of resource limitations, they chose to instead increase the number of pathogens reported at existing EIP sites. They told us they determined this was a better use of the limited funds, and that existing EIP sites are sufficient for current EIP efforts related to antibiotic resistance.

- Updated the domestic tuberculosis surveillance system by incorporating advanced drug susceptibility testing and reporting and by developing capacity for state surveillance systems to report their tuberculosis test data electronically to CDC laboratories.
- Supported state and local health departments to better track, investigate, and prevent resistant foodborne disease, among other things, through the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS). For example, the system can now carry out whole genome sequencing for all the pathogens it tracks, which enhances its detection and response capabilities, such as by expanding CDC's ability to detect new and emerging resistance, according to CDC officials.
- Launched the Enhanced Gonococcal Isolate Surveillance Program (eGISP), which augments the main Gonococcal Isolate Surveillance Program (GISP). Whereas GISP only collects samples from the urethras of men with symptoms of gonorrhea, in select sexually transmitted disease clinics, eGISP also collects samples from women and from other sites on the body, such as the throat. The specimens are sent to regional laboratories for resistance testing.³⁰

CDC has also worked with international partners to expand surveillance of antibiotic resistance abroad. These efforts involved CDC collaborations with WHO, the European Center for Disease Prevention and Control, the government of the United Kingdom, other governments, and other multi-country efforts, such as the Surveillance and Epidemiology of Drug-Resistant Infections Consortium and the Transatlantic Taskforce on

³⁰Regional laboratories for gonorrhea resistance testing as part of GISP and eGISP are located in Maryland, Tennessee, Texas, and Washington.

Antimicrobial Resistance (TATFAR).³¹ The collaborations aimed to develop technical guidance to help improve surveillance in other nations and to organize an international forum. CDC also launched its Antibiotic Resistance (AR) Solutions Initiative, which invests in national and international infrastructure to address resistant infections across health care settings and communities and from food.

The Precise Magnitude and Trends of Antibiotic Resistance Are Unknown, in Part Because of Challenges CDC Faces in Three Areas

CDC faces three general challenges in tracking and reporting trends in antibiotic resistance. First, it faces limitations in data reporting and resistance testing from hospitals, as well as challenges ensuring that its resistant gonorrhea surveillance system is representative of the U.S. population. Second, CDC faces challenges in reporting complete and timely information on the magnitude of and trends in antibiotic resistance. Finally, CDC faces challenges to detecting resistance threats abroad.

Challenges in Tracking Resistance

The first challenge CDC faces in tracking trends in resistance is addressing low hospital participation in a new option of CDC's National Healthcare Safety Network (NHSN) system intended to address some limitations in NHSN. NHSN is, among other things, an online system for tracking health care-associated infections. It provides facilities, states, regions, and the nation with data needed to identify problem areas,

³¹The UK-based charitable organization the Wellcome Trust launched the Surveillance and Epidemiology of Drug-Resistant Infections Consortium to help countries track, share, and analyze information about antimicrobial resistance. The consortium brings together international experts in infectious diseases, epidemiology, and human and animal health to identify gaps in surveillance, help countries strengthen and sustain their capacity to collect data on drug-resistant pathogens, and improve global coordination. The group also provides technical expertise and knowledge to help improve surveillance networks and look at how technology can be used to better understand resistance mechanisms and how infections spread. TATFAR was created in 2009 to address the urgent threat of antibiotic resistance. TATFAR's technical experts from Canada, the European Union, Norway, and the United States collaborate and share best practices to strengthen domestic and global efforts.

measure the progress of prevention efforts, and ultimately eliminate health care-associated infections, according to CDC.³²

Health Care-Associated Infections

Patients in settings such as hospitals and long-term care facilities (e.g., nursing homes) in many cases already have a weakened immune system or an underlying illness, making an antibiotic-resistant infection especially dangerous, according to the Centers for Disease Control and Prevention (CDC). A high proportion of the morbidity and mortality associated with antibiotic resistance is seen in health care-associated infections. Tracking resistance in health care settings is therefore critical to national surveillance efforts.

Source: GAO summary of CDC documents. | GAO-20-341

CDC established three modules within NHSN that allow hospitals to report select antibiotic-resistant infections, among other things, which include reporting required by states or by CMS, according to agency officials. Two modules track patients who have an infection associated with a medical device or resulting from a surgical procedure. Hospitals only report on resistance in these modules for specific combinations of antibiotics and bacteria, such as carbapenem-resistant Enterobacteriaceae. The third module tracks certain hospital patients who test positive for certain multidrug-resistant infections, including methicillin-resistant *Staphylococcus aureus* (MRSA)—a type of bacteria found on people’s skin that is usually harmless but can cause serious infections, according to CDC.³³ However, according to CDC, many antibiotic-resistant infections detected during hospital care do not fall into one of these three modules and therefore would not be captured in NHSN, limiting CDC’s ability to identify important new resistances or trends.

In 2014, to help address this limitation, CDC officials told us they introduced a new option for hospitals to report data on antibiotic resistance—the Antimicrobial Resistance Option (AR Option). This option allows for reporting of data on antibiotic resistance for certain bacteria, regardless of whether the patient has a health care-associated infection.³⁴ In contrast to the other three modules, reporting to the AR Option is voluntary.

As a result, while about 86 percent of the 17,529 eligible U.S. health care facilities participate in at least one of the older three antibiotic-resistance reporting modules, only about 10 percent of the 6,836 eligible hospitals participate in the newer, voluntary AR Option, according to our analysis of

³²CDC, VA, and DOD are collaborating to report some antibiotic resistance data to CDC via NHSN.

³³The module tracks methicillin-resistant *Staphylococcus aureus* (MRSA), *C. difficile*, and carbapenem-resistant Enterobacteriaceae, among others.

³⁴Hospital types in NHSN include general acute care hospitals, critical access hospitals, children’s hospitals, oncology hospitals, long-term acute care hospitals, and inpatient rehabilitation facilities. The AR Option is part of a reporting module called the Antimicrobial Use and Resistance Module (AUR Module) that also tracks antimicrobial use through an “AU Option.”

NHSN hospital participation data as of January 2020.³⁵ The hospital participation rate among U.S. states and territories ranged from no participation (in nine states and territories) to about 27 percent.³⁶ Representatives from a national association of state public health officials we interviewed said that this low rate limits the value of the data, a view that echoed the findings of a 2018 report by the Joint Public Health Informatics Task Force.³⁷

CDC officials acknowledged that participation in the AR Option is low and cited reasons for this, including hospital resource limitations, and—in many cases because participation is voluntary—because hospitals do not prioritize submitting data to the AR Option. According to CDC officials, it is particularly challenging for many smaller hospitals and Indian Health Service facilities with resource constraints to participate, as it requires significant information technology investment.³⁸ The Joint Public Health Informatics Task Force report noted two other common challenges: low capacity for information technologies needed to support data submission to the AR Option, and a lack of motivated leadership, such as a facility “champion,” to oversee the development and maintenance of needed reporting infrastructure. For example, the maintenance of reporting infrastructure could address changes to electronic medical records that are not immediately compatible with the AR Option reporting format.

³⁵Fewer facilities are eligible for the AR Option because that option does not extend to, for example, dialysis clinics or long-term care facilities. These totals do not include military bases outside the United States.

³⁶Our analysis found there were no hospitals in the five U.S. territories participating in the AR Option as of June 2019, although some hospitals were enrolled in NHSN and eligible to participate in the AR Option.

³⁷The Joint Public Health Informatics Task Force is a coalition of nine national public health associations, co-chaired and staffed by the Association of State and Territorial Health Officials and the National Association of County and City Health Officials, that helps U.S. governmental public health agencies build modern information systems across a spectrum of public health programs.

³⁸Beginning 2018, facility participation in the AUR Module was incentivized through making it an option for public health registry reporting under the Promoting Interoperability Program established by CMS to encourage clinicians and eligible hospitals, including critical access hospitals, to adopt, implement, upgrade, and demonstrate meaningful use of certified electronic health record technology. CDC officials told us that the AUR Module requires all data to be reported electronically, because manual reporting of these data would be time and staff prohibitive.

CDC officials told us the agency is taking some steps to increase participation in the AR Option. For example, it is encouraging the over 1,500 hospitals (as of December 31, 2019) that are participating in a related reporting effort—known as the Antimicrobial Use Option (AU Option)—but not in the AR Option to participate in both. In addition, the agency is working with vendors of equipment and electronic health record software to make it easier for hospitals to participate in the AR Option.

One of CDC's goals for the AR Option is to use reported data to conduct regional and national assessments of resistance. To help meet this goal, officials said they would like participation by all eligible hospitals in the AR Option, but they have not determined the needed participation rates or appropriate distribution of participating hospitals. Our past work has shown that leading practices for federal strategic planning include articulating specific goals, establishing a method to assess progress toward these goals, and aligning the plans and goals with the agency's mission.³⁹ By taking steps to determine the participation rates and distribution of participation hospitals needed for CDC to meet its goal of conducting regional and national assessments of antibiotic resistance of public health importance, CDC would have more reasonable assurance that it can achieve its goal.

The second challenge CDC faces is ensuring representativeness of its resistant gonorrhea surveillance system. CDC has classified resistant gonorrhea as one of the most urgent antibiotic-resistance threats in the nation, affecting over half a million patients annually. According to the agency, resistant gonorrhea warrants this designation because of the limited remaining treatment options, the high number of gonorrhea infections, potential adverse outcomes (such as increased transmission of

³⁹We have previously reported that the strategic planning practices required at the federal agency level by the Government Performance and Results Act of 1993 (GPRA) and the GPRA Modernization Act of 2010 can serve as leading practices for planning at lower levels within agencies such as individual programs or initiatives. GAO, *Performance.gov: Long-Term Strategy Needed to Improve Website Usability*, [GAO-16-693](#) (Washington, D.C.: Aug. 30, 2016); Government Performance and Results Act of 1993, Pub. L. No. 103-62, 107 Stat. 285 (Aug. 3, 1993) and GPRA Modernization Act of 2010, Pub. L. No. 111-352, 124 Stat. 3866 (Jan. 4, 2011). These practices and associated Office of Management and Budget (OMB) guidance, together with practices we have identified, provide a framework of leading practices in federal strategic planning. OMB defines a strategic goal as a "statement of aim or purpose" that "articulate[s] clear statements of what the agency wants to achieve." OMB Circular No. A-11, *Preparation, Submission, and Execution of the Budget*, Pt. 6, § 200.22 (Washington, D.C.: June 28, 2019).

HIV), and the prospect that gonorrhea may become incurable if new resistance arises and spreads.

The Urgent Threat of Resistant Gonorrhea

According to the Centers for Disease Control and Prevention (CDC), gonorrhea is the second most commonly reported notifiable disease in the United States, with over 500,000 infections reported in 2017. However, CDC estimates that the true number could be as many as 820,000 each year. In addition to being a very common infection, gonorrhea is developing resistance to treatment options. As recently as 2006, CDC had five recommended options, but it estimates that nearly half of U.S. infections are now resistant to available antibiotics, including combinations. Consequently, it now recommends only one regimen. In 2014, a case of dual-therapy failure was reported in the United Kingdom, and in February 2018, a similar case in the United Kingdom was reported that also failed to respond to the last-resort therapy, spectinomycin, resulting in treatment failure. As of June 2019, CDC reported that it had not received any reports of verified clinical treatment failures to any cephalosporin in the United States.

Source: GAO summary of CDC and other information. | GAO-20-341

It is not clear, however, that GISP data are representative of the general U.S. population because GISP draws on a limited sample of that population.⁴⁰ Specifically, GISP collects culture specimens—called isolates—and accompanying epidemiologic data from only the first 25 men with inflammation of the urethra consistent with gonorrhea visiting each participating sexually transmitted disease clinic each month. It does not collect culture specimens from women. In addition, the number of participating clinics each year has varied from 21 to 30 (see fig. 2 for the current sites).⁴¹ CDC estimates that the cases of gonorrhea identified through GISP surveillance represent only about 1 to 2 percent of all reported cases of gonorrhea in the United States each year. Further, the GISP sample design also over-represents cases in the western United States, where antibiotic-resistant gonorrhea has tended to initially emerge, according to CDC.⁴² According to CDC, this design allows for more rapid detection of emerging resistance by ensuring a sufficient sample size from the western United States because resistance tends to emerge from that area. CDC has two projects—Strengthening the United States Response to Resistant Gonorrhea (SURRG) and eGISP—intended to, among other things, enhance domestic gonorrhea surveillance and learn more about the representativeness of GISP through limited testing of women and of body sites other than urethras, respectively.⁴³

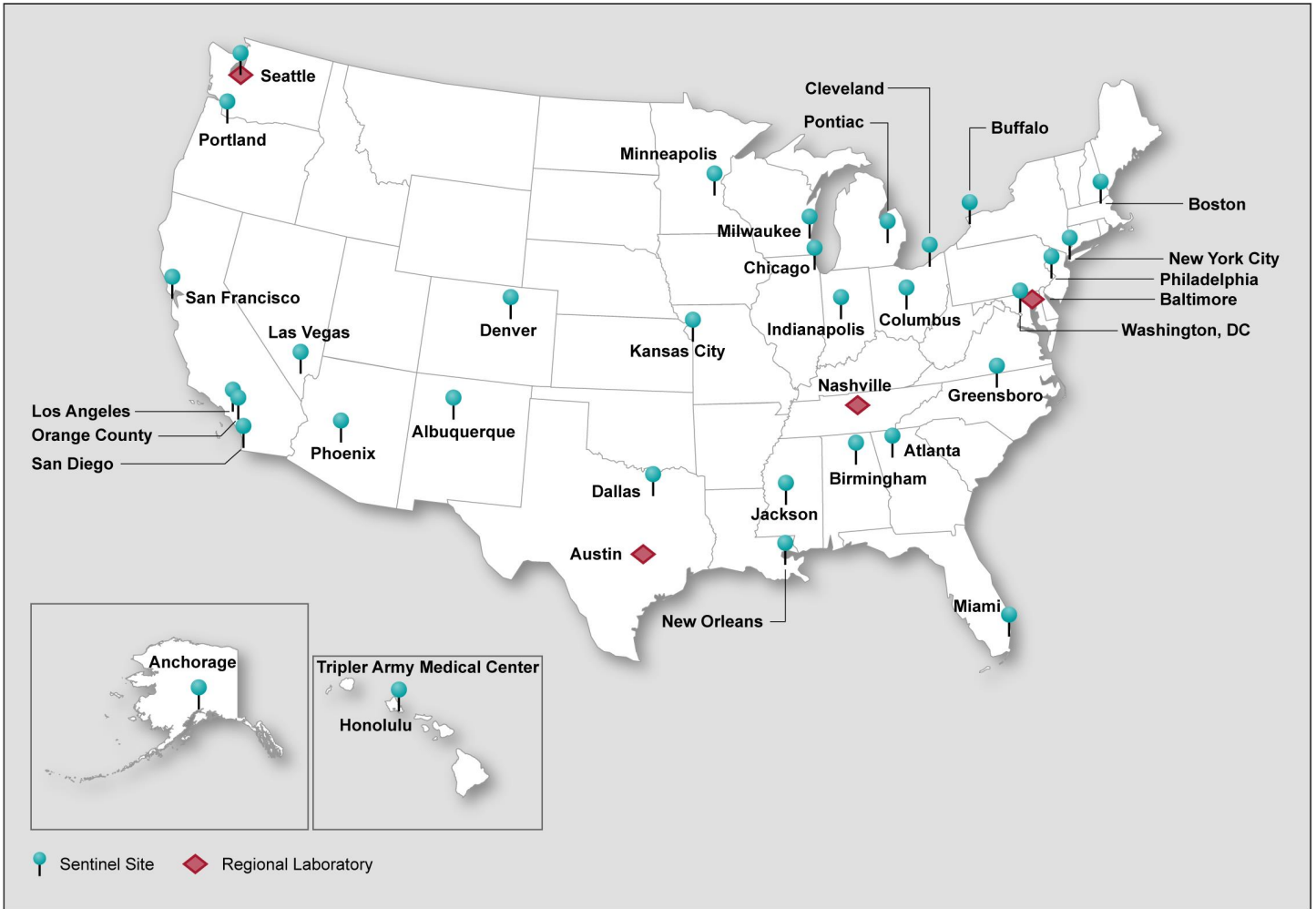
⁴⁰GISP was established in 1986 not only to monitor resistance trends in gonorrhea, but also to provide a basis for the selection of therapies to treat gonorrhea. GISP data are thus important for informing treatment recommendations, which can directly affect health care provider prescribing practices.

⁴¹According to CDC officials, each sentinel site has used a standard protocol, sampling methods, and culture-based laboratory methods consistently since GISP's inception, allowing for interpretation of trends over time. Sentinel surveillance is the study of disease rates in a specific cohort, such as in a geographic area or population subgroup to estimate trends in a larger population.

⁴²According to CDC, isolates from the western United States are over-represented in GISP compared with the geographic distribution of nationally reported gonococcal infections in men. For example, CDC reported that in 2014, isolates from the West represented 40 percent of GISP isolates but less than 25 percent of reported cases.

⁴³SURRG is a project to enhance domestic gonorrhea surveillance and infrastructure and build capacity for rapid detection and response to resistant gonorrhea, among other things. eGISP was mentioned earlier in this report.

Figure 2: Resistant Gonorrhea Sentinel Surveillance Sites and Regional Testing Laboratories, 2018



Source: Centers for Disease Control and Prevention. | GAO-20-341

Data table for Figure 2: Resistant Gonorrhea Sentinel Surveillance Sites and Regional Testing Laboratories, 2018

Sentinel Site

- Albuquerque
- Anchorage
- Atlanta
- Birmingham
- Boston
- Buffalo
- Chicago

- Cleveland
- Columbus
- Dallas
- Denver
- Greensboro
- Indianapolis
- Jackson
- Kansas City
- Las Vegas
- Los Angeles
- Miami
- Milwaukee
- Minneapolis
- New Orleans
- New York
- Orange County
- Philadelphia
- Phoenix
- Pontiac
- Portland
- San Diego
- San Francisco
- Seattle
- Tripler Army Medical Center, Honolulu
- Washington D.C.

Regional Laboratory

- Seattle
- Austin
- Nashville
- Baltimore

Note: Sentinel surveillance is the study of disease rates in a specific cohort, such as in a geographic area or population subgroup to estimate trends in a larger population. In the Gonococcal Isolate Surveillance Program, selected demographic and clinical data are abstracted from medical records, and isolates are tested for antibiotic susceptibility at regional laboratories.

However, CDC's current methodology may limit its ability to establish a representative trend. According to CDC officials, GISP could improve its representativeness by adding clinics or covering more of the population at its current sites. However, efforts to expand GISP would be difficult due to limited local capacity (see text box).

Barriers to Expanding the Gonococcal Isolate Surveillance Program (GISP)

GISP currently tracks a limited sample of the U.S. population. According to Centers for Disease Control and Prevention (CDC) officials, a more thorough expansion of GISP would be more difficult because of limited local capacity to conduct culture-based testing for resistance in gonorrhea. Specifically, laboratories increasingly use newer gonorrhea testing technology that gives more rapid results but cannot currently be used to test for resistance. This trend has contributed to the reduced capability of many laboratories to perform the gonorrhea culture-based testing for antibiotic susceptibility testing, to the point that many clinics cannot collect specimens for testing, according to CDC officials. Furthermore, officials said that adding new clinics to GISP would require financial and other resources for, among other things, establishing culture testing for resistance and information technology needed to report data to the system.

Most gonorrhea cases are diagnosed outside sexually transmitted disease clinics. However, expanding GISP to non-sexually transmitted disease clinic sites could be particularly costly and inefficient, officials said, because these sites tend to see many fewer gonorrhea cases per year compared to sexually transmitted disease clinics; therefore they may not be able to contribute significant data to GISP. Through the Strengthening the United States Response to Resistant Gonorrhea (SURRG) project, CDC is currently exploring options to work with states to enhance gonorrhea testing capacity. This program was established in 2016 but has not received the funding needed to expand capacity to the extent CDC had planned. In addition, physicians and other providers have limited time to devote to data collection and reporting needed to participate in GISP. CDC officials also told us the reimbursement rates for providers for these services are inadequate.

Source: GAO summary of CDC documents and interview with CDC officials. | GAO-20-341

CDC has taken some steps to assess the representativeness of the current GISP design, but it has not conducted a comprehensive study to assess the representativeness of the trends identified in GISP. A 2015 CDC evaluation concluded that the representativeness of GISP was “good” on a scale of fair, good, or great.⁴⁴ However, the evaluation covered only part of fiscal year 2014 and consisted of a limited comparison of selected demographic characteristics captured in gonorrhea cases identified in GISP to those captured through the National Notifiable Diseases Surveillance System, according to CDC officials, and which has its own limitations. Further, the results of this evaluation have not resulted in any changes to the GISP design. CDC officials told us they hope to learn more about the representativeness of GISP urethral isolates from testing women, patients in non-sexually transmitted disease clinic sites in the SURRG project and eGISP, and testing at other body sites, and then comparing some of these results to those of GISP. However, these efforts overall were not specifically designed to fully assess the representativeness of GISP and may not

⁴⁴A 2007 evaluation of GISP noted that only males are represented; private practice patients are not included; the system relies on urethral cultures, so isolates from pharyngeal and rectal cultures are not represented; only 25-30 cities are represented; and these cities are weighted toward the West Coast.

provide a sufficient assessment for impacting changes to the GISP design.

CDC's guidelines of efficient and effective public health surveillance systems state that, in order to be representative, the data from a public health surveillance system should accurately reflect the characteristics of the health-related outcome—such as resistant gonorrhea—under surveillance.⁴⁵ A more precise evaluation of the representativeness of the surveillance system can be done via carefully designed studies to obtain complete and accurate data for the health event in question—namely, the urgent threat of antibiotic-resistant gonorrhea. By evaluating the surveillance system for resistant gonorrhea to ensure that it includes measures of its representativeness, such as by comparing the trends in the sample population with those in the overall U.S. population, using specially designed studies if needed, CDC would have better assurance that the trends detected in GISP accurately reflect the characteristics of the health-related outcome the system is designed to monitor.

In addition to the limited design of GISP, CDC faces the challenge of competing priorities under reduced funding that precluded it from completing its plans to expand the SURRG project. The SURRG expansion was designed to address a National Action Plan goal of controlling resistant gonorrhea, among other things, but also affects surveillance, as CDC officials told us SURRG was established to address some limitations in GISP surveillance. Specifically, one of the plan's milestones assigned to CDC is to maintain advanced capacity for rapid response to antibiotic-resistant gonorrhea for at least 20 state health departments. Such capacity includes detection, diagnosis, and investigation of suspected resistant cases within their state or region and assistance for health care providers in appropriately treating infected patients. CDC officials told us that because they received about half of the appropriations they had requested, CDC had to make cuts in some of

⁴⁵These characteristics generally relate to time, place, and person. Department of Health and Human Services, Centers for Disease Control and Prevention, "Updated Guidelines for Evaluating Public Health Surveillance Systems," *Morbidity and Mortality Weekly Report*, vol. 50, no. RR-13 (2001).

their projects, and SURRG was one of those that CDC chose to reduce.⁴⁶ Eight SURRG sites, rather than the 20 recommended by the National Action Plan, collect and analyze data. However, in its progress reports covering the first 4 years of the National Action Plan's implementation, the CARB Task Force did not identify plans to address barriers related to expanding the SURRG project.⁴⁷ The CARB Task Force coordinators told us that the progress reports have not identified plans to address barriers largely because the task force focused on reporting the agencies' accomplishments in implementing the National Action Plan. The coordinators also said that, in response to our inquiries during this review, the task force intends to identify agencies' plans for addressing barriers in the progress report to be published in fall 2020.

The Executive Order directs the CARB Task Force to provide annual updates to the President on federal government actions to combat antibiotic resistance, including progress made in implementing the National Action Plan, plans for addressing any barriers preventing its full implementation, and recommendations for any new or modified actions, taking federal government resources into consideration. Without reporting its plans to address such barriers, the CARB Task Force has not provided all the information required by the Executive Order and has not fully carried out its role to facilitate and monitor implementation of the National Action Plan, which may reduce the effectiveness of federal efforts to combat antibiotic resistance.

The third challenge CDC faces tracking antibiotic resistance is addressing limitations to the use of test results in surveillance in health care settings. For example, some health care facilities are not using the most up-to-date testing methods for determining whether the bacteria causing an infection are resistant to certain antibiotics, according to CDC officials and a report

⁴⁶For example, CDC officials provided documentation establishing that it requested \$264.3 million for fiscal year 2016 for combating antibiotic-resistant bacteria initiatives. CDC also provided documentation supporting that its fiscal year 2016 operating plan included about \$160 million for these initiatives; thus, CDC chose not to allocate the resources to implement all activities outlined in the National Action Plan, including the full implementation of the SURRG sites.

⁴⁷CARB Task Force, *National Action Plan: Progress Report for Years 1 and 2*, *National Action Plan: Progress Report: Year 3*, and *National Action Plan: Progress Report: Year 4*.

from the Antibiotic Resistance Surveillance Task Force.⁴⁸ In addition, laboratories may only report an interpretation of the test result to CDC (e.g., whether the bacteria is resistant or susceptible to an antibiotic) and not the quantitative results (e.g., measures of the growth of bacteria in the presence of the antibiotic). This presents a challenge for comparing data from different laboratories, since they may not be using consistent testing thresholds for determining antibiotic resistance. Another limitation is that some test equipment may be designed to give limited results for the purposes of guiding treatment recommendations and stewardship efforts, which may also limit the information available to CDC.⁴⁹ For example, the test may inform the user that the infection is susceptible to one antibiotic but “suppress” information on susceptibility to other antibiotics, in order to guide the user toward treatment with the preferred first-line treatment. The Antibiotic Resistance Surveillance Task Force report noted that some suppression is done by the testing equipment itself and some by software systems that record, manage, and store data for clinical laboratories. CDC officials told us they are working with some diagnostic test manufacturers to explore these issues and develop solutions to address them. The Antibiotic Resistance Surveillance Task Force is also working to address the diagnostic test challenges related to antibiotic resistance surveillance.

Challenges in Reporting Complete and Timely Information on Magnitude and Trends

CDC also faces challenges in reporting timely and complete information on the magnitude of and trends in antibiotic resistance in the agency’s Threats Reports. One challenge is in providing information in these reports on the uncertainties in reported numbers of deaths from antibiotic-resistant infections. Another challenge is in issuing such reports in regular, timely intervals. As a result of these challenges, among others, the true magnitude of, and trends in, antibiotic resistance over time are unknown, including trends in various places and among people with various characteristics.

⁴⁸The 2018 report from the Antibiotic Resistance Surveillance Task Force, led by the Council of State and Territorial Epidemiologists, indicated that although FDA has adopted new breakpoints for antibiotic resistance tests and equipment manufacturers are able to implement them, many clinical laboratories use some old breakpoints. The task force further noted that standardized and widely used up-to-date breakpoints are fundamental to quality of data and the effective and coordinated action based on the data.

⁴⁹We discuss antibiotic stewardship later in this report.

Surveillance for antibiotic resistance is complex and costly, according to experts at our meeting, CDC officials, and literature we reviewed. Experts told us such surveillance encompasses diverse pathogens, diseases, and health care settings and requires a variety of data sources and collection efforts. Furthermore, experts from our meeting told us the fundamental data required—such as data on the number of illnesses and deaths attributable to resistance and data on related health care costs—are currently insufficient. One expert added that there is a lack of real-time monitoring data, such as data that are available within hours or days of being generated. The data gaps are especially large for infections acquired in the community, as opposed to in a health care setting, because there is very limited tracking of such infections and whether they are resistant. As a result, CDC officials said, it is challenging to provide ranges of uncertainty, a critical component of any effort to measure and report on magnitude and trends.⁵⁰

Neither the 2013 Threats Report nor the 2019 Threats Report provided quantitative measures of uncertainty, such as confidence intervals, for CDC's estimates of morbidity and mortality resulting from antibiotic-resistant infections. For example, the report stated that there are at least 23,000 deaths a year as a direct result of antibiotic-resistant infections, but it did not include an upper limit or a single point estimate for this number. Similarly, the 2019 Threats Report stated that there are at least 35,900 deaths a year, without an upper limit or a single point estimate. A recent re-estimate by a group of scientists has put the likely minimum number of deaths annually in the United States at approximately 153,000, or about four times the 2019 CDC minimum estimate.⁵¹

CDC officials told us that because of several limitations, its estimates were the best that could be derived from the data available. For example, for the 2013 Threats Report, CDC only had data from a national hospital survey intended to produce estimates of all health care-associated infections and indirect estimates of the proportion of infections that were

⁵⁰One type of uncertainty range is the confidence interval, which gives a range of values that is likely to include the true value. In the case of CDC's 2013 Threats Report and the *Antibiotic Resistance Threats in the United States, 2019* report, confidence intervals would provide a range for the number of infections and deaths, along with a degree of confidence—usually expressed as a percentage—that the true values fall within that range.

⁵¹J. P. Burnham, M. A. Olsen, and M. H. Kollef, "Re-estimating Annual Deaths Due to Multidrug-Resistant Organism Infections," *Infection Control & Hospital Epidemiology*, vol. 40, no. 1 (2019): pp. 112-113. This recent estimate by a group of scientists has put the likely minimum number of deaths annually in the United States at approximately 153,000.

resistant. These data did allow CDC to calculate confidence intervals for infections by specific pathogens, but this information was not disclosed in the Threats Reports. Because the data sources were not intended for this purpose, the 2013 intervals were wide, from approximately 26 percent to 380 percent of the point estimates for each pathogen. CDC officials told us they elected not to include these ranges of uncertainties to avoid confusion in the 2013 Threats Report, because the report was intended for a variety of audiences, including the general public. Officials told us they planned to provide confidence intervals in an appendix of the 2019 Threats Report, but they did not.⁵² CDC officials explained that they elected not to include confidence intervals in the 2019 Threats Report because several publications are pending that provide more granular data for many of the estimates included in the report.⁵³ It is thus unclear whether CDC plans to include any measures of uncertainties in future Threats Reports.

Federal standards for agency dissemination of information it produces stipulate that when information products are disseminated, error estimates are calculated and disseminated to support assessment of the appropriateness of the uses of the estimates or projections.⁵⁴ Providing measures of uncertainties in antibiotic resistance estimates, such as standard errors or confidence intervals, as appropriate, in its Threats Reports would help CDC and others compare information within and across reporting efforts, without having to consult multiple documents over time. CDC and others could use this information to draw appropriate conclusions about the characteristics of antibiotic resistance in the United States, including limitations associated with reported findings and conclusions.

Additionally, CDC does not have a plan for timely, regular issuance of their Threats Reports. It took CDC over 6 years to update the 2013 Threats report. CDC officials told us this length of time between reports

⁵²Both the 2013 and 2019 CDC Threats Reports have an appendix that discusses sources of data and methodologies but does not provide estimates of uncertainties. In some cases, CDC disclosed ranges, such as for the attributable costs of certain *C. difficile* infections.

⁵³CDC officials told us they wanted to publish CDC's methodology in a peer-reviewed journal to allow for stakeholder input. They said multiple publications, including articles containing confidence intervals for some pathogens in the 2019 Threats Report, are pending.

⁵⁴Office of Management and Budget, *Standards and Guidelines for Statistical Surveys* (September 2006).

was in part because, following issuance of the 2013 Threats Report, the agency was focused on implementing priority actions to improve antibiotic resistance surveillance data, including those efforts prescribed by the National Action Plan. In some cases, implementing these actions involved new data collection efforts that took time to establish, including that it can take up to 2 years to get new surveillance variables cleared by the Office of Management and Budget (OMB), CDC officials told us. In addition, CDC officials said it is time consuming to coordinate across the decentralized structure of antibiotic-resistance tracking at CDC to compile a consolidated report.

However, lack of timely, regular updates may affect the information available to the public as well as policy-makers. For example, the 2013 Threats Report stated that there are at least 23,000 deaths a year as a direct result of antibiotic-resistant infections. The 2019 report stated the number of deaths each year to be at least 35,900 deaths a year. This report also revised the 2013 estimate from 23,000 to 44,000 deaths a year, suggesting a nearly two-fold revision to the initial 2013 estimate.

CDC officials told us they would like to publish the report more frequently than every 6 years, and that it is reasonable they would develop such a plan for frequency of publication following the 2019 report. However, they said the agency does not currently have a plan for how often it will release future consolidated reports.⁵⁵ CDC's attributes of efficient and effective public health surveillance systems include timely data dissemination for planning, implementing, and evaluating public health policies and programs.⁵⁶ By developing a plan for more frequent dissemination of consolidated reporting on priority pathogens at regular intervals, CDC would have more timely trend data and other information necessary for users of the data, including policymakers, to prioritize, plan, implement, and evaluate public health actions to address antibiotic resistance.

⁵⁵According to the 2013 Threats Report, CDC stated it would update the assessment of priority bacteria at least every 5 years, although it did not specify that the reporting of the priority bacteria would occur every 5 years.

CDC officials told us CDC shares antibiotic resistance data at regular intervals, such as through GISP reports, but these are for specific pathogens or subsets. This does not address the timing of regular reporting of CDC's consolidated reports, such as the 2013 and 2019 Threats Reports.

⁵⁶Department of Health and Human Services, Centers for Disease Control and Prevention, "Updated Guidelines for Evaluating Public Health Surveillance Systems."

Challenges in Tracking and Assessing the Global Threat

Through interviews with WHO and CDC officials, experts at our meeting, and document reviews, we identified three key challenges to CDC's ability to detect antibiotic resistance threats from abroad.⁵⁷ These challenges are as follows:

The Global Antimicrobial Resistance Surveillance System

In October 2015, the World Health Organization (WHO) launched the Global Antimicrobial Resistance Surveillance System (GLASS). The objectives of GLASS are to foster national surveillance systems and harmonized global standards and estimate the extent and burden of antimicrobial resistance globally by selected indicators, among other things. As of November 2019, 86 countries were enrolled in GLASS, a 25 percent increase over 2018. Participants were in various stages of economic development (13 lower-income countries, 23 lower-middle-income countries, 17 upper-middle-income countries, and 33 high-income countries) and in all WHO regions. Seventy-five countries provided descriptive information on their surveillance systems for tracking antimicrobial resistance, and 57 countries provided resistance data for 2018.

Source: GAO summary of WHO information. | GAO-20-341

- **Data completeness, quality, and representativeness.** Data on antibiotic resistance from the national surveillance systems of some countries are incomplete because of a lack of capability and resources for implementing standardized protocols, according to WHO officials. Moreover, most information on antibiotic-resistant infections is limited to laboratory test data and does not include epidemiological data, such as data on the patient and location, which could provide additional insight about the circumstances around the resistant infection. Also, a lack of a sampling strategy for the detection of cases that are antibiotic-resistant may bias the representativeness of the data and interpretation of results. Specifically, when case identification is done only on the population of patients that seeks medical care and is tested, or when testing of the population varies such as across health care settings, the incidence and trends determined from this population may not represent the total population of concern.
- **Aggregated data reporting.** Some countries report aggregated, rather than isolate, or infection-level, data to the WHO's Global Antimicrobial Resistance Surveillance System (GLASS), a practice that WHO officials stated creates a challenge for data analysis and results interpretation.⁵⁸ According to officials, such aggregation limits statistical analysis that can be performed and limits analysis of factors such as the specific antibiotic-resistant bacteria, or the age or gender of the patient, among other things.

⁵⁷International surveillance, including surveillance of antimicrobial resistance, is a key component of the 2018 U.S. National Biodefense Strategy. Specifically, the strategy states that "Goal 1: Enable risk awareness to inform decision-making across the biodefense enterprise" is to build risk awareness by ensuring that domestic and international biosurveillance and information-sharing systems are coordinated and are capable of timely bioincident prevention, detection, assessment, response, and recovery. The White House. *National Biodefense Strategy, 2018* (Washington, D.C.: September 2018).

⁵⁸An expert from our meeting later told us that WHO has begun to collect some isolate-level data within the GLASS platform, and it is working to expand these isolate-level reporting modules.

- **Surveillance is a complex function.** Many different health care and public health professionals are involved in the multistep process for generating data, according to a WHO report on GLASS. According to WHO officials, obtaining the staff commitment and training needed to ensure high-quality data can pose a challenge to public health agencies and health care organizations.

As we noted above, CDC has worked with, and continues to work with, international partners to expand surveillance of antibiotic resistance abroad, including through U.S. participation in GLASS. For example, CDC has helped develop technical guidance for surveillance programs in other countries and has organized international forums for surveillance. CDC officials also told us portions of domestic surveillance systems data collection include collection of patient travel history.

Federal Agencies Have Helped Advance Diagnostic Tests and Promoted Their Use, but These Efforts Have Limitations

Federal agencies have helped advance the development of new FDA-authorized tests and the use of existing tests for diagnosing antibiotic-resistant infections, but these efforts have limitations. Specifically, HHS and DOD have funded studies and taken other steps to advance testing, but they have not defined leadership, roles, and responsibilities to address a key barrier to the use of tests: a lack of clinical outcome studies. FDA has taken additional steps to advance testing; however, it has not regularly monitored test updates.

Agency Efforts toward the Development and Use of Diagnostic Tests

Challenges in Addressing Diagnostic Test Gaps

According to federal documents and literature, challenges to diagnostic test development include:

- Lengthy and costly regulatory requirements, including additional regulatory hurdles in other countries
- Limitations in technical feasibility assessments due to intellectual property protection and conflict of interest requirements
- Differences in expertise between manufacturers and regulatory bodies
- Limited evidence on cost-effectiveness and clinical outcomes for using tests
- Limited resources in some settings to transport specimens, conduct, and maintain tests

Source: GAO summary of Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria and other documents. | GAO-20-341

HHS and DOD Have Funded the Development of New Tests

HHS and DOD have awarded grants and contracts for the development of new FDA-authorized tests for diagnosing antibiotic-resistant infections.⁵⁹

Some of these awards address specific needs in the current availability of FDA-authorized tests, while others support more general research and development efforts. In addition, these agencies have taken steps to help reduce the chances of duplicative funding. According to experts, tests for antibiotic resistance not only help clinicians decide what antibiotics to use, they also provide important information for surveillance, including the number of cases of resistant infections in a population and the mechanisms of resistance.

Agencies have funded the development of some tests to address critical needs. We identified three such needs through interviews with federal agency officials and with experts. Specifically, according to agency officials and experts, there are no FDA-authorized tests that can do the following:

- Detect resistant gonorrhea or resistant campylobacter infection, which CDC identified as urgent and serious threats, respectively, in both the 2013 and 2019 Threats Reports.

⁵⁹This report focuses on FDA-authorized tests, which account for the majority of tests used in the United States, according to experts. According to FDA officials, there are non-FDA-authorized diagnostic tests for resistance available for all bacteria, including all of those on the 2013 threats list. Non-FDA-authorized tests can only be conducted by laboratory personnel meeting proficiency standards set by the Clinical Laboratory Improvement Amendment. However, experts told us the majority of tests used in the United States are FDA-authorized tests. For example, one expert estimated that more than 95 percent of laboratories using culture-based tests—tests that examine how well bacteria grow in the presence of an antibiotic—in the United States use some FDA-authorized tests.

- Rapidly detect resistance for seven other priority bacteria, according to the 2013 Threats Report.⁶⁰
- Differentiate between viral and bacterial infections. Such a test would be useful primarily in preventing use of antibiotics for viral infections, which can contribute to the development of resistance in bacteria, among other things.

HHS and DOD have awarded funding to address these needs. For example:

- CARB-X—a program supported by NIH and BARDA within HHS—has awarded funding to a company to develop a rapid test to both diagnose gonorrhea and test for antibiotic resistance.
- CARB-X is funding other companies to, among other things, develop rapid testing for identification of and resistance in bloodstream infections, including for some priority bacteria.
- In September 2016, NIH and BARDA announced the Antimicrobial Resistance Rapid, Point-of-Need Diagnostic Test Challenge. As of December 2019, there were five finalists, working on such projects as developing a rapid test to differentiate viral from bacterial infections and developing a test that can identify or detect antibiotic-resistant bacteria, including antibiotic-resistant gonorrhea.⁶¹
- Within DOD, the Defense Advanced Research Projects Agency officials told us that the agency used fiscal year 2015 funding on contracts for the development of rapid molecular tests for resistant gonorrhea and to distinguish between viral and bacterial infections.

Federal agencies have also funded more general research and development efforts related to resistance testing. For example:

⁶⁰The seven priority bacteria are non-typhoidal *Salmonella*, *Salmonella typhi*, *Shigella*, *Streptococcus pneumoniae*, vancomycin-resistant *Staphylococcus aureus*, erythromycin-resistant Group A *Streptococcus*, and clindamycin-resistant Group B *Streptococcus*. FDA officials noted there is no test for resistant *C. difficile*, but we do not count this as a gap because CDC's priority bacteria list does not include resistant *C. difficile*, only *C. difficile*.

There is no single federal definition of the term "rapid." It can range from minutes to hours, depending on context.

⁶¹According to NIH officials, NIH is responsible for the overall coordination, oversight, and management of the challenge. It is anticipated that all tests will have a maximum time to result of 90 minutes.

- NIH officials told us their agency has supported extramural projects related to the development of tests for antibiotic resistance by issuing grants and entering into contracts since fiscal year 2015.
- Separately from the Antimicrobial Resistance Diagnostic Challenge, BARDA entered into contracts with three organizations to develop tests focusing on the advanced stages of test development, including clinical trials, according to BARDA officials.
- Within DOD, the Defense Threat Reduction Agency is funding three projects using Other Transaction Authority or direct funding to a DOD Service laboratory, for developing tests.⁶²

Federal agencies have also taken steps to help reduce the chances of duplicative funding, including working with some international efforts to develop tests, according to agency officials. For example, NIH reviews current and pending support of key project personnel prior to issuing of any research award, to help ensure NIH support complements support from other agencies and organizations. Similarly, officials from HHS's Office of Global Affairs worked during the creation and launch of the NIH-BARDA challenge and an analogous United Kingdom innovation foundation competition called the Longitude Prize to help ensure these programs were designed to support different aspects of needed diagnostics.⁶³

HHS Has Funded Some Studies of Clinical Outcomes, but Has Not Clearly Identified Leadership, Roles, and Responsibilities

HHS has funded some studies to assess the extent to which testing patients to identify whether they have antibiotic-resistant infections leads to improved clinical outcomes, such as more effective treatment for patients or more judicious use of antibiotics.⁶⁴ However, HHS has not

⁶²Other Transaction Authority, in this case, is the term used by DOD to refer to legal acquisition instruments other than contracts, grants, or cooperative agreements, to carry out certain prototype projects. 10 U.S.C. § 2371b.

⁶³The Longitude Prize, run by a United Kingdom-based innovation foundation, is a 10 million pound prize with an 8 million pound payout intended to foster the development of an affordable, rapid, point-of-care test that will conserve antibiotics and improve delivery of global health care. See "Longitude Prize," accessed May 22, 2019, <https://longitudeprize.org>.

⁶⁴Previously, we reported that clinical benefits have not been well-established for some types of tests for infectious diseases. GAO, *Medical Devices: Challenges and Capabilities to Enable Rapid Diagnoses of Infectious Diseases*, GAO-17-347 (Washington, D.C.: Aug. 14, 2017).

identified relevant leadership, roles, and responsibilities among the HHS agencies that could fund such studies.

Clinical outcome studies are important for encouraging the use of diagnostic tests for antibiotic resistance, among other things, because such studies can demonstrate the benefits of those tests. According to PACCARB, there is very limited information on why clinicians sometimes forgo diagnostic testing, but one possible explanation is that there may be limited data demonstrating the value of such testing. In the absence of such data, a clinician may choose to treat the patient immediately rather than using a test for antibiotic resistance that has unknown value. Research into the clinical outcomes associated with such testing could therefore be used to help promote the use of those resistance tests that are found to be beneficial. As a result, patient care could be improved and clinicians could be guided towards appropriate antibiotics to prescribe.

Two HHS agencies have awarded grants for studies on the clinical outcomes of resistance testing, according to agency officials. For example, NIH provided grant support for a study that found, among other things, that using a rapid blood test for a range of potential bacteria and antibiotic resistance led to more judicious use of antibiotics.⁶⁵ Similarly, officials from the Agency for Healthcare Research and Quality (AHRQ) stated that the agency is funding investigator-initiated grant studies to assess the impact of tests on antibiotic stewardship. However, agency officials only mentioned these and a few other examples of studies they have funded on clinical outcomes.

⁶⁵R. Banerjee et al., "Randomized Trial of Rapid Multiplex Polymerase Chain Reaction-Based Blood Culture Identification and Susceptibility Testing," *Clinical Infectious Diseases*, vol. 61, no. 7 (2015): pp. 1071-1080, and E. L. Tsalik et al., "Advancing Diagnostics to Address Antibacterial Resistance: The Diagnostics and Devices Committee of the Antibacterial Resistance Leadership Group," *Clinical Infectious Diseases*, vol. 64, no. S1 (2017): pp. S41-S47.

International Needs for Diagnostic Tests for Antibiotic Resistance

To better understand international needs for antibiotic resistance tests, we interviewed officials from international organizations and the Office of Global Affairs within the Department of Health and Human Services (HHS). A Public Health England official told us that United Kingdom users are not confident that these tests will have a clinical impact or be cost effective. Similarly, an official from a trade organization of British medical test manufacturers told us that the value of tests for antibiotic resistance needs to be captured and disclosed, especially because people are more willing to pay for treatment than for tests.

However, other factors could also be important in determining which tests will be useful internationally. World Health Organization officials told us that they are working to determine what characteristics health care providers worldwide identify as key to making tests useful, so industry can develop such tests. They noted that tests designed for use in the United States may not be suitable for use in other countries. They also noted that laboratories in developing countries may not have the capacity to culture bacteria, so many need to use culture-independent tests.

Office of Global Affairs officials told us that a big challenge is developing accessible tests for use internationally. Their ideal test would be inexpensive, rapid, and capable of point-of-care use. They noted that cost and usability are the barriers to test use, not technology, and that use of existing tests remains limited, including within the United States.

Source: GAO summary of interviews with HHS and international organizations | GAO-20-341

Agency officials and experts agree that more needs to be done to evaluate clinical outcomes associated with use of diagnostic tests for antibiotic resistance. For example, in 2017, PACCARB reported that “there is a lack of clinical and economic outcome studies showing that any diagnostic test could prevent the emergence of antibiotic-resistant bacteria and would be cost effective.”⁶⁶ Officials we interviewed from AHRQ, BARDA, CDC, FDA, and NIH all agreed with that PACCARB statement. Additionally, experts told us that such studies are lacking but important for advancing the use of tests. For example, one health care organization official told us the decision to adopt a test is based at least in part on whether there will be a clinical benefit. An infectious disease expert noted that to provide incentives for test use there needs to be some evidence that tests affect and improve care, but that most tests do not come with any evaluation of how they perform in practice. International organizations expressed similar opinions.

One reason for the relatively low number of studies is that those agencies that could conduct or fund diagnostic outcome studies have not clearly identified leadership, roles, and responsibilities for doing so. Although they agree that more such studies are needed, they have not identified which agency or agencies should take the lead, and what the roles of the other agencies should be. Instead, agencies have offered differing views on what each agency could do. For example, BARDA officials told us their agency has not funded such studies because it generally does not play a role in test adoption. BARDA officials, as well as officials from DOD and NIH, said that CDC should play a role in funding or conducting the studies. However, CDC officials told us that a lack of resources has prevented their agency from doing so, and that the responsibility should fall at least partly on BARDA.

Our previous work shows that key practices for interagency collaboration include identifying a lead agency (or, if leadership is shared, clearly identifying roles and responsibilities among the lead agencies), as well as clarifying the roles and responsibilities of all participating agencies.⁶⁷ By taking these actions, agencies—including AHRQ, BARDA, CDC, FDA, and NIH—could more effectively address the need for clinical outcome

⁶⁶Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic Resistance* (Washington, D.C.: September 2017).

⁶⁷GAO, *Managing for Results: Key Considerations for Implementing Interagency Collaborative Mechanisms*, [GAO-12-1022](#) (Washington, D.C.: September 27, 2012).

studies. Those studies, in turn, could help demonstrate the value of diagnostic tests for antibiotic resistance, potentially increasing their use, improving patient care, and enhancing stewardship efforts.

CMS and FDA Have Taken Steps to Advance the Use of Tests, but Experts Have Identified Challenges with Payments

CMS and FDA have taken some steps to advance the use of tests, including those to identify antibiotic-resistant bacteria. For example, FDA established a Payor Communication Task Force, which helps facilitate communication between test manufacturers and payors.⁶⁸ Such communication is important because payors decide whether tests will be covered by insurance, among other things. According to an FDA web page, by communicating with payors, test manufacturers could, for example, learn what data payors need to approve a test for coverage and then use this information to design clinical trials to provide that information. This process could reduce the time between when a test is cleared or approved by FDA and when it is covered.⁶⁹

A similar step FDA and CMS took to advance the use of tests was to extend the Parallel Review program indefinitely, a move they announced in 2016. This program established a mechanism for FDA and CMS to simultaneously review clinical data, with the aim of reducing the time between FDA's approval and CMS's decision on whether to pay for the test.⁷⁰

Experts told us challenges remain with test payments that may result in lower test use. For example, a PACCARB report states that "currently, [payment] for many diagnostic tests is not aligned with the value of the test," and noted that supplementing payments for tests could drive test

⁶⁸According to an FDA web page, payors include public payors such as CMS, private health plans, health technology assessment groups, and others who provide input into coverage, procurement, and reimbursement decisions. See Food and Drug Administration, "Payor Communication Task Force," accessed September 26, 2019, <https://www.fda.gov/about-fda/cdrh-innovation/payor-communication-task-force>. FDA told us this task force was established approximately 5 years ago.

⁶⁹CMS officials told us they prefer the term "payment" to describe what documents such as the National Action Plan and PACCARB report call "reimbursement."

⁷⁰This mechanism would pertain to tests receiving marketing authorization as de novo devices, but not to tests cleared under the 510(k) process based on a determination of substantial equivalence to an already legally marketed test.

development and use. BARDA officials also told us that a major factor affecting adoption of new tests is the cost of the test relative to reimbursement. Additionally, experts, including those at our meeting, told us that test payments remain insufficient to encourage broad test use.⁷¹ For example, two experts from our meeting said that there is not always a clear link between the medical value of a test and the payment level for that test. One of these experts added that their laboratory decided not to adopt a test because low payment levels relative to costs made doing so a money-losing proposition. Three other experts we interviewed agreed that disparities between cost and payment can discourage test adoption.

Regarding federal payments for tests involving CMS and their payments through Medicaid and Medicare, there are limits to CMS's ability to address any disparities. For example, CMS officials told us the payments for some tests are based on a weighted, median, private-payor rates pursuant to the Protecting Access to Medicare Act of 2014, so CMS cannot specify the methodology used to set those rates.⁷² Further, for inpatient tests, Medicare pays hospitals a single, bundled payment per patient stay, which is based on multiple factors, including the patient's diagnosis and treatment strategy, rather than on a specific service. As such, a separate payment for individual tests is not made under Medicare.

⁷¹We did not independently verify expert claims regarding payments for test use.

⁷²Pub. L. No. 113-93, § 216, 128 Stat. 1040, 1053 (codified in pertinent part at 42 U.S.C. § 1395m-1(b)).

FDA Efforts to Advance the Development of New Tests

FDA Has Taken Steps to Speed the Development of Tests for Newly Approved Antibiotics

FDA has taken steps toward the development of FDA-authorized tests for resistance for newly approved antibiotics—a process that currently can take months to years, according to experts and agency officials.⁷³ The delay stems in part from the need for a critical testing threshold known as a breakpoint—the threshold that is used to help a clinician decide whether or not a pathogen is resistant to the antibiotic (see text box).⁷⁴ The breakpoint of a new antibiotic is generally finalized only when FDA has approved the antibiotic. This means that breakpoints may often not be available for test manufacturers until after a new antibiotic is FDA-approved.⁷⁵ As a result, test manufacturers generally may not be able to complete developing FDA-authorized culture-based tests for resistance to a specific antibiotic until after the antibiotic is commercially available. The result is that the development of such culture-based tests may be generally delayed even after the new antibiotic is approved by FDA. This delay could affect the ability of clinicians to treat patients. For example, according to an expert, such a delay could lead to underuse of a newly available antibiotic, among other things, because a clinician may not be willing to prescribe the antibiotic without test results to guide treatment.

⁷³According to FDA, different types of tests generally have different times for development after FDA approval of a new antibiotic. For example, some automated tests are the most delayed in being submitted for FDA clearance because of the sophistication of such tests. FDA officials told us one exception is for a type of test called “disk diffusion tests” that are evaluated as part of the drug approval process for new antibiotics. Such tests are often cleared within weeks of drug approval.

⁷⁴Culture-based tests examine how well bacteria grow in the presence of an antibiotic. Another type of resistance test is a genotypic test, which directly detects genes that can make bacteria resistant. We focus on culture-based tests.

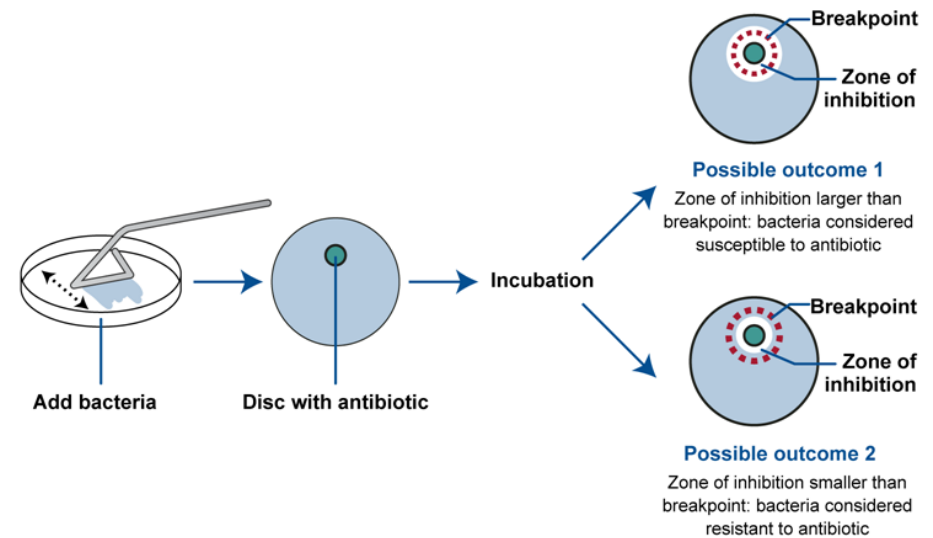
⁷⁵One test manufacturer stated that there is a risk that the new antibiotic will ultimately not be approved by FDA. Thus, test manufacturers may wait for more certainty regarding the approval of a new antibiotic before committing resources to developing a test for it.

How Breakpoints Are Used to Interpret Tests

According to officials from the Food and Drug Administration (FDA), breakpoints, also referred to as “susceptibility test interpretive criteria,” are used to define susceptibility and resistance to antibiotics to help guide patient care. Culture-based tests rely on breakpoints to provide a determination of resistance to clinicians. In the United States, breakpoints (based on clinical or microbiological data) are established by standards-development organizations such as the Clinical and Laboratory Standards Institute (CLSI) and FDA.

One example of how breakpoints are used involves the Kirby-Bauer disk diffusion test. This test is conducted by spreading bacteria on a laboratory agar plate containing bacterial nutrients, and then placing paper disks containing a known amount of antibiotics on the “lawn” of bacteria. Plates are observed after overnight incubation to determine the extent of bacterial growth. Closer to the disk, there is a higher concentration of antibiotic, and the concentration declines with distance. Around most disks, there is a “zone of inhibition,” where the concentration of antibiotic is too high for bacteria to grow. After allowing the bacteria to grow for a defined period of time, the diameter of the zone of inhibition is measured in millimeters.

Procedure for Assessing Antibiotic Resistance Using Breakpoints



Source: GAO analysis of literature and technical documents. | GAO-20-341

If the diameter is larger than or equal to the breakpoint, then the strain of bacteria is considered susceptible to the antibiotic, suggesting that the antibiotic can be used to treat infections caused by that strain. If the diameter is smaller than the breakpoint, then the strain is considered resistant, suggesting that the antibiotic should not be used. According to FDA, in most cases, there is a range of “intermediate” or “susceptible dose-dependent” diameters for which treatment might be effective.

Other types of culture-based diagnostic tests for resistance have analogous breakpoints for interpreting the test. For example, the minimum inhibitory concentration—the lowest concentration of an antibiotic that prevents growth of bacteria—can be compared to a breakpoint to establish whether the bacteria are considered resistant.

Source: GAO summary of interviews and documents from FDA and others. | GAO-20-341

In addition to antibiotic developers waiting until FDA approves an antibiotic before a breakpoint is finalized, there are technical hurdles in developing a test for some new antibiotics, according to FDA officials. For example, it may be challenging for certain automated test manufacturers to address unique growth properties of certain bacteria in the presence of specific antibiotics or combinations of antibiotics. According to a test manufacturer, these hurdles include the need for additional studies, and such studies may not be straightforward because of the need to determine what clinical data FDA requires.⁷⁶ In addition, in the case of automated tests, a representative from a test manufacturer association told us the software used to run and interpret a new test needs to be revised, which can be time consuming.

The delay between approval of an antibiotic and the availability of a test for resistance could result in suboptimal treatment and increase burdens on the health care system. For example, one expert stated that during this delay, laboratories need to create or modify tests and then validate those tests instead of using a FDA-authorized test, which increases the time required and places demands on facility personnel and budgets. This expert added that to conduct validation studies, the laboratories need a variety of samples for testing, called “isolates,” which may not be available. A second expert said that the delay leads to both overuse and underuse of the new antibiotic: in the absence of a test, some clinicians will prescribe the antibiotic when it may be inappropriate, leading to overuse; some other clinicians refrain from prescribing the antibiotic, even if appropriate, leading to underuse.

To help address this delay, FDA has created a process known as coordinated development, whereby test manufacturers can submit a coordinated development plan to FDA describing the test manufacturer’s intent to coordinate with the antibiotic manufacturer. The plan is submitted

⁷⁶FDA officials told us FDA provides guidance documents that can help address this issue. These include Department of Health and Human Services, Food and Drug Administration, *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems* (Aug. 28, 2009) and Department of Health and Human Services, Food and Drug Administration, *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program, Guidance for Industry and Food and Drug Administration Staff* (May 7, 2019).

prior to, or shortly after, submission of an application to market a new drug.⁷⁷

Under the coordinated development program, FDA shares breakpoint information from the antibiotic manufacturer with a prospective test manufacturer.⁷⁸ It then reviews the test application at the same time as the antibiotic application and takes other steps to facilitate more timely clearance of the test. FDA officials told us this process has significantly reduced the delay between approval of the antibiotic and clearance of the test.⁷⁹

Another FDA step to help test manufacturers speed development of tests is the establishment, in collaboration with CDC, of a centralized repository of bacterial strains with well-characterized antibiotic resistance profiles. These strains are available to test manufacturers and others to help them design, validate, and evaluate tests by checking that they give the correct results for bacteria whose profile of antibiotic resistance is known.⁸⁰ Finally, FDA officials also said that they offer pre-submission advice, whereby a test manufacturer can ask for initial guidance on the design of clinical studies for their tests.

⁷⁷Department of Health and Human Services, Food and Drug Administration, *Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices: Guidance for Industry and Food and Drug Administration Staff; Availability*, 84 Fed. Reg. 1152 (Feb. 1, 2019). FDA guidance pertaining to the development of antimicrobial drugs may apply to drugs that inhibit or destroy bacteria or fungi. See 21 U.S.C. § 321(jj); 42 U.S.C. § 247d-5(k).

⁷⁸FDA officials told us this information can only be shared if the drug and test manufacturers permit it.

⁷⁹For specific drugs approved since coordinated development was implemented, FDA provided some examples of the time from drug approval to device clearance for those tests that used coordinated development versus those that did not. While we did not independently confirm the times that resulted from the coordinated development process, examples of tests FDA provided us that used coordinated development had shorter times from drug approval until test clearance compared to tests that did not.

⁸⁰See Food and Drug Administration, "The CDC and FDA Antimicrobial Resistance Isolate Bank," accessed January 21, 2020, <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm454677.htm>. CDC stated it is responsible for the collection, maintenance, and restocking of these specimen banks. FDA noted that the day-to-day operation and the vast majority of the financial support is provided by CDC.

FDA Has Taken Steps to Improve Breakpoint Recognition

In the United States, breakpoints are established and updated by organizations such as the Clinical and Laboratory Standards Institute (CLSI).⁸¹ After CLSI establishes a breakpoint, FDA may review and recognize the breakpoint, according to FDA officials. Test manufacturers rely on breakpoints recognized by FDA to support marketing authorization of their tests.⁸²

An expert who works for CLSI identified more than 50 breakpoints that have not been recognized by FDA, and for which CLSI considers FDA recognition important in order to help make FDA-authorized tests available.⁸³ Experts, including one from our meeting, cited the following examples of breakpoints needing recognition:

⁸¹The 21st Century Cures Act authorized FDA to recognize breakpoints developed by a nationally or internationally recognized standard development organization if the standard development organization meets specified criteria. 21st Century Cures Act, Pub. L. No. 114-255, §3044, 130 Stat. 1115-16 (Dec. 13, 2016), codified at 21 U.S.C. § 360a-2. According to FDA, CLSI is the only organization for which FDA has made such a determination. Additionally, FDA also recognizes breakpoints that are different from CLSI, due to basic disagreements in scientific rationales for those breakpoints, among other reasons. One expert at our meeting told us that a common reason for FDA not recognizing a breakpoint is that the breakpoint may be associated with an unapproved, or “off-label,” use of an antibiotic, such as use of the antibiotic at an unapproved dose. Once FDA approves a drug, clinicians sometimes prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient. However, our report is not only about unapproved uses. FDA-recognized breakpoints are available online as part of the 21st Century Cures Act requirements. See Food and Drug Administration, “Antibacterial Susceptibility Test interpretive Criteria,” last accessed February 28, 2020, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm>.

⁸²Genotypic tests do not rely on breakpoints and can still be cleared by FDA in the absence of breakpoints.

FDA told us when FDA does not recognize a breakpoint, it may still identify a separate breakpoint, or interpretive criteria, appropriate for use by a test manufacturer in the development of its tests, under section 511A(b)(2)(B), 511A(c)(1) and (c)(2) of the Federal Food, Drug, and Cosmetic Act, codified at 21 U.S.C. §§ 360a-2(b)(2)(B), 360a-2(c)(1), and 360a-2(c)(2), but FDA has not yet done so.

⁸³While we did not independently verify the claim of importance, we confirmed that there are over 50 breakpoint discrepancies between a list provided by an expert working with CLSI in October 2018, and the breakpoints listed on the FDA website. See Food and Drug Administration, “Antibacterial Susceptibility Test Interpretive Criteria.” CLSI does not consider all 50 breakpoints to be of the same priority, according to the expert. We did not confirm the list provided by the expert against CLSI documentation.

- CDC recommends a dual therapy of antibiotics—azithromycin and ceftriaxone—to be taken together to treat gonorrhea.⁸⁴ However, FDA does not recognize any azithromycin breakpoints for *N. gonorrhoeae*, which an expert from our meeting told us could be a barrier to developing FDA-authorized culture-based tests for *N. gonorrhoeae* resistance to the recommended dual therapy.⁸⁵
- Colistin is an antibiotic used in hospitals because of its efficacy against carbapenem-resistant bacteria, according to one manufacturer of a test for colistin resistance. This manufacturer markets its test in many countries but not in the United States, because FDA does not recognize colistin breakpoints.⁸⁶

FDA has taken some steps to address unrecognized breakpoints, which are a potential barrier to developing some tests for antibiotic resistance.⁸⁷ For example, FDA officials told us that the agency conducts regular internal reviews of breakpoints. According to FDA officials, the agency reviewed the 2019 CLSI breakpoint standards and updated FDA's

⁸⁴According to CDC officials, CDC is currently in the process of updating their treatment guidelines for gonorrhea. The earlier recommendation for dual therapy for gonorrhea with azithromycin and ceftriaxone was based on the theoretical benefit of providing a shield (azithromycin) to protect ceftriaxone from increasing gonorrhea resistance. See K. A. Workowski and G. A. Bolan, "Sexually Transmitted Treatment Guidelines, 2015," *Morbidity and Mortality Weekly Report Recommendations and Reports*, vol. 64, no.3 (2015). Given increasing resistance to azithromycin now found in numerous pathogens and the continued importance of applying antibiotic stewardship principles to treatment decisions that impact the public's health, CDC is currently reviewing optimal gonorrhea treatment options for incorporation into forthcoming sexually-transmitted disease treatment guidelines.

⁸⁵There are other challenges with making a test for resistant gonorrhea, including challenges in culturing the bacteria. However, without FDA-recognized breakpoints, surmounting those other challenges may not result in an FDA-authorized diagnostic test.

FDA officials told us they received a comment requesting recognition of this breakpoint in June 12, 2019.

⁸⁶According to FDA, it published a notice on June 10, 2019, concluding that the scientific data available do not support recognizing breakpoints for colistin at this time.

⁸⁷FDA officials told us that the biggest challenge that they see to recognizing breakpoints is the lack of necessary data to support breakpoint changes. FDA also told us it may not identify or recognize updated breakpoints unless there are data to support a scientific finding that breakpoints should be changed, under section 511A(a)(3) and (c)(2) of the Federal Food, Drug, and Cosmetic Act, codified at 21 U.S.C. §§ 360a-2(a)(3) and (c)(2).

website with changes to recognized breakpoints as of June 2019. FDA has been posting such updates since December 13, 2017.⁸⁸

FDA also accepts public comments requesting the recognition of new breakpoints, according to agency officials.⁸⁹ However, we found there was some confusion between CLSI officials and experts and the FDA involving the number of comments FDA could review each year, which FDA later clarified on its website. One expert at our meeting later told us that CLSI adjusts its process for submitting comments based in part on their understanding of FDA's communication. This expert added that FDA making a public commitment to a specific number of comments they would review would help CLSI improve its planning.

FDA officials told us there is no legal requirement for FDA to communicate the number of comments the agency can review, but that in previously published notices of opportunities for public comments, there was nothing that indicated there would be limits. However, after we informed FDA officials of concerns by experts regarding the number of comments FDA could review, FDA updated their webpage to clarify that they will review all submitted comments.⁹⁰

⁸⁸Food and Drug Administration, "Notice of Updates," accessed May 29, 2019, <https://www.fda.gov/drugs/development-resources/notice-updates>. These updates may reflect FDA's recognition of revised CLSI breakpoints or may reflect other types of changes to FDA's listed breakpoints, such as initial breakpoints identified by FDA at the time that a new drug is approved. FDA officials told us FDA is required by the 21st Century Cures Act to evaluate any appropriate new or updated breakpoints established by a standards development organization, as appropriate, every 6 months. Pub. L. No. 114-255, § 3044(a), 130 Stat. 1114, codified at 21 U.S.C. § 360a-2(c)(1)(A).

⁸⁹FDA reviews recommendations made in public comments under section 511A(c)(2) and (c)(3) of the Federal Food, Drug, and Cosmetic Act, codified at 21 U.S.C. §§ 360a-2(c)(2) and (c)(3).

⁹⁰FDA officials told us they updated their breakpoint webpage to include the statement, "FDA will review all substantive submissions to support updating of susceptibility test interpretive criteria," to ensure clarity about FDA's commitment to reviewing all comments to the public docket. See Food and Drug Administration, "FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria," accessed January 22, 2020, <https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria>.

FDA Has Taken Limited Steps to Monitor Use of Updated Breakpoints

FDA has taken limited steps to monitor whether FDA-authorized tests are using new breakpoints after these breakpoints are updated and accepted by FDA. Because bacteria can develop increasing resistance to antibiotics, it is sometimes important to change the breakpoints used for determining whether or not bacteria are resistant to a given antibiotic. Using tests with out-of-date breakpoints could result in misidentifying a resistant infection as non-resistant, which can lead to treating a patient with an ineffective antibiotic and the further spread of the infection. FDA officials told us the agency has taken limited steps to monitor the status of breakpoint updates, and that out-of-date breakpoints being used in tests should be a rare occurrence.⁹¹

In contrast, a CDC official told us that keeping tests updated is a significant concern. This official cited the example of carbapenem-resistant Enterobacteriaceae infection, which triggers specific procedures to limit the spread of these bacteria. If the test breakpoint is out of date, the infection may not be detected in a timely manner, and the pathogen could spread broadly as a result. A recent study looking at hypothetical scenarios in one U.S. county estimated that a 32-month delay in updating tests to match CLSI breakpoints for carbapenem-resistant Enterobacteriaceae would have resulted in an average of almost 2,000

⁹¹For example, FDA officials told us of its implementation of “change protocols” in 2019 for certain tests that were first implemented in 2019. These protocols permit device manufacturers, under certain conditions, to update test breakpoints frequently for cleared tests without the need to submit a new 510(k) for FDA review. FDA told us it expects this protocol will significantly reduce the time frame for updating device breakpoints when new breakpoints are published, while maintaining test safety and efficacy. FDA officials explained that this protocol will encourage manufacturers to incorporate up-to-date breakpoints in their tests by not requiring a regulatory submission in most, if not all, instances. However, FDA did not explain how this relates to FDA’s monitoring, or addressing of existing out-of-date breakpoints.

additional carriers of these bacteria county-wide.⁹² Additionally, an expert told us that use of out-of-date breakpoints could lead to improper patient care, improper surveillance reporting, and slower detection of emerging resistance.⁹³ However, the true impact of this issue is challenging to discern (see text box).

The Extent of Any Negative Effects of Out-of-Date Breakpoints on Public Health Is Unclear

Experts and agency officials voiced a range of opinions on the public health effects of tests with out-of-date breakpoints. For example, one Centers for Disease Control and Prevention (CDC) official told us that despite the lack of breakpoint updates, cases of a type of carbapenem-resistant Enterobacteriaceae were likely ultimately caught by hospitals because a second test was used by all but a small number of hospitals. One expert stated that how quickly test breakpoints are updated is less important when deciding what test to adopt than other factors, such as ease of use. However, another expert noted that laboratories addressing emerging threats may feel the need to use non-Food and Drug Administration (FDA) cleared tests, because they are aware that FDA-cleared tests may not be updated as quickly as needed. Test updates may be an issue for smaller laboratories, which do not have dedicated personnel keeping track of breakpoint revisions, Department of Veterans Affairs officials told us.

Source: GAO summary of interviews with CDC and others. | GAO-20-341

FDA officials told us that because manufacturers are strongly motivated to keep their tests current, only a few tests have out-of-date breakpoints.⁹⁴

⁹²S. M. Bartsch et al., “Impact of Delays between Clinical and Laboratory Standards Institute and Food and Drug Administration Revisions of Interpretive Criteria for Carbapenem-Resistant Enterobacteriaceae,” *Journal of Clinical Microbiology* vol. 54, no. 11 (2016): pp. 2757-2762. The countywide average is the average number of additional carriers among facility types—acute care hospitals, long-term acute care facilities, and free-standing nursing homes. The reported countywide average from a 2.5-year delay was 1,821.0 more carbapenem-resistant Enterobacteriaceae carriers (95 percent confidence interval: 1,009.6 to 2,632.4). FDA officials noted that this publication predated enactment of the 21st Century Cures Act, which provides for a more streamlined process for incorporating up-to-date information into tests. However, FDA did not discuss how the Act might affect the outcomes discussed in the study.

⁹³FDA officials told us genomic tests are important for identifying bacteria such as carbapenem-resistant Enterobacteriaceae and that some genomic tests are increasingly used. However, they did not address how genomic tests may affect the use of existing tests with out-of-date breakpoints.

⁹⁴FDA told us that it considers this to be the case mainly because manufacturers want to make sure their devices are updated. However, FDA did not provide evidence for this assertion, and one test manufacturer told us they question this assessment.

However, the only confirmation FDA officials offered for this statement was to mention an unofficial internal survey of FDA's database of existing tests, conducted in March 2019, which concluded that all FDA-authorized tests had implemented breakpoint updates made since December 13, 2017.⁹⁵ They said this survey is not conducted regularly. They also stated that it is possible that some tests have not been updated to reflect breakpoint updates made prior to December 13, 2017, but that FDA is unaware of any such tests that also pose a public health threat.⁹⁶

To assess the extent to which there are FDA-authorized tests using out-of-date breakpoints, we spoke with experts and stakeholders and reviewed studies they identified. We identified several FDA-authorized tests with breakpoints that were changed nearly a decade ago. Some of these tests could be used for diagnosing infection with carbapenem-resistant Enterobacteriaceae, which CDC identified as an urgent threat. One manufacturer told us that one of their tests has not been updated with new breakpoints nearly 10 years after a breakpoint revision. FDA officials acknowledged it is possible some FDA-authorized tests might continue to rely on outdated breakpoints.⁹⁷ Further, in 2019, a scientific article listed four different test manufacturers offering tests that have not been fully updated to reflect revised breakpoints, including some affecting

FDA recommends, but does not require, that test manufacturers update their labeling to conform to new, publicly available breakpoints within 90 days. Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry, Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices; Availability*, 74 Fed. Reg. 31740 (July 2, 2009).

⁹⁵FDA restricted its survey to those breakpoint updates listed on the FDA's breakpoint web site and excluded newly approved drugs, since it does not consider breakpoints for new drugs to be breakpoint changes.

⁹⁶FDA officials noted that no actual harm has to occur to be considered a public health threat. They told us they assess public health threats using a risk-assessment framework, in which FDA analyzes the frequency or severity of an inaccurate result, among other things. Additional information can be found at Department of Health and Human Services, Food and Drug Administration, *Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions: Guidance for Industry and Food and Drug Administration Staff* (Rockville, Md.: Dec. 27, 2016). FDA told us that some tests using out-of-date breakpoints may not pose a public health concern due to various mitigating factors. FDA noted that identifying cause of concern is complicated and requires deep analysis.

⁹⁷FDA officials told us that the tests being asked about provide information for the user to interpret based on criteria other than FDA-recognized breakpoints. However, using this approach typically requires additional studies by the test user.

antibiotics for some types of carbapenem-resistant Enterobacteriaceae.⁹⁸ Finally, CDC officials told us they asked hospital laboratories in a survey for 2017 and 2018 if they had updated their tests to reflect revisions in breakpoints for carbapenem-resistant Enterobacteriaceae that were implemented in 2010. According to CDC, nearly 1,000 of over 5,000 responding hospital laboratories had not implemented the revised breakpoints, and, of these, over 85 percent were using FDA-authorized tests.⁹⁹

One CDC official stated that there is significant concern for patient safety associated with out-of-date breakpoints, and another said that there are few justifications for failing to update the tests after 8 years. FDA officials told us they have not received reports of suspected device-associated deaths, serious injuries, or malfunctions that are specific to out-of-date carbapenem-resistant Enterobacteriaceae breakpoints in FDA-authorized tests using such breakpoints. The officials added that it is possible to detect carbapenem-resistant Enterobacteriaceae under certain situations, even if the test had an out-of-date breakpoint for a given antibiotic against these bacteria.

However, FDA does not know the actual negative effect, if any, of out-of-date breakpoints because it does not know how many FDA-authorized tests rely on such breakpoints. Since December 2017, FDA has conducted one unofficial survey of tests to assess breakpoint updates that was limited in scope and is not a regular event. Other than that, FDA is relying on market incentives to drive manufacturers to make sure their devices are updated.¹⁰⁰

According to FDA and others, the extent of the problem is not clear. However, PACCARB identified updating test breakpoints as an important

⁹⁸R. M. Humphries, A. N. Abbott, and J. A. Hindler, "Understanding and Addressing CLSI Breakpoint Revisions—A Primer for Clinical Laboratories," *Journal of Clinical Microbiology*, vol. 57, no. 6 (2019): pp. e00203-19.

⁹⁹In some cases, diagnostic test users could choose not to update their test(s). For example, VA officials note that there may be good reasons why test users may not want updated breakpoints, such as different antibiotic resistance patterns in their locale.

¹⁰⁰FDA told us they also evaluate risk by review of medical devices reports, attendance at major scientific meetings, and participation in CLSI activities, among other activities. However, evaluation of risk is not the same as monitoring status.

issue in a 2017 report.¹⁰¹ Additionally, one of the sub-objectives in the National Action Plan notes that rapid updating of breakpoints is essential to provide accurate information to guide appropriate drug treatment.¹⁰² Finally, the Standards for Internal Control in the Federal Government directs management to establish and operate monitoring activities to monitor its internal control systems and evaluate the results.¹⁰³ In this case, monitoring and evaluation of the status of breakpoint updates in FDA-authorized tests could help FDA identify and address the National Action Plan sub-objective, as well as a strategic priority in the mission statement of its Center for Devices and Radiological Health: “FDA assures that patients and providers have timely and continued access to safe, effective and high-quality medical devices.”¹⁰⁴

FDA officials said they do not believe the issue is a significant problem, but the agency has also not regularly evaluated any effects of using tests for antibiotic resistance with out-of-date breakpoints.¹⁰⁵ FDA officials stated that there may be resource constraints to their ability to conduct regular monitoring and evaluation. By regularly monitoring and evaluating FDA-authorized tests, FDA would be better positioned to determine the extent of tests relying on out-of-date breakpoints and may be better positioned to provide assurance that patients and providers have timely access to safe and effective tests. Furthermore, by regular monitoring, FDA would be able to determine whether test manufacturers are updating breakpoints as needed, and help ensure that patient care and infection control efforts are effective.

¹⁰¹Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics*. The relevant report section focused on microbiology laboratories’ updating of technologies, in addition to breakpoints, which could fall under CMS actions. We focus on FDA given that the majority of tests in use are FDA-authorized tests, and our primary attention is on breakpoint updates.

¹⁰²The White House, *National Action Plan*, sub-objective 1.1.5, p. 19.

¹⁰³[GAO-14-704G](#).

¹⁰⁴Food and Drug Administration, *2018-2020 Strategic Priorities: Center for Devices and Radiological Health* (January 2018), p. 3.

¹⁰⁵FDA officials told us they continue to use various postmarket surveillance tools to monitor device performance, detect device-related safety issues, and contribute to benefit-risk assessment of devices including these tests. However, they did not discuss how these tools enable FDA to proactively determine whether tests are not being updated in a timely manner.

Federal Efforts Have Not Fully Addressed Challenges to Developing New Treatments for Antibiotic-Resistant Infections

Experts, federal officials, and antibiotic developers have identified economic and other challenges to developing new antibiotics. Federal agencies, including HHS and DOD, have engaged in efforts to address some of the challenges; however, experts said these efforts are not sufficient and that additional federal incentives are needed to encourage the development of new antibiotics.

Economic and Other Challenges to Developing New Treatments Exist

Experts are concerned about a void in the discovery of new antibiotic classes and the current pipeline of antibiotics in development. According to The Pew Charitable Trusts, a nonprofit public policy organization that tracks the pipeline of antibiotics, no new classes of antibiotics approved for human use have been discovered since 1984.¹⁰⁶ In addition, experts are concerned that the number of antibiotics in clinical development is insufficient to meet the threat of antibiotic resistance. For example, according to The Pew Charitable Trusts, only 42 antibiotics were in clinical development globally—meaning clinical trials were being conducted to test their safety and efficacy in humans—as of June 2019, and only 24 of them targeted bacteria on CDC’s or WHO’s priority lists.¹⁰⁷ According to a recently published analysis, the authors found that the pipeline of antibiotics that target gram-negative bacteria is dominated by derivatives of existing classes of antibiotics and “does not sufficiently

¹⁰⁶This discovery void is concerning because when bacteria become resistant to one type of antibiotic, it is often resistant to others within the same class. Drugs can be classified according to similarities in chemical structure, among other ways.

¹⁰⁷The Pew Charitable Trusts, “Antibiotics Currently in Global Clinical Development,” accessed June 4, 2019, <https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development>.

address the problem of extensively drug-resistant gram-negative bacteria”.¹⁰⁸

Experts from our meeting, antibiotic developers, and federal officials we spoke with identified major economic challenges to developing new antibiotics that commonly result from a poor return on investment. Antibiotics, like other types of pharmaceutical drugs, require substantial investment and many years to bring a new drug to market. We previously reported that for a new drug, the entire R&D process, including basic research, drug discovery, clinical trials, and FDA review, can take up to 15 years, often accompanied by high costs.¹⁰⁹ We also previously reported that an important incentive for pharmaceutical R&D investment is the potential for high revenue typically associated with a large number of patients or high drug prices.¹¹⁰ However, sales revenues for brand-name antibiotics are often low. For example, studies found that median annual sales for brand name antibiotics between 2011 and 2015 ranged from \$24 million to \$75 million, whereas annual sales for most new, brand-name oncology drugs were more than \$500 million during the same period.¹¹¹ Antibiotic developers we interviewed and experts have

¹⁰⁸U. Theuretzbacher et al., “Analysis of the Clinical Antibacterial and Antituberculosis Pipeline,” *The Lancet Infectious Diseases*, vol. 19, no. 2 (2019): pp. 40-50. Specifically, the authors found that the pipeline does not sufficiently address the bacteria *A. baumannii*, *P. aeruginosa*, and Enterobacteriaceae.

¹⁰⁹GAO, *Drug Industry: Profits, Research and Development Spending, and Merger Acquisition Deals*, [GAO-18-40](#) (Washington, D.C.: Nov. 17, 2017).

For example, one study estimated the average cost per new molecular compound that received FDA approval between 2005 and 2013 to be \$1.4 billion. See J. A. DiMasi, H. G. Grabowski, and R. W. Hansen, “Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs,” *Journal of Health Economics*, vol. 47 (2016): pp. 20-33. Other studies suggest lower development costs. For example, another study estimated a median cost to develop cancer drugs of \$0.6 billion. See V. Prasad and S. Mailankody, “Research and Development Spending to Bring Single Cancer Drug to Market and Revenues After Approval,” *JAMA Internal Medicine*, vol. 177, no. 11 (2017): pp. 1,569-1,575.

¹¹⁰[GAO-18-40](#).

¹¹¹Duke Margolis Center for Health Policy, *Value-Based Strategies for Encouraging New Development of Antimicrobial Drugs*, and IMS Institute for Healthcare Informatics, *Medicines Use and Spending in the U.S. A Review of 2015 and Outlook to 2020* (Parsippany, N.J.: April 2016).

The Duke Margolis Center also reported that only five of the 16 new brand-name antimicrobials approved since 2000 generated annual sales above \$100 million.

identified multiple factors that can limit the profitability of new antibiotics when they reach the market, including:

- Prices for new antibiotics are considered low compared to other life-saving drugs, such as cancer drugs, because they must compete with inexpensive generic antibiotics, which remain effective enough to influence pricing of new antibiotics.¹¹²
- Antibiotics are typically used for a short duration, unlike drugs for chronic diseases that patients use for many months or years.
- Antibiotic stewardship principles encourage the appropriate use of antibiotics to help prevent resistance. According to the Duke University Margolis Center for Health Policy, most novel treatments for antibiotic-resistant infections have a narrow set of patients for whom the treatment would be appropriate.¹¹³

As a result of the perceived poor return on investment, many large pharmaceutical companies have discontinued their antibiotic development in recent years. In 2018, according to The Pew Charitable Trusts and other published sources, four large pharmaceutical companies worldwide had antibiotics in clinical development globally compared to 1990, when 18 were involved in antibiotic R&D.¹¹⁴ Two antibiotic companies declared bankruptcy in 2019; in the case of one, the company filed for bankruptcy only 10 months after its antibiotic, which targets resistant bacteria, received FDA approval.¹¹⁵ The majority of antibiotics in the development pipeline are being developed by smaller companies that do not have other drugs on the market to help cover their R&D costs. However,

¹¹²Some experts believe the prices of new antibiotics do not reflect their public health value—that is, the value they provide not just to the patient, but also to society—because effective treatment prevents the antibiotic-resistant bacteria from spreading. See Duke Margolis Center, *Value-Based Strategies for Encouraging New Development of Antimicrobial Drugs*.

¹¹³Duke Margolis Center, *Value-Based Strategies for Encouraging New Development of Antimicrobial Drugs*.

¹¹⁴The Pew Charitable Trusts, “Tracking the Global Pipeline of Antibiotics in Development,” accessed November 29, 2019, <https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2019/03/tracking-the-global-pipeline-of-antibiotics-in-development>; and P. Sharma and A. Towse, Office of Health Economics, *New Drugs to Tackle Antimicrobial Resistance: Analysis of EU Policy Options* (London, England: April 2011).

¹¹⁵A third company, which gained FDA approval for an antibiotic that treats complicated intra-abdominal infections in 2018, announced in 2019 that it would reduce its workforce and cease research functions to focus its financial resources on commercializing its approved antibiotic. In March 2020, the company announced it would be acquired by another company.

representatives from three small antibiotic developers we spoke with noted that their field is struggling because it is difficult to raise funds from private investors due to the low return on investment potential.

Further complicating these economic challenges, federal officials and antibiotic developers we spoke with also identified challenges in conducting clinical trials for antibiotics, which can make it difficult to meet FDA's regulatory requirements for approval.¹¹⁶ This is particularly true for antibiotics that would treat antibiotic-resistant infections. Specifically, they noted the following three challenges:

Overview of Clinical Trials

Before approving a new drug, the Food and Drug Administration (FDA) generally requires a drug's developer to conduct clinical trials in humans to assess its safety and effectiveness against a specific disease or illness—called an "indication." Two types of trials that may be used are:

- Superiority trials, which aim to show that the drug being investigated is more effective than an existing drug.
- Non-inferiority trials, which aim to demonstrate that the difference between the effectiveness of the drug being investigated and an existing drug is small enough to show that the drug being studied is also effective.

Typically, there are three phases of clinical trials, with the sizes of the trials increasing with each phase. FDA generally prefers that when conducting clinical trials, developers demonstrate the effectiveness of a new drug by showing its impact on a clinical endpoint—a direct measure of how a patient feels, functions, or survives. FDA also accepts surrogate endpoints, which are laboratory measures or physical signs used as a substitute for a clinical endpoint that reasonably predict a clinical benefit.

Source: GAO and FDA. | GAO-20-341

- **Enrolling patients in clinical trials.** Identifying and enrolling patients with bacterial infections into certain clinical trials prior to initiating treatment can be difficult due to a lack of available rapid diagnostic tests to identify the type of infection and the urgent need to begin treatment immediately for acute infections. According to FDA officials, this is problematic for clinical trials because any prior treatment could obscure the true efficacy of the drug under investigation. Recognizing this often unavoidable issue, FDA has issued guidance giving antibiotic developers additional, but limited, flexibility with their clinical trial protocols in certain cases.¹¹⁷

In addition, certain types of antibiotic-resistant infections are rare and, therefore, antibiotic developers and federal officials told us it can be difficult to find patients to enroll in clinical trials to test antibiotics that target resistant bacteria. FDA officials told us that, for some types of bacterial infections, only 5 to 10 percent of patients have an infection caused by a resistant bacterial strain.

- **Demonstrating superiority of a new antibiotic.** Two antibiotic developers told us that, for most antibiotics, it is difficult to conduct superiority clinical trials and more feasible to conduct non-inferiority

¹¹⁶Before approving a new drug, FDA generally requires the developer to conduct clinical trials in humans to assess its safety and effectiveness against a specific disease or illness—called an "indication."

¹¹⁷For example, in its guidance about developing drugs for complicated urinary tract infections, FDA states that up to 25 percent of patients in a clinical trial may have received another type of drug before receiving the drug under investigation. Department of Health and Human Services, Food and Drug Administration, *Complicated Urinary Tract Infections: Developing Drugs for Treatment: Guidance for Industry* (Silver Spring, Md.: June 2018).

trials, because the latter allows for smaller enrollment.¹¹⁸ (See side bar for an explanation of clinical trial types.) They told us that the inability to demonstrate their drug's superiority limits their ability to market the drug, because it can be difficult to convince purchasers (e.g., hospitals) to choose the newly approved antibiotic over existing antibiotics, especially when the new antibiotic is significantly more expensive.

- **Gaining approval for multiple indications.** FDA generally approves drugs for a specific indication; therefore, antibiotic developers told us they tend to design their clinical trials around common infection types, largely because of the relative ease of enrolling patients. However, some antibiotics can treat infections in multiple parts of the body, which may not have been studied in a clinical trial.¹¹⁹ While providers are able to prescribe drugs for "off-label" use—that is, for a condition or patient population for which the drug has not been approved—they may lack information on the safety and efficacy of the drug for such use. In addition, such off-label use may not be reimbursed by the patient's insurance.

¹¹⁸According to literature we reviewed, ethical clinical trial design for serious and life-threatening infections requires trials to compare the drug being studied to an existing treatment for that infection, if it is known to be safe and efficacious. However, it is unlikely that superiority of a new drug would be observed when the bacteria are susceptible to both drugs. See H. Boucher et al., "White Paper: Developing Antimicrobial Drugs for Resistant Pathogens, Narrow-Spectrum Indications, and Unmet Needs," *The Journal of Infectious Diseases*, vol. 216, no. 2 (2017): pp. 228-236.

¹¹⁹In 2017 guidance, FDA stated that it would allow antibiotic developers flexibility to include, in certain superiority trials, patients with infections in multiple body sites caused by the same bacteria. However, superiority trials are often difficult to conduct for antibiotics, as described above. Department of Health and Human Services, Food and Drug Administration, *Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases; Guidance for Industry; Availability*, 82 Fed. Reg. 35973 (Aug. 2, 2017).

Nontraditional Products in Development

According to The Pew Charitable Trusts, there were 29 nontraditional antibacterial products in clinical development for the U.S. market in June 2019. Among the 29 products in the pipeline, nine were antibodies, seven were vaccines, seven were live biotherapeutic products, and six were other types of products. No bacteriophages were in clinical development. More than half of these products are for the treatment of *Clostridioides difficile* or *Staphylococcus aureus* infections.

Source: The Pew Charitable Trusts. | GAO-20-341

Experts, antibiotic developers, and federal officials also said it is scientifically challenging to develop new antibiotics that can overcome existing mechanisms of resistance. One expert at our meeting explained that it is necessary to develop an antibiotic that works differently than existing antibiotics so that bacteria are not resistant to it. In particular, experts and federal officials have noted that it is challenging to develop antibiotics that can kill certain types of bacteria, called gram-negative bacteria, largely due to their double membrane that makes it difficult for antibiotics to enter the bacterial cell, and to pumps that can remove the drug once it enters. Three antibiotic developers we spoke to explained that as bacteria continue to evolve new ways to resist antibiotics, it is difficult for scientists to keep pace by developing new treatments that can overcome those mechanisms. In addition, experts noted that scientists have already discovered most of the antibiotics from known sources, such as soil. As a result, scientists are now exploring new sources of chemicals with antibiotic properties, such as insects.¹²⁰

As the rate of antibiotic discovery has slowed, scientists have also begun to explore alternatives to traditional antibiotics—which we call “nontraditional products” in this report.¹²¹ Many types of nontraditional products are currently being researched and developed to treat antibiotic-resistant infections, including, among others, live biotherapeutic products, antibodies, and bacteriophages.¹²² For example, one type of nontraditional product in use for the treatment of recurrent *C. difficile*-associated disease—which causes diarrhea, abdominal cramps, and an estimated 15,000 deaths in the United States each year, according to CDC—is fecal microbiota for transplantation, more commonly known as fecal transplants.¹²³ (See text box.) However, scientists and companies

¹²⁰For example, scientists have recently discovered that chemicals within insects and komodo dragons have antibiotic properties, which could potentially be used as the basis for developing synthetic antibiotics in the future.

¹²¹According to NIAID, nontraditional products are antibacterial agents or approaches that differ in mechanism from traditional small-molecule agents that kill bacteria or inhibit their growth.

¹²²Live biotherapeutic products are products that contain live organisms, such as bacteria. Antibodies are proteins naturally produced by the body’s immune system to help remove potentially harmful pathogens. Antibodies can be harvested and used as medicines. Bacteriophages are viruses that can kill bacteria.

¹²³CDC considers *C. difficile* to be an urgent threat. While *C. difficile* is not usually resistant to antibiotics, it is caused by the same factors that drive antibiotic resistance—antibiotic use and the spread of germs.

researching and developing certain types of nontraditional products face development challenges. For example, according to a paper written by BARDA officials and others, certain types of nontraditional products target only one or a few types of bacteria, which makes enrollment of patients in clinical trials difficult and potentially cost-prohibitive.¹²⁴ The authors also stated that additional research is needed to evaluate side effects and measure the efficacy of some types of nontraditional products. According to another published paper, more than half of the nontraditional products in development are intended to be used concurrently with a traditional antibiotic, and it can be difficult to demonstrate the additional clinical benefit of adjunctive therapies in clinical trials.¹²⁵ The authors also noted that additional clinical trial endpoints still need to be developed and validated for such nontraditional products.

¹²⁴B. N. Tse et al., "Challenges and Opportunities of Nontraditional Approaches to Treating Bacterial Infections," *Clinical Infectious Diseases*, vol. 65, no. 3 (2017): pp. 495-500.

¹²⁵U. Theuretzbacher et al., "The Global Preclinical Antibacterial Pipeline," *Nature Reviews Microbiology* (Nov. 19, 2019).

Fecal Transplants

The goal of a fecal transplant—which involves collecting stool from healthy donors and transferring it to patients via enema, oral capsule, or another modality—is to restore a healthy gut microbiome for recipients. According to the National Institutes of Health (NIH), multiple research studies have indicated that these transplants are effective, but their long-term safety has not been established. Questions remain about the Food and Drug Administration’s (FDA) policy regarding stool banks that collect, prepare, and distribute fecal transplant products. FDA issued guidance in 2013 indicating its intention to exercise enforcement discretion regarding Investigational New Drug requirements for the use of fecal transplants to treat *Clostridioides difficile* infections, provided that the treating physician obtained adequate consent from the patient or his or her legally authorized representative. In other words, FDA’s guidance indicated it would not require fecal transplant products to satisfy the Investigational New Drug requirements—which refer to the requirements for FDA’s approval before beginning clinical trials to test a product on humans. [FDA, *Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation To Treat Clostridium difficile Infection Not Responsive to Standard Therapies; Guidance for Industry; Availability*, 78 Fed. Reg. 42965 (Jul. 18, 2013).] However, FDA later issued draft guidance in 2016 stating that FDA did not intend to extend enforcement discretion with respect to the Investigational New Drug requirements applicable to stool banks distributing fecal products. [FDA, *Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation To Treat Clostridium difficile Infection Not Responsive to Standard Therapies; Draft Guidance for Industry; Availability*, 81 Fed. Reg. 10632 (Mar. 1, 2016).] FDA has not finalized the 2016 draft guidance, which leaves the final guidance from 2013 as the current policy. According to FDA, the agency received many comments from patients and industry groups in response to the 2016 draft guidance expressing concern about the effect that the requirement for clinical trials would have on access to these products. In March 2019, FDA officials told us they were still reviewing comments to the 2016 draft guidance and were unable to say whether or not it would be finalized. In November 2019, FDA held a public hearing to obtain further input on the use of fecal transplants to treat *C. difficile* infection not responsive to standard therapies and to better understand the effect of FDA’s enforcement policy on product development.

Source: GAO analysis of information from NIH and FDA. | GAO-20-341

Federal Agencies Have Made Some Progress toward Addressing Treatment Development Challenges

Multiple federal agencies have supported the development of new antibiotic treatments, including providing funding for antibiotic R&D, issuing guidance related to antibiotic clinical trials, and implementing Medicare payment mechanisms. Agencies have made available both “push” incentives, which directly support antibiotic R&D, and “pull” incentives, which offer financial benefit, either directly or indirectly, to developers of successful antibiotics after they reach the market.

Federal funding for antibiotic R&D. Several federal agencies award grants or contracts, create public-private partnerships, or use other approaches to provide researchers the funding for R&D of new

treatments for antibiotic-resistant infections (see table 3). This type of pre-market R&D support is considered a “push incentive.”

Table 3: Examples of Federal Agencies’ Funding of Research and Development for New Treatments for Antibiotic-Resistant Infections

Agency	Examples of efforts
Department of Health and Human Services (HHS) Biomedical Advanced Research and Development Authority (BARDA)	<p>BARDA officials told us BARDA has awarded \$959 million in the form of grants, cooperative agreements, and contracts to developers of 24 antibiotic drugs and one nontraditional product since 2010.^a As of September 2019, three of these antibiotics had been approved by the Food and Drug Administration for marketing.</p> <p>BARDA created public-private partnerships with four antibiotic development companies that are developing a total of seven antibiotic candidates among them, investing a total of nearly \$403 million since 2013, according to BARDA officials.</p> <p>BARDA led the creation of the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) in 2016, an international public-private partnership that provides funds to support preclinical research (i.e., research prior to beginning testing in humans) and phase 1 clinical trials. BARDA has committed to provide up to \$250 million of funding to CARB-X.^b According to its 2019 annual report, CARB-X had funded 47 projects, totaling up to \$133.5 million.^c</p>
Department of Health and Human Services (HHS) National Institutes of Health (NIH)	<p>NIH officials estimated that the National Institute of Allergy and Infectious Diseases (NIAID) awarded \$158 million in fiscal year 2017 and \$148 million in fiscal year 2018 in grants, contracts, and other funding mechanisms for the study of treatments for antibiotic-resistant infections. These figures do not include funding of basic research that can lead to the development of new treatments or the improvement of existing treatments.</p> <p>NIH supports CARB-X by providing research services to support awardees and holding key governance roles.</p>
Department of Defense (DOD) Defense Threat Reduction Agency, U.S. Army Medical Research and Materiel Command, and others	<p>DOD funds and conducts research on treatments for antibiotic-resistant infections, with total awarded funding of about \$271 million since 2012, according to DOD officials.^d For example, the Defense Threat Reduction Agency has awarded 21 projects, totaling approximately \$178 million, and the U.S. Army Medical Research and Materiel Command has awarded 50 projects, totaling \$66.2 million.^e</p>

Source: GAO summary of information from HHS and DOD officials and agency documentation. | GAO-20-341

^aAccording to BARDA officials, funding for these awards is provided from the Public Health and Social Services Emergency Fund.

^bAccording to HHS officials, BARDA’s funding for CARB-X is provided from the Public Health and Social Services Emergency Fund. Other contributors to CARB-X include the Wellcome Trust—a global health charitable foundation, the governments of the United Kingdom and Germany, and the Bill and Melinda Gates Foundation.

^cCARB-X requires grantees to share in the costs of research and development by contributing at least 30 percent of the cost of the project.

^dAccording to DOD officials, they use grants, contracts, direct funding, and other transaction authority. Other Transaction Authority, in this case, is the term used by DOD to refer to legal acquisition instruments other than contracts, grants, or cooperative agreements, to carry out certain prototype projects. 10 U.S.C. § 2371b

^eAccording to DOD officials, the U.S. Army Medical Research and Materiel Command was redesignated as the U.S. Army Medical Research and Development Command in June 2019.

CARB-X's Portfolio

The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) had funded 47 projects, with the following in its portfolio as of July 2019:

- 12 antibiotics,
- 10 nontraditional therapies,
- 3 vaccines, and
- 5 diagnostic tests.

Among the products in the CARB-X portfolio, 12 would represent a new antibiotic class (if approved) and 14 target a novel molecular bacterial target. Awardees were based in six countries.

Source: CARB-X 2018-2019 Annual Report. | GAO-20-341

See appendix III for additional examples of efforts to support antibiotic R&D by NIH and DOD.

Issued guidance to support clinical trials. FDA has implemented programs and issued guidance that help address some regulatory challenges and encourage antibiotic development. In 2012, through the Generating Antibiotic Incentives Now provisions of the Food and Drug Administration Safety and Innovation Act, Congress created the Qualified Infectious Disease Product (QIDP) designation.¹²⁶ Drugs that FDA designates as QIDPs, which include antibiotics and antifungals, may qualify for 5 years of additional exclusivity and fast-track or priority review designation during the FDA review process.¹²⁷ The additional exclusivity conferred to QIDP designees is a type of “pull incentive,” because it offers the potential for enhanced financial gain after a drug receives FDA approval and reaches the market. According to FDA officials, as of September 2019, FDA had granted 192 QIDP designations, 24 of which it has approved for marketing.¹²⁸

Also in response to the Generating Antibiotic Incentives Now Act, FDA released final guidance in August 2017 to streamline clinical development of antibiotics for patients with an unmet medical need—that is, those with a serious bacterial disease that has few or no treatment options.¹²⁹ FDA explains in this guidance that it may consider drugs for these patients that have higher risks than would be acceptable for a broad patient population

¹²⁶Pub. L. No. 112-144, tit. 8, §§ 801 et seq., 126 Stat. 993, 1077 (2012). The Generating Antibiotic Incentives Now Act defines a QIDP as an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections. Pub. L. No. 112-144, § 801, 126 Stat. 1077 (codified in pertinent part at 21 U.S.C. § 355f(g)). In this report, we refer to title 8 of Pub. L. No. 112-144 as the Generating Antibiotic Incentives Now Act.

¹²⁷Pub. L. No. 112-144, §§ 801-803, 126 Stat. 1077-1079 (codified in pertinent part as amended at 21 U.S.C. §§ 355f (a), (d) (exclusivity extension and QIDP designation), 360n-1 (priority review), 356 (b) (fast track)).

In this report, our use of the term “exclusivity” refers to exclusive marketing rights granted by law for certain periods upon approval of a drug application, if certain requirements are met. QIDP exclusivity is granted as an extension to certain other exclusivity for which the applicant qualifies under the Federal Food, Drug, and Cosmetic Act.

¹²⁸For example, FDA approved a new drug for the treatment of a specific type of highly drug-resistant tuberculosis in August 2019.

¹²⁹Pub. L. No. 112-144, § 806, 126 Stat. 1082 (codified at 21 U.S.C. § 355 note). Food and Drug Administration, *Antibacterial Therapies for Patients with an Unmet Medical Need; Guidance for Industry*.

and provides information on types of antibiotics that could be eligible for approval based on smaller, shorter, or fewer—as few as only one—clinical trials.

The 21st Century Cures Act required FDA to establish a Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD).¹³⁰ In June 2018, FDA issued draft LPAD guidance, as required by the Act.¹³¹ Under LPAD, eligible products—which are drugs and biologics intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs—may follow a streamlined development program, similar to the approaches described in its earlier unmet medical need guidance.¹³² A biotechnology association noted in its public comments to the draft LPAD guidance the need for FDA to issue additional guidance to clarify its expectations for acceptable types of efficacy data when clinical trials are small and to clarify its interpretation of a “limited population of patients” for the purpose of the LPAD pathway.¹³³ An expert who attended our meeting later told us there is a great need to address how to develop narrow-spectrum antibiotics—those designed to treat a single or small number of bacterial pathogens—using LPAD. FDA held a public meeting in July 2019 to solicit stakeholder comments on the draft LPAD pathway guidance, and FDA officials told us they expect to finalize the guidance by February 2020. However, as of March 17, 2020, FDA had not yet issued final guidance.

¹³⁰Pub. L. No. 114-255, § 3042, 130 Stat. 1112-14 (Dec. 13, 2016) (codified at 21 U.S.C. § 356). LPAD applies to eligible drugs and biological products regulated by Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, respectively.

¹³¹Department of Health and Human Services, Food and Drug Administration, *Limited Population Pathway for Antibacterial and Antifungal Drugs (Draft Guidance for Industry)* (Silver Spring, Md.: June 2018).

¹³²Drug developers seeking approval under the LPAD pathway may also seek QIDP designation and approval under other applicable provisions, such as accelerated approval, breakthrough therapy, or priority review.

As of August 2019, FDA had approved two drugs under the LPAD pathway: Arikayce for the treatment of lung disease caused by a group of bacteria in a limited population of patients who do not respond to conventional treatment, and Pretomanid for the treatment of a specific type of highly treatment-resistant tuberculosis of the lungs.

¹³³In the draft LPAD guidance, FDA states its interpretation of “limited population” to mean “a group of patients that is limited in such a way that is clinically relevant to health care providers.” Food and Drug Administration, *Limited Population Pathway for Antibacterial and Antifungal Drugs (Draft Guidance for Industry)*: p.3.

In addition to issuing guidance, and to help inform future guidance, FDA engages with industry stakeholders to discuss and identify possible solutions to challenges related to the clinical development of antibiotics and nontraditional products. For example, FDA has held multiple public workshops, including one in November 2019 with experts from NIH's National Institute of Allergy and Infectious Diseases, the Infectious Disease Society of America, and The Pew Charitable Trusts to better understand the current state of antibiotic clinical trials in the United States, and how to enhance enrollment and research in these trials.

FDA officials told us they believe it is too early to issue guidance that would be broadly applicable and useful to nontraditional product developers. They explained that for certain types of nontraditional products, the approaches and specifics of product development are varied and evolving quickly. Instead, FDA's Center for Biologics Evaluation and Research has a program in place that allows developers to meet with FDA prior to beginning clinical trials to obtain advice on a wide range of development-related topics.¹³⁴

Implemented Medicare payment mechanisms. CMS uses Medicare payment mechanisms to help increase reimbursement to hospitals for certain antibiotics. For qualifying antibiotics, these payments are a form of indirect pull incentive because they have the potential to increase the demand for the new antibiotics after they reach the market, which could in turn improve their financial performance. Beginning in fiscal year 2020, CMS updated how it will pay hospitals for treating Medicare patients who have an antibiotic-resistant infection.¹³⁵ Specifically, CMS changed the eligibility criteria and payment amount for antibiotics that qualify for "new technology add-on payments" and how it pays hospitals for treating Medicare patients with antibiotic-resistant infections. These payment changes are:

¹³⁴This program is called INTERACT—Initial Targeted Engagement for Regulatory Advice on CBER products.

¹³⁵Department of Health and Human Services, Centers for Medicare & Medicaid Services, *Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospitals*, 84 Fed. Reg. 42044 (Aug. 16, 2019).

- **Revised eligibility criteria for and amount of add-on payments.** New technology add-on payments provide hospitals with additional compensation for a period of 2 or 3 years when they use qualifying new technologies or drugs that offer substantially improved clinical treatment, and when regular Medicare payments for the hospital stay are inadequate to cover the cost of the new technology or drug.¹³⁶ Generally, medical services and technologies must be new and must demonstrate a substantial clinical improvement over existing services or technologies to receive the additional payment.¹³⁷ However, CMS has acknowledged the difficulty antibiotic developers face in demonstrating such substantial clinical improvement due to manufacturers seeking FDA approval for most antibiotics on the basis of noninferiority clinical trials, as described above. To make it easier for antibiotics to qualify for the additional payments, under the revisions to the CMS payment policy beginning in fiscal year 2021, CMS will consider all antibiotics with a QIDP designation from FDA to be “new” for purposes of the add-on payment, and these antibiotics will not have to meet the substantial clinical improvement criteria.¹³⁸

In addition, CMS has increased the amount of the temporary add-on payment for qualifying antibiotics. Prior to this change, the add-on payments for qualifying antibiotics were limited to 50 percent of the cost of the drug. Under the new policy, the payment percentage increased to a maximum of 75 percent of the cost of the drug.¹³⁹ CMS has specified that two antibiotics are eligible for new technology add-on payments in fiscal year 2020.¹⁴⁰

¹³⁶The new technology add-on payments are made on top of the payment made under the inpatient prospective payment system. Under the inpatient prospective payment system, Medicare pays hospitals a single bundled payment per patient stay, which is based on multiple factors. 42 C.F.R. § 412.87 (2018).

¹³⁷In addition, the diagnosis related group rate otherwise applicable to discharges involving the medical service or technology must also be determined inadequate. 42 C.F.R. § 412.87(b) (2018).

¹³⁸84 Fed. Reg. 42044, 42292, and 42611 (adding a new paragraph (c) to 42 C.F.R. § 412.87) (Aug. 16, 2019).

¹³⁹84 Fed. Reg. 42044, 42297, and 42612 (revising paragraphs (a) and (b) of 42 C.F.R. § 412.88 (Aug. 16, 2019).

¹⁴⁰ The antibiotics that qualify for Medicare new technology add-on payments in fiscal year 2020 are Vabomere and Zemdri. 84 Fed. Reg. 42044, 42188 (Vabomere), and 42191 (Zemdri) (Aug. 16, 2019).

- **Increased payment for hospital stays.** CMS changed the severity level designation for certain antibiotic resistance-related diagnosis codes, in recognition of the added clinical complexity and cost of treating patients with antibiotic resistance.¹⁴¹ This change in severity level can result in higher payments to hospitals when treating patients diagnosed with antibiotic resistance, which, according to the Administrator of CMS in an August 2019 blog post, will create “financial flexibility for physicians to prescribe the appropriate new antibiotics.”¹⁴² The Administrator also noted that CMS made this policy change because it recognized that new technology add-on payments are temporary and “further action was needed to realign financial incentives for antibiotics for the long-term.”

See appendix III for additional examples of efforts to support antibiotic R&D by these and other federal agencies.

Federal Efforts Have Not Fully Incentivized Antibiotic Development, and HHS Lacks a Strategy to Develop New Incentives

Experts and antibiotic developers told us that the economic challenges have remained despite the available federal push and pull incentives for antibiotic R&D. Currently available premarket push incentives include grants and awards from NIH and BARDA that fund antibiotic R&D; currently available postmarket pull incentives include the additional market exclusivity available through QIDP designation and Medicare add-on payments for antibiotics. (See fig. 3.) Both of the antibiotic companies that declared bankruptcy in 2019 had received push incentives from BARDA and pull incentives through Medicare New Technology Add-on Payments and the QIDP 5-year extension of market exclusivity.¹⁴³

¹⁴¹84 Fed. Reg. 42044, 42150 (Aug. 16, 2019). CMS changed the severity designation for these diagnosis codes from “non-CC” to “CC,” which recognizes the presence of a complication or comorbidity that requires the hospital to dedicate more resources for the care of that patient than typically needed for the specific diagnosis.

¹⁴²S. Verma, “Aligning Payment and Prevention to Drive Antibiotic Innovation for Medicare Beneficiaries,” *Health Affairs Blog*, August 2, 2019, <https://www.healthaffairs.org/doi/10.1377/hblog20190802.505113/full/>

¹⁴³As of September 2019, one of the companies had received about \$136 million and the other had received about \$60 million from BARDA.

Figure 3: Examples of Currently Available Federal Incentives for Antibiotic Development



Source: GAO summary of information from the Department of Health and Human Services and literature. | GAO-20-341

Data for Figure 3: Examples of Currently Available Federal Incentives for Antibiotic Development

Pre-market

- National Institutes of Health grants
- CARB-X awards
- Biomedical Advanced Research and Development Authority awards
- Push incentives directly support antibiotic research and development

Post market

- Market exclusivity
- Medicare add-on payments
- Pull incentives offer financial benefit to antibiotic developers after their product reaches the market

Note: CARB-X is the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator.

While experts at our meeting and antibiotic developers told us that push incentives have been helpful, they also said push incentives alone are not sufficient to sustain antibiotic development. For example, two antibiotic developers we spoke with explained that push incentives have provided needed funding for conducting R&D, but said that push incentives will not

help cover the costs they will incur after their drug reaches the market—for example, to manufacture and market their product.¹⁴⁴

Experts and antibiotic developers have indicated that the effects of the existing pull incentives, QIDP market exclusivity, and Medicare add-on payments on stimulating development of new antibiotics have been limited for the following reasons:

- **QIDP and market exclusivity.** As we previously reported, several pharmaceutical companies told us that the market exclusivity incentive may not stimulate the development of new antibiotics, because the extension is unlikely to extend past the typical patent life of a new drug.¹⁴⁵ In addition, a representative from The Pew Charitable Trusts said that, while the passage of the Generating Antibiotic Incentives Now Act initially bolstered private investments in antibiotics, it did not ultimately stabilize the pipeline of antibiotics in development, noting that since then, several large pharmaceutical companies have discontinued their antibiotics R&D programs.
- **Medicare updates to hospital payments.** While CMS recently increased new technology add-on payments for certain antibiotics beginning in fiscal year 2020 to help improve access to antibiotics, these payments are limited to antibiotics used to treat Medicare patients.¹⁴⁶ In addition, although Medicare increased the add-on

¹⁴⁴One expert at our meeting noted that antibiotic companies face a “second wave” of costs after a drug reaches the market—costs to manufacture the drug and to conduct additional clinical studies for populations and indications beyond the original FDA approval.

¹⁴⁵Market exclusivity and patent life generally run concurrently. While market exclusivity can range from about 3 to 7 years from drug approval, according to FDA, a drug patent generally expires 20 years from the date the patent holder filed its application with the United States Patent and Trademark Office. See GAO, *Antibiotics: FDA Has Encouraged Development, but Needs to Clarify the Role of Draft Guidance and Develop Qualified Infectious Disease Product Guidance*, [GAO-17-189](#) (Washington, D.C.: Jan. 31, 2017).

HHS stated in a 2017 report to Congress that it was still too early to assess whether the Generating Antibiotic Incentives Now Act was addressing the need for new antibiotics because all 12 of the approved QIDP drugs were already in development before the incentives were created. Department of Health and Human Services, *Generating Antibiotic Incentives Now: Required by Section 805 of the Food and Drug Administration Safety and Innovation Act. Public Law 112-144* (2017), p.12.

¹⁴⁶Department of Health and Human Services, Centers for Medicare & Medicaid Services, *Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific*

payment amount to up to 75 percent of the estimated costs of qualifying antibiotics in excess of the regular Medicare payment, hospitals could still face costs for providing these drugs that are not covered by the Medicare payment. Furthermore, representatives from an antibiotic company and a biotechnology trade association told us the add-on payments do not directly incentivize hospital pharmacies to purchase the drug, because the add-on payment may not flow back to the pharmacy department's budget. For these reasons, it remains to be seen whether the Medicare new technology add-on payments to hospitals for inpatient antibiotics will help improve the return on investment for antibiotic developers and further stimulate the antibiotic development pipeline. Similarly, it remains to be seen how CMS's policy change that provides increased payments for hospital stays when Medicare patients have been diagnosed with certain types of antibiotic-resistant infections will affect hospitals' use of new antibiotics.

In light of the limitation of existing incentives for antibiotic development, experts, federal officials, and antibiotics developers have called for additional postmarket pull incentives to reinvigorate the pipeline of antibiotics under development. For example, PACCARB issued recommendations to the Secretary of HHS in September 2017 and July 2019 for the adoption of pull incentives, calling for the development of market entry rewards and options for plausible business models.¹⁴⁷ In addition TATFAR—of which officials from BARDA, CDC, FDA, and NIH are members—reported that it is critical to develop a pull incentive strategy now to ensure that enough antibiotics are available in the future.¹⁴⁸ Former FDA Commissioner Dr. Scott Gottlieb also stated in 2018 that he was “deeply concerned that without stronger pull incentives that encourage more R&D, we’ll see a far less robust pipeline of products

Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospitals, 84 Fed. Reg. 42044 (Aug. 16, 2019).

¹⁴⁷See section I-3.1 of Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics*, and goal 4, priority 1 of *Priorities for the National Action Plan on Combating Antibiotic-Resistant Bacteria: 2020-2025: A Report with Recommendations* (July 2019).

¹⁴⁸C. Ardal et al., “Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance,” *Clinical Infectious Diseases*, vol. 65, no. 8 (2017). TATFAR was created in 2009 with the goal to improve international coordination of efforts to fight antibiotic resistance. It includes representatives from the United States, Canada, the European Union, and Norway. CDC currently serves as the secretariat for TATFAR.

than we need to address antimicrobial resistance.”¹⁴⁹ Eight of the antibiotic developers we interviewed told us they think additional financial incentives are needed.¹⁵⁰ For example, one developer said that sales revenues from antibiotics will never be sufficient to justify R&D investments, and another noted that financial incentives are needed during the first few years after a new antibiotic reaches the market to cover not only these costs, but also to conduct additional clinical trials to help expand the drug’s possible market. Finally, several experts at our expert meeting noted that, without pull incentives, most of the small companies currently developing antibiotics are unlikely to survive, and large pharmaceutical companies will likely continue to exit the antibiotic market.

Advisory groups and others have identified multiple options for how postmarket pull incentives could be designed, including market entry rewards—either in the form of lump sum payments or transferable vouchers that could be sold to confer additional market exclusivity to other pharmaceutical drugs—or reimbursement reform, such as licensing arrangements or add-on payments for hospital-administered antibiotics. (See fig. 4.) The four advisory groups whose papers we reviewed each recommended market entry rewards as effective pull incentive options. While Commissioner of the FDA, Dr. Scott Gottlieb proposed an antibiotics licensing arrangement, which he called a subscription model, in a 2018 speech.

¹⁴⁹See S. Gottlieb, “FDA’s Strategic Approach for Combating Antimicrobial Resistance” (speech), September 14, 2018, remarks as prepared for delivery, <https://www.fda.gov/news-events/speeches-fda-officials/fdas-strategic-approach-combatin-g-antimicrobial-resistance-09142018>.

¹⁵⁰We asked the developers, “what other incentives, if any, could be offered by U.S. federal agencies or other entities to promote the development of new antibiotics and nontraditional products?” Of the remaining three developers we interviewed, one did not respond to this question, one discussed changes they would like FDA to make regarding clinical trials, and one said they could not think of any additional incentives.

Figure 4: Examples of Possible Postmarket Incentive Options to Encourage the Development of Antibiotics Identified by Advisory Groups and Others

Market entry reward		Reimbursement reform	
A market entry reward could be awarded in addition to, or in replacement of, sales revenues			
<p>Lump sum payment</p> <ul style="list-style-type: none"> • Monetary reward paid to developers of new antibiotics • Could be paid over multiple years 	<p>Transferable voucher</p> <ul style="list-style-type: none"> • Voucher that could be sold or auctioned and would confer additional market exclusivity for a different pharmaceutical drug 	<p>Licensing arrangement</p> <ul style="list-style-type: none"> • Antibiotic purchasing arrangement in which hospitals would pay a fixed fee to access the drug, which would allow them to use a certain number of doses 	<p>Add-on payment</p> <ul style="list-style-type: none"> • Payments to hospitals for use of certain antibiotics that are made in addition to the bundled payment the hospital already receives for a patient's inpatient stay

Source: GAO summary of publicly available proposals. | GAO-20-341

Data for Figure 4: Examples of Possible Postmarket Incentive Options to Encourage the Development of Antibiotics Identified by Advisory Groups and Others

Market entry reward

A market entry reward could be awarded in addition to, or in replacement of, sales revenues

Lump sum payment

- Monetary reward paid to developers of new antibiotics
- Could be paid over multiple years

Transferable voucher

- Voucher that could be sold or auctioned and would confer additional market exclusivity for a different pharmaceutical drug

Reimbursement reform

Licensing arrangement

- Antibiotic purchasing arrangement in which hospitals would pay a fixed fee to access the drug, which would allow them to use a certain number of doses

Add-On payment

- Payments to hospitals for use of certain antibiotics that are made in addition to the bundled payment the hospital already receives for a patient's inpatient stay

Views on the utility of reimbursement reform as a pull incentive strategy are mixed. For example, representatives from The Pew Charitable Trusts stated their view that, while CMS's recent changes to Medicare payment for antibiotics will likely be helpful to some degree, no reimbursement policy on its own would be able to increase antibiotic sales revenues sufficiently to transform the business model for antibiotics. An antibiotic developer we spoke to also told us that reimbursement policies would not be sufficient to support their business model because of low sales volumes for new antibiotics. The developer explained that it can take 2 or 3 years of antibiotic sales to recoup their R&D costs and finance their ongoing business operations, and that while larger pharmaceutical companies can rely on other profitable drugs to offset those costs, they could not because they did not have other drugs on the market. However, a representative from a biotechnology trade association told us that increasing reimbursement could help alleviate some of the economic challenges faced by developers of antibiotics that are already on or about to reach the market while policy makers explore longer-term pull incentive strategies. TATFAR cautioned that simply increasing reimbursement for antibiotics could potentially limit patient access, particularly for patients without health insurance—including those in low-and middle-income countries—and it could incentivize only antibiotics for common types of infections with a large market potential, rather than for rare, yet dangerous, types of pathogens.

Advisory groups and others have evaluated potential market entry reward models, taking into consideration factors such as format, value, funding sources, and eligibility criteria. Some have proposed that receipt of a market entry reward should be delinked, fully or partially, from sales revenues—that is, the developer would have to forgo some or all sales revenue as a condition of receiving the reward. Proponents of delinkage believe that separating revenues from antibiotics sales volumes would discourage aggressive sales that could lead to overuse. An expert who attended our meeting later told us that policies to incentivize use of new antibiotics must be balanced with policies to monitor prescribing of new drugs to prevent inappropriate use. Generally, advisory groups stipulate that to maximize the public health benefit, only antibiotics that treat what

are deemed to be high priority bacteria should be eligible for a reward.¹⁵¹ Specific recommendations and conclusions included the following:

- TATFAR concluded in 2017 that a partially delinked market entry reward of approximately \$500 million would be the least disruptive option but noted that additional assessment would be necessary to select the most appropriate model and determine governance and other design elements.¹⁵²
- PACCARB expressed support for a delinked model, in which a company accepting a market entry reward would be required to forgo marketing activities and profits based on sales volume. In addition, they suggested the establishment of an antibiotic incentive fund supported by an antibiotic usage fee or the sale or auction of transferable exclusivity vouchers as plausible options for financing pull incentives.
- The Duke University Margolis Center for Health Policy recommended in 2017 a delinked, public-private market entry reward model. This model was comprised of publicly funded market entry rewards for qualifying antibiotics for the first 5 or 6 years, followed by privately funded “value-based” contracts between antibiotic developers and health care payors, in which the payor could agree, for example, to pay a predetermined amount for full access to the antibiotics for a given population.¹⁵³ The Duke-Margolis Center proposal did not specify a funding source, but it noted multiple options for consideration, including general government funds, antibiotic use taxes, or the sale of transferable exclusivity vouchers.
- The European DRIVE-AB project recommended in 2018 an internationally funded, partially delinked market entry reward valued at approximately \$1 billion per antibiotic, paid over the course of 5 or

¹⁵¹C. M. Morel and S. E. Edwards, “Encouraging Sustainable Use of Antibiotics: A Commentary on the DRIVE-AB Recommended Innovation Incentives,” *The Journal of Law, Medicine & Ethics*, vol. 46, no. S1 (2018).

¹⁵²C. Ardal et al., “Pull Incentives for Antibacterial Drug Development.” TATFAR also published a literature review in 2016 that summarized twelve reports by researchers and advisory groups who analyzed possible antibiotic pull incentive strategies. See K. Sciarretta et al., “Economic Incentives for Antibacterial Drug Development: Literature Review and Considerations from the Transatlantic Task Force on Antimicrobial Resistance,” *Clinical Infectious Diseases*, vol. 63, no. 11 (2016).

¹⁵³Duke Margolis Center, *Value-Based Strategies for Encouraging New Development of Antimicrobial Drugs*.

more years.¹⁵⁴ Recipients of a market entry reward would be allowed to sell their drug on the private market, but they would agree to certain marketing restrictions to discourage inappropriate use.

HHS may need to request authority and appropriations to create and implement certain types of market entry rewards. For example, HHS does not currently have authority to offer transferable exclusivity vouchers to antibiotic developers, since that would require a change in statute. Advisory groups also noted that the various pull incentive approaches would require additional public or private expenditures and offered possible sources of funding. For example, in addition to general fund revenues, PACCARB suggested that pull incentives could be funded through antibiotic usage fees, the auctioning of transferable exclusivity vouchers, or by allowing developers of new antibiotics to earn a transferable exclusivity voucher. The Duke-Margolis Center suggestions included funding market entry rewards through a yearly per-member fee for all health insurance plans. Transferable exclusivity vouchers may not require an independent funding source, because the value of the reward is based on the sale of the voucher to another drug developer. However, vouchers would still increase public and private health care expenditures, because expenditures would likely increase for drugs for which the extra period of exclusivity was purchased due to the delayed entry of lower-priced generics. Finally, reimbursement reform could increase health care expenditures for health care payors, including Medicare and private health insurance carriers.

Although PACCARB, TATFAR, and other experts have called for additional postmarket pull incentives to increase the antibiotic pipeline, as of January 2020 HHS has not developed a strategy for creating these incentives. HHS officials told us that the department created an interagency workgroup within HHS in spring 2019 to identify possible pull incentive options, among other things.¹⁵⁵ The recently convened HHS interagency workgroup is a step in the right direction toward exploring options for new antibiotic development incentives. Through this workgroup, HHS has an opportunity to determine which types of

¹⁵⁴The DRIVE-AB project, which is the short name for the “Driving Re-investment in R&D and Responsible Antibiotic Use,” was funded by the Innovative Medicines Initiative, which received financial contributions from the European Union and the European Federation of Pharmaceutical Industries and Associations.

¹⁵⁵In addition, to further assess the market economics for antibiotics, the HHS Office of the Assistant Secretary for Planning and Evaluation funded a study in 2018 to assess whether there are market failures that lead to suboptimal investment in antimicrobial drugs. The study is due to be completed in 2021.

postmarket incentives it believes would most effectively incentivize the development of new treatments for antibiotic-resistant infections. However, it is unclear whether the HHS interagency workgroup's efforts will include consideration of such incentives because, according to HHS officials in January 2020, the interagency workgroup was still considering possible recommendations for HHS leadership and had not produced any specific documents to share with us.

The Government Performance and Results Act of 1993 (GPRA) and the GPRA Modernization Act of 2010, which significantly enhanced agencies' responsibilities under GPRA, include principles for federal agencies to consider related to developing strategies for achieving results, among other principles.¹⁵⁶ We have previously reported that these principles can serve as leading practices for planning at lower levels within agencies, such as individual programs or initiatives.¹⁵⁷ Our past work has shown that strategic frameworks can serve as a basis for guiding policy makers, including congressional decision makers and agency officials, when making decisions about resources, programs and activities, particularly in relation to issues that are national in scope, such as antibiotic development.¹⁵⁸ Developing a strategic framework that outlines new postmarket pull incentives and their key design elements—such as monetary value, eligibility criteria, and guidelines to prevent overuse—would be a first step toward identifying potential authorities and resources that may be needed to create the incentives, and toward determining agency roles for implementation and oversight of the incentives. Until such incentives are developed, more drug companies may exit the antibiotic development sector, and the pipeline of new treatments for antibiotic-resistant infections may continue to decrease. Furthermore, the current significant federal investment in push incentives to support antibiotic R&D will remain a high-risk enterprise, if companies receiving large R&D grants are unable to sustain their business once their treatment reaches the market.

¹⁵⁶Pub. L. No. 103-62, 107 Stat. 285 and Pub. L. No. 111-352, 124 Stat. 3866.

¹⁵⁷[GAO-16-693](#).

¹⁵⁸GAO, *Prescription Drugs: Strategic Framework Would Promote Accountability and Enhance Efforts to Enforce the Prohibitions on Personal Importation*, [GAO-05-372](#) (Washington, D.C.: Sept. 8, 2005).

Federal Agencies Have Undertaken Several Efforts to Promote the Appropriate Use of Antibiotics, but Key Challenges Remain

Federal agencies have undertaken several efforts to promote the appropriate use of antibiotics through stewardship programs and activities. However, four key challenges remain that have limited this progress.

Federal Agencies Have Undertaken Several Efforts to Promote the Appropriate Use of Antibiotics through Stewardship Programs

To promote the appropriate use of antibiotics across health care settings through antibiotic stewardship programs and activities, federal agencies have undertaken several efforts that aim to reduce inappropriate antibiotic use, reduce health care costs, improve patient outcomes, and combat antibiotic resistance. Selected examples of these efforts are discussed below. (For more detailed information on agencies' efforts to promote the appropriate use of antibiotics, see app. IV.)

Published Requirements for Hospitals, Long-Term Care, and DOD and VA Facilities to Implement Antibiotic Stewardship Programs

Federal agencies require certain types of health care facilities to implement antibiotic stewardship programs, as follows:

- **CMS.** In September 2019, CMS finalized new health and safety requirements for hospitals and critical access hospitals to implement antibiotic stewardship programs by March 30, 2020, as a condition of their participation in the Medicare and Medicaid programs.¹⁵⁹ Under

¹⁵⁹Department of Health and Human Services, Centers for Medicare & Medicaid Services, *Medicare and Medicaid Programs; Regulatory Provisions to Promote Program Efficiency, Transparency, and Burden Reduction; Fire Safety Requirements for Certain Dialysis Facilities; Hospital and Critical Access Hospital (CAH) Changes to Promote Innovation, Flexibility, and Improvement in Patient Care*, 84 Fed. Reg. 51732 (Sept. 30, 2019) (pertinent provisions to be codified at 42 C.F.R. §§ 482.42 (d), 485.640).

these requirements, hospitals and critical access hospitals are required, among other things, to implement these programs facility-wide (which includes emergency departments) and to adhere to nationally recognized antibiotic prescribing guidelines.¹⁶⁰ Nearly 3 years prior, CMS published similar requirements for nursing homes and skilled nursing facilities—collectively known as long-term care facilities—to establish antibiotic stewardship programs by December 4, 2017.¹⁶¹ Experts, including those at our meeting and the PACCARB, credit these requirements with being a powerful lever for promoting the appropriate use of antibiotics; Medicare comprises a significant portion of the nation’s health care expenditures—\$741 billion in 2018, covering 59.9 million beneficiaries.¹⁶²

- **DOD.** DOD published a policy, effective October 2017, requiring the establishment of antibiotic stewardship programs within its military

The final health and safety (also known as Conditions of Participation) requirements for antibiotic stewardship programs in hospitals also apply to inpatient rehabilitation facilities (which are considered post-acute care facilities) and long-term acute care hospitals. 84 Fed. Reg. 51732, 51780 (Sept. 30, 2019).

“Critical access hospital” is a designation given to eligible rural hospitals by states and certified by CMS. 42 U.S.C. § 1395i-4(c)(2)(B), 42 C.F.R. § 485.606(b). Congress created the critical access hospital designation through the Balanced Budget Act of 1997 in response to a string of rural hospital closures in the 1980s and early 1990s. Among other criteria, eligible hospitals must have 25 or fewer acute-care inpatient beds and be located more than 35 miles from another hospital, although exceptions may apply. See Balanced Budget Act of 1997, Pub. L. No. 105-33, § 4201, 111 Stat. 251, 369-71 (codified in pertinent part at 42 U.S.C. §§ 1395f(l), 1395i-4, 1395m(g), (l)(8)). As of October 2019, there were 1,349 critical access hospitals in the United States.

¹⁶⁰Professional medical societies, such as the American Academy of Pediatrics, publish nationally recognized antibiotic prescribing guidelines for their specialties. In addition, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have jointly published evidence-based guidelines for implementing an antibiotic stewardship program in acute inpatient, long-term care, and emergency department care settings. See, for example, T. F. Barlam et al., “Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America,” *Clinical Infectious Diseases*, vol. 62, no. 10 (2016): pp. e51–e77.

¹⁶¹Department of Health and Human Services, Centers for Medicare & Medicaid Services, *Medicare and Medicaid Programs; Reform of Requirements for Long-Term Care Facilities*, 81 Fed. Reg. 68688, 68697 (Oct. 4, 2016) (pertinent provision codified at 42 C.F.R. § 483.80(a)(3) (2018)).

¹⁶²Centers for Medicare & Medicaid Services, “Trustees Report & Trust Funds,” accessed September 15, 2019, <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ReportsTrustFunds/index>.

medical treatment facilities and, one year later, issued guidance for implementation.¹⁶³ Among other things, the policy specified that these facilities' antibiotic stewardship programs include components such as (1) leadership commitment by each facility; (2) accountability; (3) pharmacy expertise, including antibiotic prescribing and use evaluation; (4) implementation of action for change that would demonstrate commitment to the program; and (5) training for clinicians regarding antibiotic resistance and prescribing practices. DOD officials told us that all of these facilities (both inpatient and outpatient) were in different stages of implementing the antibiotic stewardship policy.

- **VA.** In January 2019, VA updated its 2014 policy directive for the implementation and maintenance of antibiotic stewardship programs in its health care facilities, which provide both inpatient and outpatient services to veterans.¹⁶⁴ This policy directive includes requirements for its facilities to develop a written policy, conduct an annual evaluation of stewardship activities, ensure that adequate staff and resources are in place, and identify medical and pharmacy personnel as stewardship "champions." According to department officials, VA has successfully implemented antibiotic stewardship programs in all of its health care facilities.

Developed Incentives for Clinicians to Implement Antibiotic Stewardship Activities

CMS has developed incentives for eligible clinicians in any type of health care facility to improve antibiotic use and stewardship, as part of the

¹⁶³Department of Defense, DOD Instruction 6025.26, "DOD Program for Combating Antibiotic-Resistant Bacteria (CARB)" (Oct. 31, 2017) and Defense Health Agency Procedural Instruction Number 6025.09, "DOD Program for Combating Antibiotic-Resistant Bacteria (CARB)" (Oct. 2, 2018).

DOD's military medical treatment facilities include hospitals and medical centers located at military installations across the United States and abroad, plus ambulatory care clinics and dental clinics, and provide health care for active-duty service members, their dependents, and other eligible beneficiaries.

¹⁶⁴Department of Veterans Affairs, Veterans Health Administration Directive 1031, "Antimicrobial Stewardship Programs (ASP)" (Washington, D.C.: Jan. 30, 2019).

agency's broader efforts to improve care for Medicare patients.¹⁶⁵ Through the Merit-based Incentive Payment System (MIPS) launched in 2017, CMS offers hundreds of quality measures and nearly 100 "improvement activities" on a wide range of topics—including the appropriate use of antibiotics—on which eligible clinicians can choose to report their performance to the agency.¹⁶⁶ CMS then adjusts payments higher for clinicians who report data and achieve a performance-based, final score above a certain threshold—and penalizes clinicians who do not achieve that threshold with lower payments.

Published Guidance on Implementing Antibiotic Stewardship Programs

Federal agencies have published guidance for health care facilities on how to implement antibiotic stewardship, as follows:

- **AHRQ.** Through a 5-year nationwide project, the AHRQ Safety Program for Improving Antibiotic Use has provided technical assistance and CDC's guidance to hospitals, long-term care settings, and physicians' offices to promote implementation of antibiotic stewardship activities and help clinicians select optimal antibiotic treatment regimens. In December 2018, AHRQ completed implementation of this guidance in more than 400 hospitals, which

¹⁶⁵The Medicare Access and CHIP Reauthorization Act of 2015 required CMS to implement an incentive program for clinicians participating in Medicare to receive higher payments based on their performance. The Medicare Access and CHIP Reauthorization Act of 2015, Pub. L. No. 114-10, 129 Stat. 87, 92 (Apr. 16, 2015), codified at 42 U.S.C. § 1395w-4.

¹⁶⁶MIPS-eligible clinician types include physicians (doctors of medicine, which includes many specialties; doctors of dental surgery or dental medicine; and doctors of osteopathy), physician assistants, nurse practitioners, and others. In addition, to be eligible for MIPS in 2019, the clinician must (1) bill \$90,000 or more in allowed charges for professional services covered under the Medicare Physician Fee Schedule; (2) provide more than 200 covered professional services; and (3) furnish covered professional services to more than 200 Medicare beneficiaries. Eligible clinicians may participate in MIPS as individuals or as part of a group that includes one or more of the eligible clinician types.

For more information on MIPS, see GAO, *Health Care Quality: HHS Should Set Priorities and Comprehensively Plan Its Efforts to Better Align Health Quality Measures*, [GAO-17-5](#) (Washington, D.C.: Oct. 13, 2016) and *Medicare: Small and Rural Practices' Experiences in Previous Programs and Expected Performance in the Merit-based Incentive Payment System*, [GAO-18-428](#) (Washington, D.C.: May 31, 2018).

included six DOD facilities and 79 critical access hospitals, according to AHRQ officials.

- **CDC.** Since 2014, CDC has published a series of guidance documents—called the Core Elements of Antibiotic Stewardship (Core Elements)—to promote the appropriate use of antibiotics in health care.¹⁶⁷ The Core Elements are tailored to hospitals, nursing homes, outpatient settings, small and critical access hospitals, and low- and middle-income countries with limited resources. Common elements in these guidance documents include (1) leadership commitment, (2) implementation of policies and interventions to improve antibiotic use, (3) tracking and reporting antibiotic use, and (4) education to providers on appropriate antibiotic use.

Expanded the Collection of Antibiotic Use Data

Since we reported on antibiotic use data gaps in 2011, CDC has expanded its collection of such data regarding both inpatient and outpatient settings through its own surveillance systems, as well as from other sources.¹⁶⁸ In particular, CDC has focused its efforts to expand antibiotic use data collection from hospitals, where an estimated one in two patients receives an antibiotic for at least one day during an average hospital stay.¹⁶⁹ CDC launched its AU Option in 2011 as a voluntary, electronic reporting tool added on to the pre-existing NHSN.¹⁷⁰ The AU

¹⁶⁷Department of Health and Human Services, Centers for Disease Control and Prevention, *The Core Elements of Hospital Antibiotic Stewardship Programs* (Atlanta, Ga.: 2014) and *The Core Elements of Hospital Antibiotic Stewardship Programs: 2019* (Atlanta, Ga.: 2019), *The Core Elements of Antibiotic Stewardship for Nursing Homes* (Atlanta, Ga.: 2015), *The Core Elements of Outpatient Antibiotic Stewardship* (Atlanta, Ga.: 2016), *Implementation of Antibiotic Stewardship Core Elements at Small and Critical Access Hospitals* (Atlanta, Ga.: 2017), and *The Core Elements of Human Antibiotic Stewardship Programs in Resource-Limited Settings: National and Hospital Levels* (Atlanta, Ga.: 2018).

¹⁶⁸GAO, *Antibiotic Resistance: Data Gaps Will Remain Despite HHS Taking Steps*, [GAO-11-406](#) (Washington, D.C.: June 1, 2011).

¹⁶⁹J. Baggs et al., “Estimating National Trends in Inpatient Antibiotic Use among U.S. Hospitals from 2006 to 2012,” *JAMA Internal Medicine*, vol. 176, no. 11 (2016): pp. 1639-1648.

¹⁷⁰CDC data indicate that, as of January 1, 2020, there were 6,849 hospitals, including 13 DOD hospitals located on military bases outside the United States, that were eligible for reporting data to the AU Option. Although participation in the NHSN AU Option is generally voluntary, DOD and VA require their hospitals to report antibiotic use data to the AU Option. DOD officials told us that 44 DOD hospitals were reporting such data, as of September 30, 2019, and VA officials told us that 113 VA hospitals were reporting such data, as of January 1, 2020.

Option allows the nation's 6,849 hospitals that are already reporting to the NHSN to submit their antibiotic use data in a standardized format.¹⁷¹ CDC then aggregates such data to calculate national benchmarks and allows hospitals to compare their actual antibiotic use against those benchmarks. In addition, CDC has periodically conducted prevalence surveys through the EIP to gather data on health care-associated infections and antibiotic use in about 200 hospitals and 161 nursing homes in 10 states. With regard to outpatient settings, CDC has acquired, through a proprietary source, 8 years of pharmacy data on antibiotic prescriptions since 2011, which the agency is using to better characterize patterns in outpatient prescribing and to develop targeted interventions for high-prescribing areas.

Developed Antibiotic Stewardship Training for Various Health Care Settings

Federal agencies have developed training on antibiotic stewardship, as follows:

- **CDC.** In 2018, CDC launched a free, online training course for various types of clinicians—including physicians, dentists, pharmacists, physician assistants, and nurses—to inform them about proper antibiotic prescribing and strategies for communicating with patients.¹⁷² Clinicians can receive credit for partial completion (at least 50 percent) or full completion of this training as improvement activities under MIPS in 2019.
- **CMS.** CMS has provided training, technical assistance, and other learning opportunities to more than 4,000 hospitals, 2,400 nursing homes, and 7,600 outpatient settings on best practices for antibiotic stewardship and guidance on *C. difficile* prevention. In addition, CMS and CDC have developed and launched free, online training to help nursing homes implement antibiotic stewardship and prevent and manage *C. difficile* infections.

¹⁷¹As previously noted, hospital types that report data to NHSN include general acute care hospitals, critical access hospitals, children's hospitals, oncology hospitals, long-term acute care hospitals, and inpatient rehabilitation facilities. The AU Option is part of a reporting module called the AUR Module that also tracks antibiotic resistance through the AR Option.

¹⁷²As of late July 2019, nearly 16,000 individuals had registered for this training, according to CDC officials.

- **DOD and VA.** These departments have also offered antibiotic stewardship training to their health care facilities through webinars, workshops, or briefings.

Funded Research

Federal agencies have funded research on antibiotic stewardship, as follows:

- **AHRQ.** Since 2015, AHRQ has increased its support for research to develop improved methods to combat antibiotic resistance and promote antibiotic stewardship, including through grants for research that will total more than \$57 million, according to AHRQ officials. This research includes studies on the role of diagnostic tools in improving antibiotic use and reducing antibiotic resistance. AHRQ has also published numerous research studies on antibiotic or antimicrobial stewardship that the agency funded or authored.
- **CDC.** CDC supports research to identify, develop, and implement practices to stop the spread of resistance and to promote appropriate use of antibiotics in health care. CDC also supports research to fill gaps in knowledge related to aspects of antibiotic use and resistance that have public health impact. According to agency officials, CDC has provided approximately \$110 million since 2016 to support this research through cooperative agreements and contracts.

Continued National Public Awareness Campaign

In 2017, CDC revised a national campaign to promote public awareness about appropriate antibiotic use. The campaign, called “Be Antibiotics Aware: Smart Use, Best Care,” is aimed at both health care providers and the general public and refines the message from CDC’s earlier campaign (“Get Smart: Know When Antibiotics Work”).

Collaborated Internationally

HHS’s Office of Global Affairs has collaborated with other countries, including those participating in the TATFAR program, to promote the appropriate use of antibiotics internationally. In addition, CDC and the Office of Global Affairs launched the Antimicrobial Resistance Challenge at the United Nations General Assembly in September 2018 to catalyze global action against antibiotic resistance. A year later, CDC announced

this challenge had resulted in nearly 350 commitments from government health officials, pharmaceutical and health insurance companies, and others from 33 countries to make formal commitments that further the progress against antimicrobial resistance, such as by improving appropriate antibiotic use.

Four Key Challenges Have Limited Federal Efforts to Promote the Appropriate Use of Antibiotics

We identified four key challenges that have limited progress in federal efforts to promote the appropriate use of antibiotics, based on our analysis of documents, interviews with agency officials and experts, and other information. First, federal requirements for antibiotic stewardship programs apply only to certain types of health care facilities, and federal incentives for clinicians to adopt antibiotic stewardship activities are optional, limiting implementation of antibiotic stewardship across the health care spectrum. Second, CDC faces challenges in collecting complete antibiotic use data, limiting the agency's ability to monitor and improve antibiotic use. Third, the CARB Task Force has not identified and reported on agencies' plans to address the challenges related to expanding antibiotic stewardship programs and antibiotic use data collection across health care settings, so these plans are not publicly known. Fourth, antibiotic stewardship training for health care providers may have limited success in improving antibiotic prescribing behavior, and federal agencies indicate that it is challenging to evaluate the effectiveness of such training.

Federal Requirements and Incentives Are Limited

Federal requirements for antibiotic stewardship programs are limited to certain types of health care facilities, and federal incentives for antibiotic stewardship activities are optional and limited to eligible Medicare clinicians, such as physicians.

- **Federal requirements for antibiotic stewardship programs are limited to certain types of health care facilities.** As previously noted, federal requirements for antibiotic stewardship programs are currently limited to hospitals and critical access hospitals, long-term care facilities such as nursing homes, and DOD and VA health care facilities. However, CMS has not yet developed requirements for ambulatory surgery centers or dialysis centers to implement antibiotic stewardship programs, which the National Action Plan called for being

implemented by March 2018. CMS officials told us that the agency would develop those requirements once the rule for hospitals and critical access hospitals—which was delayed—was finalized. In addition, CMS’s health and safety requirements do not extend to other types of outpatient settings—such as physicians’ offices, retail clinics, and urgent care centers¹⁷³—where inappropriate antibiotic use has been found to be high.¹⁷⁴

In the absence of regulatory levers, CDC and AHRQ encourage those types of facilities to establish antibiotic stewardship programs on a voluntary basis. Experts, including those at our meeting, indicate that expansion of antibiotic stewardship across the health care spectrum is likely to remain limited without additional federal requirements or other meaningful incentives—thus hindering the nation from fully achieving the benefits of appropriate antibiotic use. Such benefits include better patient outcomes, lower health care costs, and slower growth of antibiotic resistance.

- **CMS incentives for clinicians to improve antibiotic use are optional, and implementation has been limited.** The MIPS program’s effect on incentivizing appropriate use of antibiotics is limited, in part, because the incentives are available only to clinicians who meet MIPS eligibility criteria and because eligible clinicians can choose not to report data to CMS. In addition, participating clinicians have a wide range and number of quality measures and improvement activities, beyond those related to antibiotics, from which the clinicians can choose to report data to CMS to meet program requirements; thus, the likelihood that clinicians will choose to report on antibiotics-related measures or activities may remain low. For example, in 2017, MIPS-eligible clinicians were generally required to select and submit

¹⁷³CMS conditions payments for Medicare services to inpatient facilities, such as hospitals and long-term care facilities, and certain outpatient facilities, such as ambulatory surgical centers and dialysis centers, on compliance with CMS’s health and safety standards (i.e., CMS’s Conditions of Participation or Conditions for Coverage requirements). In addition, CMS generally pays clinicians separately for their Medicare services, regardless of whether the treatment takes place in health care facilities for which CMS has established health and safety standards, or in facilities that are not subject to CMS’s health and safety standards, such as physician offices, retail clinics, and urgent care centers.

¹⁷⁴As previously noted, CDC has reported that at least 30 percent, and as much as 50 percent, of antibiotic use in outpatient settings is inappropriate in the United States. See also D. L. Palms et al., “Comparison of Antibiotic Prescribing in Retail Clinics, Urgent Care Centers, Emergency Departments, and Traditional Ambulatory Care Settings in the United States,” *JAMA Internal Medicine*, vol. 178, no. 9 (2018): pp. 1267-1269; and D. L. Palms et al., “First-Line Antibiotic Selection in Outpatient Settings,” *Antimicrobial Agents and Chemotherapy*, vol. 63, no. 11 (2019): pp. e01060-19.

data to CMS on six out of 271 available quality measures; we identified nine of those measures as being related to antibiotics. MIPS-eligible clinicians were also generally required to select and submit data that year for up to four out of 93 available improvement activities; we identified one such activity as being related to antibiotics.

Our analysis of CMS data on MIPS participation in 2017, the program's first performance year and the most recently available data, indicates that implementation of the antibiotics-related quality measures and improvement activities was limited. According to a CMS report, a total of 1,057,824 clinicians were eligible for MIPS in 2017, of which 1,006,319 clinicians, or 95 percent, reported data.¹⁷⁵ Based on our analysis of data contained in the CMS report's appendix, the number of 2017 MIPS-participating clinicians who reported to CMS on the nine antibiotics-related quality measures ranged from 844 clinicians to 33,631 clinicians; the measure on appropriate treatment for children with an upper respiratory infection was the most reported antibiotics-related measure.¹⁷⁶ By contrast, the most frequently reported quality measures overall in 2017 were controlling high blood pressure (510,723 clinicians), preventive care and screening for tobacco use (492,357), and breast cancer screening (473,819).

CMS's data also show that for the 2017 MIPS improvement activities, 47,645 of the 1,006,319 participating clinicians reported on the one improvement activity related to antibiotics that year: implementation of

¹⁷⁵Department of Health and Human Services, Centers for Medicare & Medicaid Services, *2017 Quality Payment Program Reporting Experience* (Baltimore, Md.: March 2019). CMS officials told us that for the first year of MIPS (the 2017 performance period), the agency estimates there were approximately 538,000 clinicians who were not eligible to participate in MIPS.

¹⁷⁶We recognize that not all types of MIPS-eligible clinicians prescribe antibiotics or treat patient populations that relate to specific MIPS antibiotics-related quality measures; thus, such measures would only be appropriate for some providers to select and report on. For example, pediatricians and other clinicians who treat children would be more likely to choose and report on measures related to the appropriate use of antibiotics in children. In addition, it is possible that some MIPS-eligible clinicians implemented antibiotics-related quality measures but chose not to report them to CMS. However, the extent of these circumstances is unknown because CMS's data did not capture this information.

an antibiotic stewardship program.¹⁷⁷ Specifically, this activity referred to implementation of an antibiotic stewardship program that measured the appropriate use of antibiotics for several different conditions (upper respiratory infections in children, pharyngitis, and bronchitis in adults), according to clinical guidelines for diagnostics and therapeutics.¹⁷⁸

CDC Faces Challenges in Collecting Complete Antibiotic Use Data, Limiting the Agency’s Ability to Monitor and Improve Appropriate Use

CDC’s ability to monitor and improve appropriate antibiotic use is limited by challenges it faces in collecting complete antibiotic use data across health care settings. According to CDC, experts we interviewed, and documents we reviewed, more data are needed to identify the extent of antibiotic use, including inappropriate use. In turn, CDC and experts say that more antibiotic use data would enable health care providers, federal agencies, and others to identify and target areas for improvement, track results over time, and adjust antibiotic stewardship activities as needed.¹⁷⁹ We have also previously reported that monitoring antibiotic use over time in both inpatient and outpatient settings is important for understanding patterns in antibiotic resistance and for targeting

¹⁷⁷We recognize that not all types of MIPS-eligible clinicians prescribe antibiotics; thus, MIPS antibiotics-related improvement activities would only be appropriate for some providers to select and report on. For example, clinicians who do not prescribe antibiotics would be unable to choose and report on an improvement activity to implement antibiotic stewardship programs. In addition, it is possible that some MIPS-eligible providers implemented antibiotic stewardship programs but chose not to report that to CMS as a MIPS improvement activity. However, the extent of these circumstances is unknown because CMS’s data did not capture this information.

¹⁷⁸In contrast, the most frequently reported improvement activities overall in 2017 were providing 24/7 access to eligible clinicians or groups that have real-time access to a patient’s medical record (190,510 clinicians), use of decision support and standardized treatment protocols (118,450), and patient-centered medical home attestation (110,057).

¹⁷⁹For example, recent studies show that antibiotics are frequently inappropriately selected for common outpatient infections and that fluoroquinolones are frequently used inappropriately in adults, pointing to key areas where antibiotic stewardship could be targeted. See A. L. Hersh et al., “Frequency of First-line Antibiotic Selection among U.S. Ambulatory Care Visits for Otitis Media, Sinusitis, and Pharyngitis,” *JAMA Internal Medicine*, vol. 176, no.12 (2016): pp. 1870-1872; and S. Kabbani et al., “Opportunities to Improve Fluoroquinolone Prescribing in the United States for Adult Ambulatory Care Visits,” *Clinical Infectious Diseases*, vol. 67, no. 1 (2018): pp. 134-136.

stewardship activities.¹⁸⁰ In addition, WHO notes that data on global antibiotic use is essential for obtaining a comprehensive picture of antibiotic resistance and for identifying areas where actions are needed.¹⁸¹

Despite progress in collecting antibiotic use data (as previously discussed), CDC faces several challenges in its efforts to collect complete antibiotic use data. For example, health care providers across various inpatient and outpatient settings do not record such data in one centralized, electronic database. In addition, CDC officials told us that there are no uniform requirements at the federal level (with the exception of DOD and VA hospitals) for providers to report their antibiotic use data to a centralized database such as the NHSN AU Option, and, according to CDC officials and experts we interviewed, data collection can be costly for CDC and health care providers. Because of these and other challenges, CDC relies on data voluntarily reported by hospitals through the AU Option, and the agency collects its own data or purchases proprietary pharmacy data to estimate antibiotic use—and, to some degree, to assess appropriateness of use—across health care settings. However, these data are incomplete owing to several limitations, as described by type of setting below.

- **Hospitals.** Our analysis of CDC data shows that although the number of hospitals participating in the AU Option has gradually risen since its launch in 2011, participation remains limited, with 1,561, or 23 percent, of the 6,849 eligible hospitals reporting at least one month of antibiotic use data as of January 1, 2020.¹⁸² (See fig. 5 for a map showing the percentage of U.S. hospitals reporting antibiotic use data to the AU Option, by state, plus the District of Columbia and Puerto Rico, as of August 2019.) While CDC officials told us they considered this level of participation to be an accomplishment given that participation is voluntary, the National Action Plan set 95 percent participation in the AU Option by 2020 as a significant outcome to

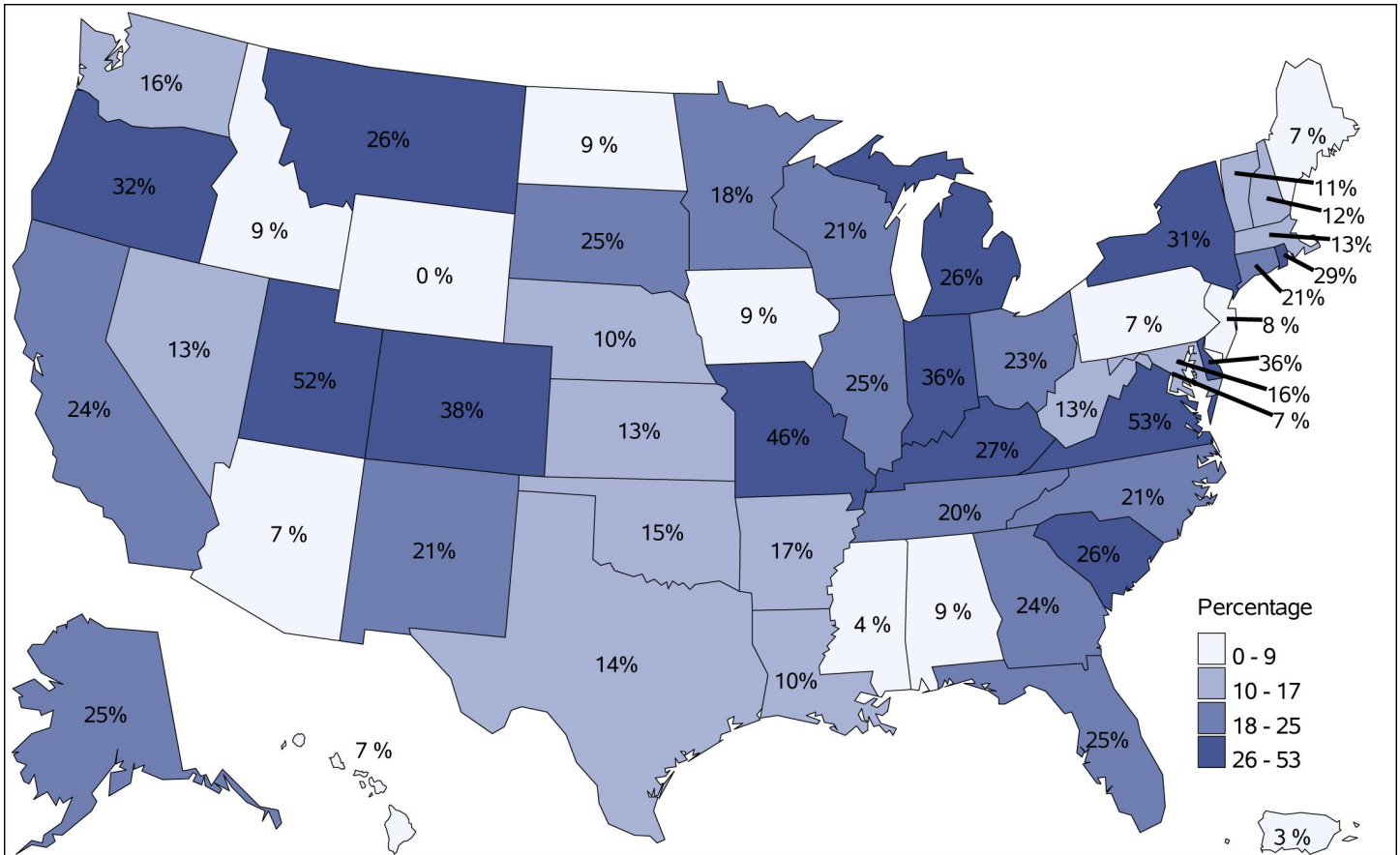
¹⁸⁰[GAO-11-406](#).

¹⁸¹World Health Organization, *WHO Report on Surveillance of Antibiotic Consumption: 2016-2018 Early Implementation* (Geneva, Switzerland: 2018).

¹⁸²CDC data indicate that, as of January 1, 2020, there were 6,849 hospitals, including 13 DOD hospitals located on military bases outside the United States, that were eligible for reporting data to the AU Option.

support the plan’s goal to strengthen national surveillance efforts to combat resistance.¹⁸³

Figure 5: Percentage of U.S. Hospitals Reporting Antibiotic Use Data to CDC’s National Healthcare Safety Network, by State, plus the District of Columbia and Puerto Rico, as of August 2019



Source: Centers for Disease Control and Prevention (CDC). | GAO-20-341

Note: U.S. hospitals can choose to report their antibiotic use data, on a voluntary basis, to CDC through the National Healthcare Safety Network’s Antimicrobial Use Option. The percentages of hospitals shown in this figure had electronically submitted at least one month of antibiotic use data to this database as of August 2019, according to CDC.

Experts, including those at our meeting, cite multiple challenges that CDC faces in collecting hospitals’ antibiotic use data through the AU Option. For example, The Pew Charitable Trusts has stated that current,

¹⁸³As previously noted, the National Action Plan contains five goals that are supported by numerous objectives, sub-objectives, agency-specific milestones, and significant outcomes.

voluntary data are limited and that mandatory reporting would provide the data needed to establish a more accurate baseline of antibiotic use, identify stewardship interventions that would be most effective, and measure progress toward reducing inappropriate prescribing.¹⁸⁴ An expert who attended our meeting later suggested that CMS could implement a pay-for-reporting program to incentivize hospitals to report data to the AU Option, and that the program could transition to a pay-for-performance program over time.¹⁸⁵ In addition, experts we interviewed told us that a participating hospital must be willing to spend as much as tens of thousands of dollars for a vendor to customize software for their electronic health record systems to use the AU Option, in addition to investing time training staff on how to use it. CDC officials also told us that the agency lacks the authority to require hospitals to report their antibiotic use data, and that there is currently no federal funding available to assist hospitals with the investment needed to participate in the AU Option. Furthermore, hospitals' voluntary participation in the AU Option may remain limited until CDC's benchmark measures are adequately risk-adjusted for different locations and patient populations.¹⁸⁶ For example, one expert we interviewed said that because the AU Option currently aggregates data on the volume of antibiotics used without adequate risk adjustment, a hospital with a patient population that might warrant higher use of antibiotics may be reluctant to report its antibiotic use data to avoid

¹⁸⁴The Pew Charitable Trusts, *Trends in Antibiotic Use, 2018* (Aug. 29, 2018).

¹⁸⁵Since the early 2000s, CMS has offered financial incentives to Medicare providers who report their performance on specified quality measures. Under a pay-for-reporting program, such as the Hospital Inpatient Quality Reporting program, a hospital may receive higher payments for reporting data on the quality measures used in the program. Under a pay-for-performance program, a hospital may receive higher payments based on its level of performance on the measures.

¹⁸⁶In 2016, CMS invited public comment on the possibility of CDC's benchmark measures' future inclusion in CMS's Hospital Inpatient Quality Reporting program, which would allow the public to access antibiotic use information on individual hospitals. Department of Health and Human Services, Centers for Medicare & Medicaid Services, *Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Proposed Policy Changes and Fiscal Year 2017 Rates; Quality Reporting Requirements for Specific Providers; Graduate Medical Education; Hospital Notification Procedures Applicable to Beneficiaries Receiving Observation Services; and Technical Changes Relating to Costs to Organizations and Medicare Cost Reports*, 81 Fed. Reg. 25197 (Apr. 27, 2016). However, CDC officials told us that it would likely be a few years before the benchmark measures would be adequately risk-adjusted and therefore ready to become a required reporting measure.

looking like an unnecessarily high prescriber.¹⁸⁷ Regarding another data source for antibiotic use in hospitals, CDC's EIP provides more granular data at the patient level that allows CDC to assess the appropriateness of antibiotic use. However, CDC officials told us that the agency has been unable to repeat its hospital prevalence survey since 2015 due to insufficient resources (the next survey is expected in 2020) and that the survey encompasses a limited number of hospitals, patients, and states.

- **Nursing homes.** According to CDC, nursing homes may be the most challenging health care setting from which the agency collects antibiotic use data; CDC officials stated that this is because electronic health record systems, from which data could be easily accessed, are less common in nursing homes.¹⁸⁸ In addition, CDC officials stated that the agency's collection of antibiotic use data through the EIP nursing homes prevalence survey has been limited in scope and frequency due to insufficient resources.
- **Outpatient settings.** Collecting data for outpatient settings, such as retail pharmacies, is also challenging. For example, CDC officials stated that one proprietary source from which CDC purchases data reflects the volume of pharmacy antibiotic prescriptions, but the data do not contain diagnostic information, preventing the agency from evaluating the appropriateness of those prescriptions. Other CDC or proprietary data sources from which the agency collects or purchases antibiotic use data are limited by the frequency with which those sources release such data, the age range of patients included in the data (i.e., whether they are over or under 65 years), or other characteristics. As previously noted, approximately 85 to 95 percent of

¹⁸⁷The AU Option's benchmark measures allow a participating hospital to compare its "observed" antibiotic use with nationally aggregated ("predicted") use for specific antibacterial agents administered to adult and pediatric patients in specific ward and intensive care unit locations. CDC notes that the measures are designed to serve as high-value targets or high-level indicators for hospitals' antibiotic stewardship programs. Thus, a given hospital's results are intended to prompt analysis of possible overuse, underuse, or inappropriate use of antibiotics; identify opportunities for improvement; and gauge the impact of stewardship efforts. CDC also notes that higher-than-average antibiotic use might be justified, while lower-than-average use might harm patients, and that additional analyses to determine the appropriateness of antibiotic use in individual instances are likely to require access to detailed, patient-level data that is beyond the scope of data collection and analysis using the AU Option.

¹⁸⁸However, CDC officials stated that the agency has partnered with electronic health record vendors and pharmacies to obtain access to and analyze nursing home antibiotic use data to inform stewardship efforts.

the nation's antibiotic use, by volume, occurred in outpatient settings from 2010 through 2015.

The CARB Task Force Has Not Identified Plans to Address Challenges Related to Expanding Stewardship Programs and Antibiotic Use Data Collection

The National Action Plan calls for strengthening antibiotic stewardship and for the timely reporting of antibiotic use data across health care settings. Executive Order No. 13676, as previously noted, directs the CARB Task Force to provide annual updates to the President on federal government actions to combat antibiotic resistance, including progress made in implementing the National Action Plan and plans for addressing any barriers preventing its full implementation.¹⁸⁹ These annual updates are to include specific goals, milestones, and metrics for proposed actions and recommendations, taking into consideration federal resources. However, in its progress reports covering the first four years of the National Action Plan's implementation—which were provided to the President and the public—the CARB Task Force has not identified plans to address barriers that agencies face in expanding antibiotic stewardship programs across health care settings.¹⁹⁰ For example, the task force did not include in the progress reports CMS's plans to address barriers to expanding its requirements for antibiotic stewardship programs in

¹⁸⁹Exec. Order No. 13676, § 3(c)(ii) (Sept. 23, 2014). The National Action Plan contains a sub-objective on strengthening antibiotic stewardship in inpatient, outpatient, and long-term care settings by expanding existing programs, developing new ones, and monitoring progress and efficacy. In addition, the National Action Plan contains a 3-year milestone, which CMS missed, for the agency to require hospitals and certain other health care settings (long-term acute care hospitals, other post-acute facilities, ambulatory surgery centers, and dialysis centers) to implement antibiotic stewardship programs through the agency's Conditions of Participation.

For the purposes of this report, we consider the terms challenges and barriers to be synonymous.

¹⁹⁰CARB Task Force, *National Action Plan: Progress Report for Years 1 and 2*, *National Action Plan: Progress Report: Year 3*, and *National Action Plan: Progress Report: Year 4*.

hospitals, which were delayed, or in certain other types of health care facilities.¹⁹¹

In addition, in its progress reports to date, the CARB Task Force has not identified plans to address the barriers to expanding the collection of antibiotic use data across health care settings.¹⁹² For example, the task force did not include in the progress reports CDC's plans to address barriers to achieving the significant outcome of 95 percent of eligible hospitals participating in the AU Option by 2020, although participation was only 23 percent as of January 1, 2020. The CARB Task Force coordinators said, in response to our inquiries during this review, that the task force intends to identify agencies' plans for addressing barriers in the Year 5 progress report to be published in fall 2020. However, the coordinators also stated that the progress reports to date have not identified plans to address barriers largely because the task force focused on reporting the agencies' accomplishments in implementing the National Action Plan. Until the CARB Task Force identifies and reports on agencies' plans to address barriers related to the expansion of antibiotic stewardship programs and the collection of antibiotic use data across health care settings to the extent feasible, the federal government will not have reasonable assurance that it is fully implementing the National Action Plan and addressing antibiotic resistance.

Antibiotic Stewardship Training May Have Limited Success in Improving Prescribing Behavior

While training is recognized as one component of an antibiotic stewardship program, such training may have limited success in improving antibiotic prescribing behavior, and federal agencies indicate

¹⁹¹CMS's notice explained that the extension of the timeline for final rule publication was due to the complexity of the rule and its substantive nature. Department of Health and Human Services, Centers for Medicare & Medicaid Services, *Medicare and Medicaid Programs; Hospital and Critical Access Hospital (CAH) Changes To Promote Innovation, Flexibility, and Improvement in Patient Care; Extension of Timeline for Publication of the Final Rule*, 84 Fed. Reg. 27069 (June 11, 2019). See 42 U.S.C. § 1395hh(a)(3)(B).

¹⁹²One of the National Action Plan's objectives is to expand and strengthen the national infrastructure for public health surveillance and data reporting and to provide incentives for timely reporting of antibiotic resistance and antibiotic use in all health care settings. In addition, to measure progress toward the goal to slow the emergence of resistant bacteria and prevent the spread of resistant infections, the National Action Plan set a significant outcome of reducing inappropriate antibiotic use by 50 percent in outpatient settings and by 20 percent in inpatient settings by 2020—a performance target that requires the collection, analysis, and reporting of antibiotic use data.

that it is challenging to evaluate the training’s effectiveness. CDC officials and experts say that inappropriate antibiotic use could be improved through stewardship training, but it is challenging because antibiotic prescribing behavior is driven by multiple factors and can be difficult to change. For example, a PACCARB report stated that prescribers often feel pressure to prescribe antibiotics—even when antibiotics may not be warranted—because of their perception that a patient is demanding such a prescription, or a patient’s actual demand.¹⁹³ In addition, CDC notes that antibiotics are frequently prescribed for respiratory conditions most commonly caused by viruses such as the common cold, against which antibiotics are ineffective. Other factors that drive antibiotic prescribing behavior, as cited by experts, include habit, which may stem from what physicians and other prescribers learn during their residencies or observe in the workplace; the time it takes to explain to a patient why an antibiotic is inappropriate; and “decision fatigue” caused by tiredness or hunger. (See table 4 for examples of factors that drive or deter antibiotic prescribing behavior.)

Table 4: Examples of Factors That Drive or Deter Antibiotic Prescribing Behavior

Factors that drive antibiotic prescribing	Factors that deter antibiotic prescribing
<ul style="list-style-type: none"> • Perception that patients want antibiotics • Fear that patients will not be satisfied with their care without a prescription, leading patients to give the provider poor ratings or reviews • Perception that it is easier and quicker to prescribe antibiotics than to explain to patients why they are unnecessary • No billing code or reimbursement for “stewardship” • Habit • Decision fatigue caused by tiredness or hunger • Worry about serious complications (without antibiotics) and a “just to be safe” mentality • Lack of financial incentives to use diagnostic tests (e.g., to determine if an infection is bacterial vs. viral) • Reluctance to wait to see if a patient’s symptoms continue before prescribing 	<ul style="list-style-type: none"> • Risks of adverse reactions • Risks of drug interactions • Recognition of the need for antibiotic stewardship • Desire to deter low-value care^a • Desire to decrease unnecessary health care spending • Preference to follow prescribing guidelines • Comparison with peers of antibiotic prescriptions data • Use of a “pre-commitment” poster/letter to patients that the medical practice is dedicated to appropriate use of antibiotics • “Accountable justification”—a pop-up window that appears on electronic health record systems, alerting providers that antibiotics are not generally indicated for the diagnosis and asking the provider to enter a reason to justify the prescription

Source: GAO summary of information from A. Mehrotra and J. A. Linder, “Tipping the Balance Toward Fewer Antibiotics,” *JAMA Internal Medicine*, vol. 176, no. 11 (2016): pp. 1649-1650; a Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria September 2017 meeting summary; a GAO expert meeting in September 2018; and experts we interviewed. | GAO-20-341

Note: This list of factors is not intended to be comprehensive but, rather, represents a summary of factors presented by the information we reviewed.

¹⁹³Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, *Key Strategies to Enhance Infection Prevention and Antibiotic Stewardship: Report with Recommendations for Human and Animal Health* (Washington, D.C.: September 2018).

^aIn health care, low-value care refers to treatments, tests, and procedures that are either wasteful or ineffective, such as an antibiotic prescription for a viral infection.

Nevertheless, federal agencies plan to evaluate the effectiveness of their antibiotic stewardship training programs to some extent, although the National Action Plan does not require the agencies to do so. For example, CDC officials told us that their online training course for various types of clinicians allows participants to fill out an evaluation that includes questions about whether the participant will be able to apply knowledge gained from the course, which the agency will use to refine and update the course.¹⁹⁴ In addition, for the antibiotic stewardship training for nursing homes that CDC and CMS jointly developed, CDC officials told us that participants will be asked 6 months after the training whether participants implemented stewardship practices—and whether there have been reductions in antibiotic use—as a result of the training. However, CMS, DOD, and VA officials noted that it is difficult to isolate and measure the effectiveness of antibiotic stewardship training specifically on antibiotic prescribing behavior—compared to other, concurrent federal efforts, such as requirements and guidance to promote appropriate antibiotic use. For example, DOD officials told us that their department has looked at antibiotic use data from DOD health care facilities as a “surrogate” to evaluate whether antibiotic stewardship in general has been effective—but noted that is an imperfect measure since there are many factors that affect antibiotic prescribing behavior, and training is only one of several interventions aimed at reducing inappropriate antibiotic use.

Conclusions

Antibiotic resistance has been characterized as one of the greatest public health threats the world faces. A concerted effort involving coordination of multiple stakeholders and countries and across health fields is critical to helping ensure that bacterial infections remain treatable. Steps by federal agencies to expand surveillance, facilitate the development and use of new diagnostic tests, fund R&D for the development of new treatments, and issue requirements and guidance for antibiotic stewardship programs are important efforts toward addressing the problem of antibiotic resistance and implementing the National Action Plan.

Significant challenges to conducting surveillance remain. For example, CDC has not determined the participation rates or appropriate distribution

¹⁹⁴CDC officials also told us that the agency piloted the online training course with target audiences prior to its release in order to improve the course.

of participating hospitals needed by the voluntary antibiotic-resistance reporting option to achieve CDC's goal of conducting regional and national assessments of resistance. By taking steps to determine the participation rates and distribution needed for this option, CDC would have more reasonable assurance that it can achieve its goal. CDC classified gonorrhea as one of the most urgent resistant threats in the nation, but collects limited specimens—representing an estimated 1 to 2 percent of the reported cases in the United States—for GISP, its primary surveillance system for resistant gonorrhea. However, CDC has not fully evaluated the representativeness of the trends identified by this surveillance system. By evaluating GISP to ensure that it includes measures of its representativeness, such as comparing the trends in the sample population with those in the overall U.S. population, using specially designed studies if needed, CDC would have better assurance that the trends detected in GISP accurately reflect the characteristics of the health-related outcome the system is designed to monitor. Further, neither the 2013 nor the 2019 Threats Reports provided quantitative measures of uncertainty for CDC's estimates of morbidity and mortality resulting from antibiotic-resistant infections. Providing such measures, such as standard errors or confidence intervals, as appropriate, in its Threats Reports would help CDC and others compare information within and across reporting efforts, and draw appropriate conclusions about the characteristics of antibiotic resistance in the United States, including limitations associated with reported findings and conclusions. Finally, there has been a 6-year interval between CDC's reports on antibiotic resistance threats. By developing a plan for more frequent dissemination of consolidated reporting on priority pathogens at regular intervals, CDC would have more timely trend data and other information necessary for users of the data, including policymakers, to prioritize, plan, implement, and evaluate public health actions to address antibiotic resistance.

HHS has funded some studies to assess whether certain tests for antibiotic resistance lead to improved clinical outcomes, including more effective treatment for patients or more judicious use of antibiotics. However, HHS agencies that are in a position to conduct or fund such studies have not identified leadership, roles, and responsibilities to help further such efforts. By taking steps to identify leadership, roles, and responsibilities, agencies could more effectively address the need for clinical outcomes studies, potentially increasing test use, improving patient care, and enhancing stewardship efforts. In addition, for its part, FDA has not regularly monitored tests for antibiotic resistance to assess breakpoint updates or evaluated any effects of using tests for antibiotic resistance with out-of-date breakpoints. By regularly monitoring and

evaluating FDA-authorized tests that rely on breakpoints, FDA would be able to determine whether test manufacturers are updating breakpoints as needed and help ensure that patient care and infection control efforts are effective.

While government push incentives to support antibiotic R&D have been helpful, experts and antibiotic developers have indicated that push incentives alone are not sufficient to sustain antibiotic development. PACCARB, TATFAR, and other experts have called for additional postmarket pull incentives to increase the antibiotic pipeline, but HHS does not have a strategy for doing so. Developing a strategic framework that outlines key design elements of new incentives would be a first step toward identifying potential authorities and resources that may be needed and determining agency roles for implementation and oversight of the incentives. Until such incentives are developed, more drug companies may exit the antibiotic development sector, and the pipeline of new treatments may continue to decrease.

Finally, in its progress reports covering the first four years of the National Action Plan's implementation, the CARB Task Force did not identify plans, as required by the Executive Order, to address barriers that agencies face in fully implementing the National Action Plan, such as expanding (1) a CDC program designed to strengthen the U.S. response to resistant gonorrhea; (2) antibiotic stewardship programs across health care settings; and (3) antibiotic use data collection, to the extent feasible. Without identifying plans to address these and other challenges, the federal government cannot assure that the country is prepared to overcome the urgent health consequences of antibiotic resistance. Until the CARB Task Force, which is coordinated by HHS officials, identifies and reports on agencies' plans to address barriers preventing full implementation of the National Action Plan, the federal government will not have reasonable assurance that it is fully implementing the National Action Plan and addressing antibiotic resistance.

Recommendations for Executive Action

We are making a total of eight recommendations, including four to CDC, three to HHS, and one to FDA. Specifically:

The Director of CDC should take steps to determine participation rates and distribution needed in the AR Option of the National Healthcare

Safety Network for conducting regional and national assessments of antibiotic resistance of public health importance. (Recommendation 1)

The Director of CDC should ensure that CDC's evaluation of its surveillance system for antibiotic-resistant gonorrhea includes measures of its representativeness, such as comparison of the trends in the sample population with those in the overall U.S. population, using specially designed studies if needed. (Recommendation 2)

The Director of CDC should provide information on uncertainties for antibiotic resistance estimates in its consolidated Threats Reports, including standard errors or confidence intervals, as appropriate. (Recommendation 3)

The Director of CDC should develop a plan for timely, consolidated reports of antibiotic resistance in priority pathogens at regular intervals. (Recommendation 4)

The Secretary of HHS should identify leadership and clarify roles and responsibilities among HHS agencies to assess the clinical outcomes of diagnostic testing for identifying antibiotic-resistant bacteria. (Recommendation 5)

The Commissioner of FDA should direct the Center for Devices and Radiological Health to conduct additional monitoring and evaluation of the status of FDA-authorized tests that rely on breakpoints, on a regular basis, to determine whether test manufacturers are updating breakpoints, seeking additional resources as needed. (Recommendation 6)

The Secretary of HHS should develop a strategic framework to further incentivize the development of new treatments for antibiotic-resistant infections, including through the use of postmarket financial incentives, and, if appropriate, make recommendations to Congress for necessary authority. (Recommendation 7)

The Secretary of HHS should direct the CARB Task Force to include in its annual updates to the President plans for addressing any barriers preventing full implementation of the National Action Plan and, as appropriate, make recommendations for new or modified actions. Specifically, the CARB Task Force should identify plans to address barriers, such as those related to expanding (1) a CDC program designed to strengthen the U.S. response to resistant gonorrhea; (2) antibiotic stewardship programs across health care settings; and (3) antibiotic use

data collection across health care settings, to the extent feasible.
(Recommendation 8)

Agency Comments and Our Evaluation

We provided a draft of this report to DOD, VA, and HHS for review and comment. DOD and VA did not provide formal comments but generally agreed with our report.

In its comments, reproduced in appendix V, HHS generally concurred with our findings and seven of our recommendations, and did not concur with one of our recommendations, as discussed below. HHS identified several actions it intends to take to address our recommendations. DOD and HHS also provided technical comments, which we incorporated as appropriate.

In response to our first recommendation, HHS concurred and CDC stated it is working with public health partners to promote the voluntary use of the AR Option, providing technical support to states that may be considering a state or local mandate to require AR and AU reporting, and developing pilot programs to assess AR Option data and other data sources for certain types of antibiotic resistance. While these actions are helpful, we believe taking additional steps, such as determining goals for participation rates and distribution for AR Option reporting, would give CDC more reasonable assurance that it can conduct regional and national assessments of resistance.

In response to our second recommendation, HHS concurred and CDC stated it is taking additional efforts to examine the representativeness of data collected through its primary surveillance system for resistant gonorrhea, including working to develop laboratory methods to reduce dependence on cultured isolates. CDC stated that steps to refine and improve collection of resistant gonorrhea data require additional resources. We believe that CDC requesting such resources would help ensure that such data are representative of the overall U.S. population.

HHS generally concurred with our third recommendation. CDC stated it feels that it is critical to publish the data after peer review and then plans to link the publications back to online resources of the 2019 Threats Report. We believe that peer-reviewed publication is important, but it is also important for CDC to take additional steps to establish and report uncertainties for the national estimates or summary data that would help

CDC and others draw appropriate conclusions about the characteristics of antibiotic resistance in the United States.

In response to our fourth recommendation, HHS concurred and CDC stated it has plans to update its enterprise-wide AR Threats Report every three years, and that it also issues regular reports on specific groups of pathogens.

In response to our fifth recommendation, HHS concurred and stated that the CARB Task Force leadership will work with relevant HHS agencies to clarify roles and responsibilities and identify leadership, if appropriate, for supporting research on clinical outcomes related to diagnostic tests.

HHS concurred with our sixth recommendation, and FDA concurred with conducting additional monitoring and evaluation of tests relying on breakpoints when FDA identifies or recognizes new breakpoints. FDA stated that it has taken major steps to help address challenges associated with updating such tests to reflect the most current breakpoints. We believe that in addition to these steps, monitoring and evaluation of current FDA-authorized tests that may still be using out-of-date breakpoints will enhance FDA's ability to provide assurance that patient care and infection control efforts are effective.

HHS did not concur with our seventh recommendation that HHS should develop a strategic framework to further incentivize the development of new treatments for antibiotic-resistant infections, including through the use of postmarket financial incentives. HHS noted that, while it agrees that additional incentives are needed to address the limited pipeline for novel and innovative treatments to combat antibiotic resistance, it is still conducting analyses to understand whether postmarket incentives should be included as a component of its forthcoming strategic framework to further incentivize the development of new treatments. However, HHS did not specify when its framework would be released. We support HHS's efforts to develop such a framework, as this is a complex issue with multiple factors to consider. However, we believe our recommendation is still warranted. Antibiotic resistance is one of the greatest global public health threats, and experts, including the WHO, have warned that the pipeline of new antibiotics in development is insufficient to combat the threat. Without an adequate arsenal of treatments, we are likely to see increasing mortality caused by these deadly infections. As we reported, experts, advisory groups, federal officials, and antibiotic developers have all called for additional postmarket incentives to reinvigorate the pipeline of antibiotics under development. The current significant federal

investment in push incentives to support antibiotic R&D is helpful but will ultimately be ineffective if companies receiving this investment are unable to sustain their business once their treatment reaches the market. Therefore, we maintain that it is important that HHS not delay the development of a strategic framework that includes postmarket incentives, which is just an initial step toward the creation of these incentives. Until additional postmarket incentives are developed, more drug companies may exit the antibiotic development sector, and the pipeline of new treatments for antibiotic-resistant infections may continue to decrease.

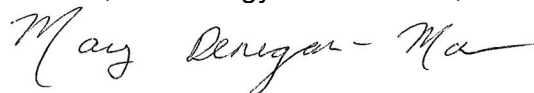
In response to our eighth recommendation, HHS concurred and stated that beginning in 2020 and continuing annually thereafter, the CARB Task Force's progress reports will include discussion of any barriers preventing full implementation of the National Action Plan, including, as appropriate, barriers that GAO has identified. We emphasize that the CARB Task Force should also identify plans to address such barriers—and, as appropriate, make recommendations for new or modified actions—in future progress reports, in accordance with Executive Order No. 13676.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to appropriate congressional committees; the Secretaries of DOD, HHS, and VA; and other interested parties. In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact us at (202) 512-6888 or personst@gao.gov, or (202) 512-7114 or deniganmacauleym@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix VI.



Timothy M. Persons, PhD, Chief Scientist and Managing Director
Science, Technology Assessments, and Analytics



Mary Denigan-Macauley, PhD, Director

Letter

Health Care

Appendix I: Objectives, Scope, and Methodology

This report examines: (1) the Centers for Disease Control and Prevention's (CDC) efforts to address surveillance of antibiotic resistance and any challenges to these efforts; (2) federal efforts to advance the development and use of diagnostic tests for identification and characterization of resistant bacteria and to address barriers to the development of diagnostic tests; (3) challenges to developing new treatments for antibiotic-resistant infections and federal efforts to address the challenges; and (4) federal efforts to promote the appropriate use of antibiotics and any challenges that remain.

We focused our review primarily on agency actions since 2015, when the *National Action Plan for Combating Antibiotic-Resistant Bacteria* (National Action Plan) was published.¹ We also focused our review on human health, as we have reported on federal efforts to address the use of antibiotics in food animals and recommended actions to improve these efforts for more than 20 years.² Additionally, we focused our review on antibiotic-resistant bacteria. We generally excluded federal efforts related to infection prevention and control in human health care, on which we have previously reported.³

To address all four objectives, we reviewed relevant agency reports and documents, such as CDC's report, *Antibiotic Resistance Threats in the United States, 2013* (2013 Threats Report); conducted interviews with

¹The White House, *National Action Plan for Combating Antibiotic-Resistant Bacteria* (Washington, D.C.: March 2015).

²GAO, *Antibiotic Resistance: More Information Needed to Oversee Use of Medically Important Drugs in Food Animals*, [GAO-17-192](#) (Washington, D.C.: Mar. 2, 2017); *Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals*, [GAO-11-801](#) (Washington, D.C.: Sept. 7, 2011); *Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals*, [GAO-04-490](#) (Washington, D.C.: Apr. 22, 2004); and *Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health*, [GAO/RCED-99-74](#) (Washington, D.C.: Apr. 28, 1999).

³GAO, *Health-Care-Associated Infections in Hospitals: Leadership Needed from HHS to Prioritize Prevention Practices and Improve Data on These Infections*, [GAO-08-283](#) (Washington, D.C.: Mar. 31, 2008).

officials from federal agencies, experts, and stakeholder organizations; and we reviewed relevant literature, policy papers, and GAO reports.⁴ We interviewed officials from federal agencies responsible for implementing the aspects of the National Action Plan related to our research objectives: the Department of Health and Human Services' (HHS) Office of the Assistant Secretary for Planning and Evaluation, the Biomedical Advanced Research and Development Authority (BARDA), CDC, the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Office of Global Affairs; as well as the Department of Defense (DOD) and the Department of Veterans Affairs. We also interviewed experts and representatives from organizations involved in public health and epidemiology, infectious diseases and microbiology, antibiotic research and development (R&D), antibiotic stewardship, and other issues relating to antibiotic resistance. Because antibiotic resistance is a global problem, we also interviewed officials from the World Health Organization (WHO), the European Centre for Disease Prevention and Control, the European Medicines Agency, the Wellcome Trust, Public Health England, and the Surveillance and Epidemiology of Drug-Resistant Infections Consortium about various aspects of our review; and we reviewed relevant documents from these entities. We identified experts and organizations through literature and other documents we reviewed and through referrals from agency officials and other experts we interviewed.⁵ In addition, we attended several meetings and reviewed summaries of meetings held by the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB). Furthermore, we attended two conferences related to antibiotic resistance: the World Anti-Microbial Resistance Congress and the Gordon Research Conference on chemical and biological threat defense, the latter of which had a session devoted to antibiotics and antibiotic resistance. For each of our objectives, we identified and reported on actions taken by federal agencies and key challenges that the agencies face in addressing antibiotic resistance. We evaluated the actions taken by federal agencies against relevant criteria, as applicable.

In addition, in September 2018, we convened a meeting of experts in antibiotic resistance epidemiology, diagnostic testing, antibiotic development, and antibiotic stewardship. This meeting of experts was

⁴Department of Health and Human Services, Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2013* (Atlanta, Ga.: Apr. 23, 2013).

⁵We assessed the studies we cite in this report for their methodological limitations and determined that they were sufficiently reliable for our purposes.

planned and convened with the assistance of the National Academy of Sciences to better ensure that a breadth of expertise was brought to bear in its preparation; however, all final decisions regarding meeting substance and expert participation are the responsibility of GAO. Any conclusions and recommendations in GAO reports are solely those of the GAO. The Board on Population Health and Public Health Practice within the National Academy of Sciences solicited expert nominations from academia, public health laboratories, industry, and other organizations working in topics relating to antibiotic resistance. From their list of 51 nominees, and additional nominees we independently identified, we convened a meeting of 18 experts selected for their knowledge and expertise related to antibiotic resistance epidemiology, diagnostic testing, antibiotic development, and antibiotic stewardship. Eleven of the 18 experts who participated in our meeting also reviewed and provided comments on a draft of our report. We refer to such experts in this report as “experts at our meeting;” appendix II contains a list of the expert participants.

To examine CDC’s efforts to address surveillance for antibiotic resistance and any challenges to these efforts, we reviewed documentation and conducted interviews with agency officials and other key stakeholders on each of the surveillance systems across CDC that track antibiotic resistance and reviewed CDC’s 2013 Threats Report and CDC’s *Antibiotic Resistance Threats in the United States, 2019* data.⁶ We further focused our review on the 17 priority disease-causing bacteria listed in CDC’s 2013 Threats Report. The CDC surveillance systems included:

- Antibiotic Resistance Laboratory Network
- Emerging Infections Program (EIP)
- Gonococcal Isolate Surveillance Program (GISP)
- National Antimicrobial Resistance Monitoring System (NARMS)
- National Healthcare Safety Network (NHSN)
- National Notifiable Diseases Surveillance System
- National Tuberculosis Surveillance System

For NHSN, we also assessed health care facility participation data by state and territory. We assessed the reliability of these data by reviewing

⁶Department of Health and Human Services, Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2019* (Atlanta, Ga.: Nov. 13, 2019).

them for any outliers or anomalies and by inquiring with agency officials about their source and any known reliability issues. We determined that these data were sufficiently reliable for assessing facility participation rates by U.S. state and territory. Stakeholder organizations we interviewed represented state and territorial epidemiologists and other public health officials (the Council of State and Territorial Epidemiologists and the Association of State and Territorial Health Officials) and an international consortium to address challenges in surveillance of antibiotic resistance (the Surveillance and Epidemiology of Drug-resistant Infections Consortium). We also reviewed reports on antibiotic resistance surveillance challenges from the Public Health Informatics Task Force and the Antibiotic Resistance Surveillance Task Force. We also reviewed documents from WHO's global surveillance system and interviewed WHO and CDC officials to identify challenges that limit CDC's ability to assess threats from abroad. We evaluated challenges and steps CDC has taken against CDC's "Updated Guidelines for Evaluating Public Health Surveillance Systems;" *Standards for Internal Control in the Federal Government*; prior GAO work; the Government Performance and Results Act of 1993 (GPRA) and the GPRA Modernization Act of 2010; the Office of Management and Budget Circular No. A-11 and *Standards and Guidelines for Statistical Surveys*; relevant National Action Plan objectives, aims, and milestones; and Executive Order No. 13676, September 2014.⁷

To examine federal efforts to advance the development and use of diagnostic tests, we also interviewed representatives from a nongeneralizable selection of six diagnostic test manufacturers to identify challenges they face in developing tests for antibiotic resistance and challenges in increasing user adoption of their tests. We further focused our review on the 17 priority disease-causing bacteria listed in CDC's 2013 Threats Report. The six manufacturers we interviewed were

⁷Department of Health and Human Services, Centers for Disease Control and Prevention, "Updated Guidelines for Evaluating Public Health Surveillance Systems," *Morbidity and Mortality Weekly Report*, vol. 50, no. RR-13 (2001); GAO, *Standards for Internal Control in the Federal Government*, [GAO-14-704G](#) (Washington, D.C.: Sept. 10, 2014); GAO, *Performance.gov: Long-Term Strategy Needed to Improve Website Usability*, [GAO-16-693](#) (Washington, D.C.: Aug. 30, 2016); Government Performance and Results Act of 1993, Pub. L. No. 103-62, 107 Stat. 285 (Aug. 3, 1993); GPRA Modernization Act of 2010, Pub. L. No. 111-352, 124 Stat. 3866 (Jan. 4, 2011); Office of Management and Budget, Circular No. A-11, *Preparation, Submission, and Execution of the Budget*, Pt. 6, § 200.22 (Washington, D.C.: June 28, 2019) and Office of Management and Budget, *Standards and Guidelines for Statistical Surveys* (September 2006); and Exec. Order No. 13676, *Combating Antibiotic-Resistant Bacteria*, 79 Fed. Reg. 56931 (Sept. 23, 2014).

Accelerate Diagnostics, Beckman Coulter, BioFire and its parent company, BioMerieux, Bruker, Cepheid, and Roche Diagnostics. We identified these manufacturers by compiling a list based on previous work we conducted, interviews with select experts, and internet search. We selected six manufacturers that were identified by more than one source while encompassing different types of tests (culture and genotypic). We limited our scope to FDA-authorized tests—that is, tests that have been reviewed and cleared by FDA for marketing in the United States—that can identify resistance in at least one type of bacteria categorized as priority bacteria in CDC’s 2013 Threats Report.⁸ Some of these tests are called antibiotic susceptibility tests, but we refer to the entire class of such tests as “tests.” We included in our scope tests that can differentiate between viral and bacterial infection because these types of tests are included in the National Action Plan. We evaluated the actions taken by federal agencies against the *Standards for Internal Control in the Federal Government*, relevant National Action Plan objectives, aims, and milestones under Goal 3, and relevant sections in the PACCARB *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic Resistance*. We also evaluated federal agency actions against the “leadership” and “clarity of roles and responsibilities” leading practices from GAO’s *Managing for Results: Key Considerations for Implementing Interagency Collaborative Mechanisms*.⁹ We focused on these key practices when there was a lack of specifically assigned roles in either the National Action Plan or the PACCARB report for key activities.

To identify challenges to developing new treatments for antibiotic-resistant infections and examine federal efforts to address these challenges, we also interviewed 11 randomly selected companies that conduct research and development on new treatments for bacterial

⁸FDA officials told us that the tests under GAO review are Class II devices and thus reviewed as 510(k) or de novo applications and are appropriately referred to as cleared when granted marketing authorization. Other types of diagnostic tests, such as laboratory-developed tests, are not within the scope of this report. FDA describes laboratory-developed tests as tests designed, manufactured, and used within a single laboratory.

⁹[GAO-14-704G](#); *National Action Plan*, Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria; Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic Resistance* (Washington, D.C.: September 2017); and GAO, *Managing for Results: Key Considerations for Implementing Interagency Collaborative Mechanisms*, [GAO-12-1022](#) (Washington, D.C.: Sept. 27, 2012).

infections.¹⁰ We included companies that are researching or developing both traditional antibiotics and alternatives to antibiotics—which we call “nontraditional products” in this report—and we included companies that had and had not received funding from the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and companies that do and do not have existing FDA-approved drugs on the market. We asked company representatives about challenges in developing new antibiotics they have identified, support they may have received from federal agencies, how effective the support has been to them, and their views on additional incentives that would promote the development of new antibiotics. We also interviewed experts on the topic of antibiotic development and industry stakeholders, specifically The Pew Charitable Trusts and the Biotechnology Innovation Organization. We interviewed federal officials from BARDA, CMS, DOD, FDA, and NIH to learn about their programs and actions to support the development of treatments for antibiotic-resistant infections and requested information about funding for antibiotic R&D from BARDA, DOD, and NIH. We included relevant agency actions that began before the National Action Plan was issued in 2015 if they continued after 2015. Finally, we reviewed literature related to antibiotic development and reports about antibiotic pull incentives written by health policy advisory groups, including the PACCARB, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), the DRIVE-AB project, and the Duke Margolis Center for Health Policy.¹¹ We evaluated the actions taken by federal agencies to help address the challenges to developing new treatments against experts’ and advisory groups’ views on additional actions needed and against the principles related to developing strategies outlined in GPRA and the GPRA Modernization Act of 2010.¹² We did not assess challenges to developing products designed to prevent infections, such as vaccines, nor federal actions related to these types of products.

To examine federal agency efforts to promote the appropriate use of antibiotics and any challenges that remain, we also analyzed CMS data and related documentation on the quality measures and improvement activities related to antibiotics as part of CMS’s Merit-based Incentive Payment System (MIPS) in 2017. Specifically, we identified CMS’s

¹⁰We initially selected 12 companies to interview, but one company declined.

¹¹DRIVE-AB is the short name for the “Driving Re-investment in R&D and Responsible Antibiotic Use.”

¹²Pub. L. No. 103-62, 107 Stat. 285 and Pub. L. No. 111-352, 124 Stat. 3866.

antibiotics-related quality measures and improvement activities by conducting a search for the words “antibiotic,” “antimicrobial,” “bacteria,” “resistance,” and “resistant” on CMS’s MIPS website.¹³ We then reviewed CMS’s data on the number of MIPS-eligible clinicians who selected and reported on these measures and activities in 2017, the most recently available data. In 2017, there were nine MIPS quality measures related to antibiotics, as follows:

- (1) acute otitis externa: systemic antimicrobial therapy - avoidance of inappropriate use;
- (2) adult sinusitis: antibiotic prescribed for acute sinusitis (overuse);
- (3) adult sinusitis: appropriate choice of antibiotic: amoxicillin with or without Clavulanate prescribed for patients with acute bacterial sinusitis (appropriate use);
- (4) appropriate testing for children with pharyngitis;
- (5) appropriate treatment for children with upper respiratory infection;
- (6) appropriate treatment of Methicillin-sensitive Staphylococcus aureus bacteremia;
- (7) avoidance of antibiotic treatment in adults with acute bronchitis;
- (8) perioperative care: selection of prophylactic antibiotic – first- or second-generation Cephalosporin; and
- (9) total knee replacement: preoperative antibiotic infusion with proximal tourniquet.

In addition, there was one MIPS improvement activity related to antibiotics in 2017: implementation of antibiotic stewardship program. We reviewed the MIPS data for any obvious outliers or anomalies, and we determined that these data were sufficiently reliable for reporting the number of clinicians who reported implementing these quality measures and improvement activities. In addition, we reviewed aggregated data from CDC on the total number of eligible U.S. hospitals voluntarily

¹³Centers for Medicare & Medicaid Services, “Quality Payment Program: Explore Measures & Activities,” accessed November 6, 2019, <https://qpp.cms.gov/mips/explore-measures>.

reporting their antibiotic use data to a CDC system (the NHSN's Antimicrobial Use Option); we then calculated the percentage of eligible hospitals reporting such data as of January 1, 2020. We assessed the reliability of the aggregated data by reviewing them for any obvious errors or missing data totals and inquiring with CDC officials about their source and any known reliability issues. We determined that these data were sufficiently reliable for reporting hospital participation rates in the system. We also reviewed selected articles on antibiotic use and stewardship—compiled from a variety of sources, including CDC documents and experts we interviewed—published in literature. In addition, we interviewed experts on antibiotic use and stewardship, including representatives from PACCARB, Emory University's School of Medicine, the University of Minnesota's Center for Infectious Disease Research and Policy, The Joint Commission, the Society of Infectious Diseases Pharmacists, The Pew Charitable Trusts, and the Association for Professionals in Infection Control and Epidemiology. We evaluated federal efforts and challenges against relevant National Action Plan objectives and milestones and Executive Order No. 13676. We focused on antibiotic use in the United States, rather than global antibiotic use.

We conducted this performance audit from February 2018 to March 2020 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Appendix II: Expert Meeting Participant List

We collaborated with the National Academy of Sciences to convene a two-day meeting of experts to inform our work on federal efforts to address antibiotic resistance; the meeting was held on September 17 and 18, 2018. The experts who participated in this meeting are listed below. Many of these experts gave us additional assistance throughout our work, including by providing additional technical expertise and answering questions, and 10 of these experts reviewed and provided comments on our draft report for technical accuracy.

Helen W. Boucher, M.D., FACP, FIDSA

Director, Infectious Diseases Fellowship Program

Director, Heart Transplant and Ventricular Assist Device Infectious Diseases Program

Professor, Tufts University School of Medicine, Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center

Boston, MA

Kate Cook

Executive Vice President

Drugs and Biological Products

Greenleaf Health, Inc.

Washington, DC

Stan Deresinski, M.D., FACP, FIDSA

Clinical Professor of Medicine

Infectious Diseases

Stanford University School of Medicine

Stanford, CA

Mary Jane Ferraro, Ph.D., M.P.H.

Pathologist, Subspecialty Co-Head, Microbiology Laboratory, Massachusetts General Hospital

Professor of Pathology & Professor of Medicine, Harvard Medical School

Boston, MA

Susan Huang, M.D., M.P.H.

Professor, Infectious Disease, Medical Director

Epidemiology and Infection Prevention

School of Medicine, University of California, Irvine

Irvine, CA

Romney Humphries, Ph.D., D(ABMM), M(ASCP)

Chief Scientific Officer
Accelerate Diagnostics
Tucson, AZ

Timothy Jinks, Ph.D.

Head of Drug Resistant Infections Priority Program
Wellcome Trust
London, UK

Marion A. Kainer, M.D., M.P.H., FRACP, FSHEA

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Professor and Special Assistant to the Provost
Department of Veterinary Preventive Medicine, Office of Academic Affairs
The Ohio State University
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Colleen S. Kraft, M.D., M.Sc.

Associate Professor
Pathology & Laboratory Medicine
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Appendix III: Additional Examples of Federal Efforts to Support Antibiotic Research and Development

This appendix contains additional examples of efforts by agencies within the Departments of Health and Human Services, Defense, and Energy to provide support for antibiotic research and development beyond those mentioned in the report. These examples do not comprise the full extent of agencies' efforts.

Table 5: Additional Examples of Federal Efforts to Support Antibiotic Research and Development

Agency	Efforts
Department of Health and Human Services	
National Institutes of Health (NIH)	<p>The NIH's National Institute of Allergy and Infectious Diseases (NIAID) offers three distinct mechanisms to support research and development of treatments for antibiotic-resistant infections:</p> <ol style="list-style-type: none"> <li data-bbox="506 1241 1484 1318">1. Grants for basic and applied research: for example, research to better understand how bacteria develop resistance and the interactions between human microbial communities and drug-resistant bacteria <li data-bbox="506 1329 1503 1407">2. Product development contracts: up to 5-year contracts to support the development of new treatments, vaccines, or diagnostic products. Contracts provide companies with funding and access to NIAID experts to decrease product development risk. <li data-bbox="506 1417 1468 1495">3. Pre-clinical and clinical services: research services provided free-of-charge to external researchers; for example, in-vitro assessment of therapeutic candidates' antimicrobial activity and services to support clinical trials for new drugs. <hr/> <p>NIAID's Antibacterial Resistance Leadership Group provides extramural researchers with funding for clinical research studies focused on: infections caused by gram-positive and gram-negative bacteria, and diagnostics development. As of June 2019, the Antibacterial Resistance Leadership Group has initiated more than 40 studies at 130 clinical trial sites.</p> <hr/> <p>Through its Centers of Excellence for Translational Research, NIAID funds research centers throughout the United States to research and develop new or improved medical countermeasures for emerging infectious diseases. Five of the 14 awarded centers are engaged in researching treatments for antibiotic resistance. For example, one center at Harvard University Medical School is researching how best to target the bacterial cell envelope for several types of antibiotic-resistant pathogens and aims to develop at least one new vaccine and three to five antibacterial compounds that demonstrate efficacy in animal models</p>

Appendix III: Additional Examples of Federal Efforts to Support Antibiotic Research and Development

Agency	Efforts
	<p>NIH officials told us NIAID convenes scientific workshops—10 since 2015—to facilitate the development of approaches to challenging scientific questions and promote collaboration among federal agencies and academic and industry researchers.</p> <p>NIAID collaborates with other countries to advance antibiotic-resistance research worldwide. For example, as a member of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), NIAID coordinates and aligns international research activities and organizes international workshops. A result of the TATFAR collaboration is the launch of a partnership between U.S. and European entities to align clinical trial networks to increase access to patients for clinical trials. NIAID has also partnered with the Chinese government to advance antibiotic resistance research activities and clinical trials.</p> <p>The National Center for Biotechnology Information maintains the National Database of Antibiotic-Resistant Organisms in partnership with several other federal agencies, including the Centers for Disease Control and Prevention, the Food and Drug Administration, the U.S. Department of Agriculture, the World Health Organization, and others. The center's efforts include collecting, curating, and disseminating genomic data on bacterial resistance, which can help provide researchers with key data to support the development of promising antibiotic candidates.</p>
Food and Drug Administration (FDA)	<p>FDA conducts and funds regulatory science research to advance scientific knowledge related to antibiotic development.^a For example, in February 2018, FDA solicited input from industry stakeholders on research ideas related to antibiotic clinical trial design, evaluating endpoints for use in antibiotic clinical trials, and other topics. In addition, according to FDA officials, FDA awarded a contract in fiscal year 2018 to develop animal models for use in preclinical research on infections caused by two types of resistant bacteria: <i>Acinetobacter baumannii</i> and <i>Pseudomonas aeruginosa</i>, and FDA is internally developing animal models for bacteriophage research.</p> <p>FDA hosts workshops related to the development of treatments for antibiotic resistance.</p> <p>According to FDA officials, FDA coordinates regularly with drug regulators in Europe, Canada, and Japan to discuss regulatory science issues about antibiotics that all three agencies face and strive to harmonize clinical trial requirements across jurisdictions where possible.</p>
Centers for Disease Control and Prevention (CDC) and FDA	<p>With input from FDA, CDC manages and operates the Antimicrobial Resistance Isolate Bank, which scientists can use when conducting antibiotic research and development. The bank contains isolates—pure samples of a bacteria—that can be used, for example, to study bacterial mechanisms of resistance or to test a drug's effectiveness. As of January 2018, the isolate bank shipped more than 2,000 isolate panels to researchers, including drug developers, diagnostic test developers, and other scientists. The Walter Reed Army Institute of Research also maintains a collection of antimicrobial resistance isolates collected from military hospitals.</p>
Department of Defense (DOD)	
Defense Threat Reduction Agency	<p>According to DOD officials, the agency has awarded 21 projects to study treatments for antibiotic-resistant infections, totaling approximately \$178 million since 2012. In addition, the agency has funded 12 projects totaling nearly \$50 million for other antibiotic resistance-related matters. Grantees include universities, the U.S. Army Medical Research Institute, and a national laboratory.</p>
U.S. Army Medical Research and Materiel Command ^b	<p>According to DOD officials, the command has funded 50 projects to study treatments for antibiotic-resistant infections since 2012, totaling \$66.2 million. Funded projects study a range of product types, including traditional antibiotics, bacteriophages, peptides, and others. The command also funds 13 projects that study vaccines and other preventive products related to antibiotic-resistant infections.</p>

Appendix III: Additional Examples of Federal Efforts to Support Antibiotic Research and Development

Agency	Efforts
Walter Reed Army Institute of Research	According to DOD officials, the institute supports 16 projects—five intramural and 11 extramural—totaling nearly \$10 million since 2016. All of the projects are studying traditional antibiotic drug candidates, and all but one target gram negative bacteria. Two of the projects are conducted jointly, through an interagency agreement, with NIH institutes. In addition, the institute runs several other internal projects, including one to develop monoclonal antibodies, one to develop animal models to test potential antibiotic treatments, and one to conduct basic research on gram negative bacteria. The institute also conducts a bacteriophage project in partnership with a private company, which, as of January 2019, had completed phase 1 clinical trials.
Defense Advanced Research Projects Agency	Through its Pathogen Predators program, the agency studied living bacteria that prey upon pathogenic gram-negative bacteria. According to DOD officials, the agency awarded a total of \$17.1 million in fiscal years 2014 through 2019 to four grantees.
Navy Medical Research Center	According to DOD officials, Navy researchers are investigating several types of nontraditional products, such as bacteriophages and probiotics, in collaboration with DOD partners, academic researchers, and industry partners. The bacteriophage research, which aims to develop treatments for <i>A. baumannii</i> and <i>Staphylococcus aureus</i> bacterial infections, is conducted jointly with the Walter Reed Army Institute of Research and a private company.
Department of Energy	
National Laboratories	According to Department of Energy officials, scientists conduct intramural research to understand the mechanisms bacteria develop to become resistant to antibiotics and how to overcome those mechanisms. For example, scientists at Lawrence Livermore National Laboratory have studied the mechanism by which microbes make compounds to become resistant to antibiotics and how enzymes in bacteria can be manipulated to allow antibiotics to pass through the bacterial cell wall. Scientists at the Sandia National Laboratory and a university have used computer models to understand how efflux pumps—which can remove antibiotics from the bacterial cell—work, and how to overcome them.

Source: GAO (summary), Departments of Health and Human Services, Defense, and Energy (data). | GAO-20-341

^aRegulatory science is defined by the FDA as the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products. We previously reported that FDA lacked measurable goals to assess its progress in advancing regulatory science and recommended FDA develop and document measurable goals, including targets and time frames, and systematically track funding across its regulatory science priority areas. As of January 2020, FDA has not yet implemented these recommendations. See GAO, *Medical Product Oversight: FDA Needs More Strategic Planning to Guide Its Scientific Initiatives*, [GAO-16-432](#) (Washington, D.C.: May 16, 2016).

^bAccording to DOD officials, The U.S. Army Medical Research and Materiel Command was redesignated as the U.S. Army Medical Research and Development Command in June 2019.

Appendix IV: Additional Information on Federal Efforts to Promote Appropriate Antibiotic Use

This appendix contains more detailed information on federal efforts to promote the appropriate use of antibiotics in health care through antibiotic stewardship programs and activities, organized by agency. These examples do not comprise the full extent of agencies' efforts.

Table 6: Examples of Federal Efforts to Promote the Appropriate Use of Antibiotics

Agency	Efforts
Department of Health and Human Services (HHS)	
Centers for Disease Control and Prevention (CDC)	<p>CDC published a series of guidance documents to promote the appropriate use of antibiotics in health care—called the Core Elements of Antibiotic Stewardship (Core Elements)—from 2014 to 2018.^a CDC tailored the Core Elements to hospitals, nursing homes, outpatient settings, small and critical access hospitals,^b and low- and middle-income countries with limited resources. Common elements in these guidance documents include (1) leadership commitment, (2) implementation of policies and interventions to improve antibiotic use, (3) tracking and reporting antibiotic use, and (4) education to providers on appropriate antibiotic use. While health care facilities and clinicians are not required to implement the Core Elements, experts we interviewed told us these guidance documents provided an important foundation for establishing antibiotic stewardship programs and conducting related activities.</p> <p>Examples of antibiotic stewardship policies and interventions that health care providers can implement, depending on the setting, to support optimal antibiotic prescribing are:</p> <ul style="list-style-type: none"> • writing formal statements in support of improving antibiotic use; • identifying individual leaders to be accountable for antibiotic stewardship activities; • documenting antibiotic dose, duration, and indication in patients' medical records; • developing and implementing facility-specific treatment recommendations, based on national guidelines and local susceptibilities; • requiring prior authorization of certain antibiotics by an expert in antibiotic use, or working with a consultant pharmacist, before therapy is initiated; • using delayed prescribing practices or watchful waiting, when appropriate; • giving antibiotic "time-outs" 48 hours after initial treatment to assess the continuing need and choice of antibiotics after obtaining diagnostic information; • automatically switching from intravenous to oral antibiotic therapy in appropriate situations, which improves patient safety by reducing intravenous access; and • providing prospective audit and feedback, conducted by an expert in antibiotic use.

Appendix IV: Additional Information on Federal Efforts to Promote Appropriate Antibiotic Use

Agency	Efforts
	<p>CDC has expanded its collection of antibiotic use data across health care settings. Since we reported on antibiotic use data gaps in 2011,^c CDC has obtained additional data regarding both inpatient and outpatient settings through its own surveillance systems as well as from other sources. In particular, CDC has focused its efforts to expand antibiotic use data collection from hospitals, where an estimated one in two patients receives an antibiotic for at least 1 day during an average hospital stay. CDC launched its Antimicrobial Use (AU) Option in 2011 as a voluntary, electronic reporting tool added on to the pre-existing National Healthcare Safety Network (NHSN). The AU Option allows the nation's 6,849 hospitals (as of January 1, 2020), including 13 Department of Defense (DOD) hospitals located on military bases outside the United States, that are already reporting to the NHSN to submit their antibiotic use data in a standardized format. CDC then aggregates such data to calculate national benchmarks and allows hospitals to compare their actual ("observed") antibiotic use against those benchmarks ("predicted" use). In addition, CDC has periodically conducted prevalence surveys through its Emerging Infections Program to gather data on health care-associated infections and antibiotic use in about 200 hospitals and 161 nursing homes in 10 states. With regard to outpatient settings, CDC has acquired, through a proprietary source, 8 years of pharmacy data on antibiotic prescriptions since 2011, which the agency is using to better characterize patterns in outpatient prescribing and to develop targeted interventions for high-prescribing areas. Through partnerships with other federal agencies, state and local health departments, and others, CDC has supported these efforts and published several analyses of antibiotic use—including state-level prescribing rates, the conditions for which antibiotics were prescribed, and the appropriateness of their use. For example, CDC has reported on geographic variations in antibiotic prescriptions in outpatient settings, by state, across the United States.</p>
	<p>To gauge progress toward one of the "significant outcomes" included in the <i>National Action Plan for Combating Antibiotic Resistance</i> (National Action Plan)—for all U.S. acute care hospitals to establish antibiotic stewardship programs by 2020—CDC tracks whether such hospitals have implemented antibiotic stewardship programs meeting each of the Core Elements. According to CDC, 85 percent of the nation's acute care hospitals reported having antibiotic stewardship programs in 2018 that met all seven of the Core Elements, compared with 41 percent in 2014.</p>
	<p>In 2018, CDC launched a free, online training course for various types of clinicians—including physicians, dentists, pharmacists, physician assistants, and nurses—to inform them about appropriate antibiotic prescribing, how to overcome barriers, and strategies for communicating with patients. Clinicians can receive credit for partial completion (50 percent or more), or full completion, of this training as improvement activities under the Merit-based Incentive Payment System (MIPS) in 2019. In addition, clinicians who prescribe antibiotics, as well as other types of health care professionals, are eligible to receive up to 8 hours of continuing education credit for completing this training. As of late July 2019, nearly 16,000 individuals had registered for this training, according to CDC officials. Agency officials also told us that CDC has collaborated with medical schools, professional health care organizations, and others to develop and promote antibiotic stewardship training. For example, CDC collaborated with Wake Forest University's School of Medicine and the Association of American Medical Colleges to develop a model curriculum on antibiotic stewardship for medical students.^d</p>
	<p>CDC supports research to identify, develop, and implement practices to stop the spread of resistance and to promote appropriate use of antibiotics in health care. CDC also supports research to fill gaps in knowledge related to aspects of antibiotic use and resistance that have public health impact. According to agency officials, CDC has provided approximately \$110 million since 2016 to support this research through cooperative agreements and contracts.</p>

Appendix IV: Additional Information on Federal Efforts to Promote Appropriate Antibiotic Use

Agency	Efforts
	<p>In 2017, CDC revised a national campaign to promote public awareness about appropriate antibiotic use. The campaign, called “Be Antibiotics Aware: Smart Use, Best Care,” is aimed at both health care providers and the general public. This campaign refines the message from CDC’s earlier campaign (“Get Smart: Know When Antibiotics Work”) and has expanded to new target audiences, such as adult patients, physicians who work in hospitals, nurse practitioners, and physician assistants. To support the campaign, CDC has produced a number of materials and resources, including posters, brochures, and fact sheets for use and display in physicians’ offices, pharmacies, and other health care and public settings. In addition, CDC has embedded stewardship messaging into other activities, including its “Get Ahead of Sepsis” campaign, which emphasizes the importance of early recognition and timely treatment of sepsis, reassessment of antibiotic therapy, and preventing infections that can lead to sepsis. CDC views these two campaigns as promoting the integration of antibiotic stewardship into sepsis management.</p> <p>CDC works with countries around the world to combat antibiotic resistance. For example, in conjunction with HHS’s Office of Global Affairs, CDC launched the Antimicrobial Resistance Challenge at the United Nations General Assembly in September 2018 to catalyze global action against antibiotic resistance. A year later, CDC announced this challenge had resulted in nearly 350 commitments from government health officials, pharmaceutical and health insurance companies, and others from 33 countries to make formal commitments that further the progress against antimicrobial resistance, such as by improving appropriate antibiotic use.</p>
Centers for Medicare & Medicaid Services (CMS)	<p>In September 2019, CMS finalized new health and safety requirements for the nation’s hospitals and critical access hospitals to implement antibiotic stewardship programs, as a condition of their participation in the Medicare and Medicaid programs, by March 30, 2020.^e Under these requirements, hospitals and critical access hospitals are required, among other things, to implement these programs facility-wide (which includes emergency departments) and to adhere to nationally recognized guidelines for prescribing antibiotics. These requirements also apply to inpatient rehabilitation facilities (which are considered post-acute care facilities) and long-term acute care hospitals.</p> <p>In October 2016, CMS published a rule that established similar requirements for nursing homes as well as skilled nursing facilities—collectively known as long-term care facilities—to implement antibiotic stewardship programs.^f Under this rule, long-term care facilities were required, in part, to have an antibiotic stewardship program in place by December 4, 2017.</p> <p>To complement the new requirements, CMS published new interpretive guidance on how to implement and survey for antibiotic stewardship in long-term care facilities, citing CDC’s Core Elements.^g CMS also updated its training webinars for surveyors—who monitor compliance with CMS’s health and safety standards using on-site surveys—to include information on antibiotic use in nursing homes.</p> <p>CMS has developed incentives for eligible clinicians in any type of health care facility to improve antibiotic use and stewardship, as part of the agency’s broader efforts to improve care for Medicare patients.^h Through MIPS, launched in 2017, CMS offers hundreds of quality measures and nearly 100 “improvement activities” on a wide range of topics, including the appropriate use of antibiotics, that eligible clinicians can choose from and report their performance on to the agency. CMS then adjusts payments higher for clinicians who report data and achieve a performance-based, final score above a certain threshold—and penalizes clinicians who do not achieve that threshold with lower payments.</p> <p>In 2014, CMS added antibiotic stewardship to its efforts to provide better care at lower cost for Medicare beneficiaries in outpatient settings. Specifically, CMS tasked its networks of health quality experts, clinicians, and others (called Quality Improvement Networks) with helping 7,629 outpatient facilities—including physician practices, emergency departments, and urgent care centers—implement CDC’s Core Elements. Under this 5-year project, CMS is providing outreach, training, and technical assistance to providers and patients to encourage the expansion of antibiotic stewardship.</p> <p>CMS has provided training, technical assistance, and other learning opportunities to more than 4,000 hospitals, 2,400 nursing homes, and 7,600 outpatient settings on best practices for antibiotic stewardship and guidance on <i>C. difficile</i> prevention. In addition, CMS and CDC have developed and launched free, online training to help nursing homes implement antibiotic stewardship and prevent and manage <i>C. difficile</i> infections.</p>

Appendix IV: Additional Information on Federal Efforts to Promote Appropriate Antibiotic Use

Agency	Efforts
Agency for Healthcare Research and Quality (AHRQ)	<p>AHRQ has increased its support since 2015 for research to develop improved methods to combat antibiotic resistance and promote antibiotic stewardship, including through grants for research that will total more than \$57 million, according to AHRQ officials. This research includes studies on the role of diagnostic tools, such as blood cultures, in improving antibiotic use and reducing antibiotic resistance. AHRQ has also published numerous research studies on antibiotic or antimicrobial stewardship that the agency funded or authored.</p>
	<p>Through a 5-year nationwide project, the AHRQ Safety Program for Improving Antibiotic Use has provided technical assistance and CDC’s guidance to hospitals, long-term care facilities, and physicians’ offices to promote implementation of antibiotic stewardship activities and to help clinicians select optimal antibiotic treatment regimens. In December 2018, AHRQ completed implementation of this guidance in more than 400 hospitals, which included six DOD facilities and 79 critical access hospitals, according to AHRQ officials. AHRQ officials also told us that preliminary data suggest that antibiotic use was reduced in this cohort, and an educational toolkit based on this cohort’s activities will be released in fiscal year 2020. The project has also recruited more than 450 nursing homes for a 1-year cohort planned to be completed in November 2019, and AHRQ planned to expand to an additional 250 to 500 ambulatory care settings in December 2019. AHRQ also plans to compile tools, resources, and lessons learned to promote implementation of antibiotic stewardship in these health care settings.</p>
	<p>AHRQ has increased dissemination of its <i>Nursing Home Antimicrobial Stewardship Guide</i>, which provides toolkits to help nursing home staff create an antibiotic stewardship program, determine whether to treat with antibiotics, choose the right antibiotic, and engage residents and families.¹</p>
Health Resources and Service Administration (HRSA)	<p>In November 2017, HRSA’s Federal Office of Rural Health Policy added a requirement for critical access hospitals participating in the Medicare Beneficiary Quality Improvement Project to implement antibiotic stewardship programs by the end of fiscal year 2021 in order to be eligible for the Medicare Rural Hospital Flexibility grant program.¹ According to HRSA officials, this requirement will apply to 99 percent of the nation’s more than 1,300 critical access hospitals.</p>
Office of Global Affairs	<p>To promote the appropriate use of antibiotics internationally, the Office of Global Affairs has collaborated with other countries and co-chairs the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) program. With respect to antibiotic stewardship, TATFAR working groups have (1) developed a common structure and indicators for antibiotic stewardship programs; (2) reviewed antibiotic use reduction goals; (3) published a resource for other countries seeking to improve their antibiotic use; (4) aligned campaigns promoting appropriate antibiotic use by collaborating with partners such as the World Health Organization in supporting World Antibiotic Awareness Week; (5) compiled resources for how to assess appropriate outpatient use in TATFAR countries; and (6) published studies on health care-associated infections and antibiotic use across health care facilities.</p>
Department of Defense (DOD)	
Defense Health Agency	<p>DOD published a policy, effective October 2017, requiring the establishment of antibiotic stewardship programs within its military medical treatment facilities and issued guidance for implementation in October 2018. These facilities include hospitals located at military installations across the United States and abroad, plus ambulatory care clinics and dental clinics, and provide health care for active-duty service members, their dependents, and other eligible beneficiaries. The policy calls for these facilities to establish antibiotic stewardship programs including the following components, at a minimum: (1) leadership commitment by each facility; (2) accountability; (3) pharmacy expertise, including antibiotic prescribing and use evaluation; (4) the creation of antibiograms—an aggregate profile of antibiotic susceptibility for a given facility, locality, region, or nation; (5) the identification and implementation of at least one action for change that would demonstrate commitment to the program; (6) training for clinicians regarding antibiotic resistance and prescribing practices; and (7) facility-specific treatment recommendations in accordance with local antibiograms. DOD officials told us that all of these facilities (both inpatient and outpatient) were in different stages of implementing the antibiotic stewardship policy, as of August 2019. In addition, as part of these requirements, DOD hospitals are to report their antibiotic use data to CDC through the NHSN AU Option. DOD officials told us that 44 of DOD’s 48 hospitals have reported their antibiotic use data to CDC, as of September 30, 2019.</p>

Appendix IV: Additional Information on Federal Efforts to Promote Appropriate Antibiotic Use

Agency	Efforts
Department of Veterans Affairs (VA)	According to department officials, DOD offers antibiotic stewardship training to its health care facilities through webinars, workshops, and briefings.
Veterans Health Administration	VA's efforts to implement antibiotic stewardship programs in its health care facilities, which provide both inpatient and outpatient services to veterans, pre-date the National Action Plan and CDC's Core Elements. In January 2019, VA updated its 2014 policy directive for the implementation and maintenance of antibiotic stewardship programs that, in part, requires each of its health care facilities to (1) develop a written policy, (2) perform an annual evaluation of stewardship activities, (3) ensure that adequate staff and resources are in place, and (4) identify medical and pharmacy personnel as stewardship "champions." The updated policy directive also requires all VA facilities with 30 or more acute care beds to report their antibiotic use data to CDC's NHSN AU Option by January 30, 2020. According to department officials, VA has successfully implemented antibiotic stewardship programs in all of its health care facilities, and 113, or more than 97 percent of, 116 eligible VA hospitals with 30 or more acute care beds were reporting their antibiotic use data to CDC, as of January 1, 2020.
	VA offers antibiotic stewardship training to its health care facilities through webinars on an ongoing basis.

Source: GAO analysis of information from HHS, DOD, and VA. | GAO-20-341

^aDepartment of Health and Human Services, Centers for Disease Control and Prevention, *The Core Elements of Hospital Antibiotic Stewardship Programs* (Atlanta, Ga.: 2014) and *The Core Elements of Hospital Antibiotic Stewardship Programs: 2019* (Atlanta, Ga.: 2019), *The Core Elements of Antibiotic Stewardship for Nursing Homes* (Atlanta, Ga.: 2015), *The Core Elements of Outpatient Antibiotic Stewardship* (Atlanta, Ga.: 2016), *Implementation of Antibiotic Stewardship Core Elements at Small and Critical Access Hospitals* (Atlanta, Ga.: 2017), and *The Core Elements of Human Antibiotic Stewardship Programs in Resource-Limited Settings: National and Hospital Levels* (Atlanta, Ga.: 2018).

The Joint Commission—a nonprofit organization that accredits and certifies more than 22,000 health care organizations and programs in the United States—added new accreditation requirements, effective in 2017, for hospitals and nursing homes to implement antibiotic stewardship programs consistent with CDC's Core Elements. On the outpatient side, The Joint Commission finalized new requirements in June 2019 for ambulatory health care organizations that it accredits to implement antimicrobial stewardship activities; these requirements go into effect in 2020. Another organization, DNV GL Healthcare USA, Inc., also issued an antibiotic stewardship standard in 2018, based on CDC's Core Elements, for the hospitals it accredits and certifies.

^b"Critical access hospital" is a designation given to eligible rural hospitals by states and certified by CMS. 42 U.S.C. § 1395i-4(c)(2)(B), 42 C.F.R. § 485.606(b). Congress created the critical access hospital designation through the Balanced Budget Act of 1997 in response to a string of rural hospital closures in the 1980s and early 1990s. Among other criteria, eligible hospitals must have 25 or fewer acute-care inpatient beds and be located more than 35 miles from another hospital, although exceptions may apply. See Balanced Budget Act of 1997, Pub. L. No. 105-33, § 4201, 111 Stat. 251, 369-71 (codified in pertinent part at 42 U.S.C. §§ 1395f(l), 1395i-4, 1395m(g), (l)(8)). As of October 2019, there were 1,349 critical access hospitals in the United States.

^cGAO, *Antibiotic Resistance: Data Gaps Will Remain Despite HHS Taking Steps to Improve Monitoring*, GAO-11-406 (Washington, D.C.: June 1, 2011).

^dWake Forest School of Medicine, "Antimicrobial Stewardship Curriculum," accessed December 18, 2019, <https://school.wakehealth.edu/Departments/Internal-Medicine/Infectious-Diseases/CAUSE/Antimicrobial-Stewardship-Curriculum>.

^eDepartment of Health and Human Services, Centers for Medicare & Medicaid Services, *Medicare and Medicaid Programs; Regulatory Provisions to Promote Program Efficiency, Transparency, and Burden Reduction; Fire Safety Requirements for Certain Dialysis Facilities; Hospital and Critical Access Hospital (CAH) Changes to Promote Innovation, Flexibility, and Improvement in Patient Care*, 84 Fed. Reg. 51732 (Sept. 30, 2019) (pertinent provisions to be codified at 42 C.F.R. §§ 482.42 (d), 485.640).

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^fDepartment of Health and Human Services, Centers for Medicare & Medicaid Services, *Medicare and Medicaid Programs; Reform of Requirements for Long-Term Care Facilities*, 81 Fed. Reg. 68688 (Oct. 4, 2016) (pertinent provision codified at 42 C.F.R. § 483.80(a)(3) (2018)).

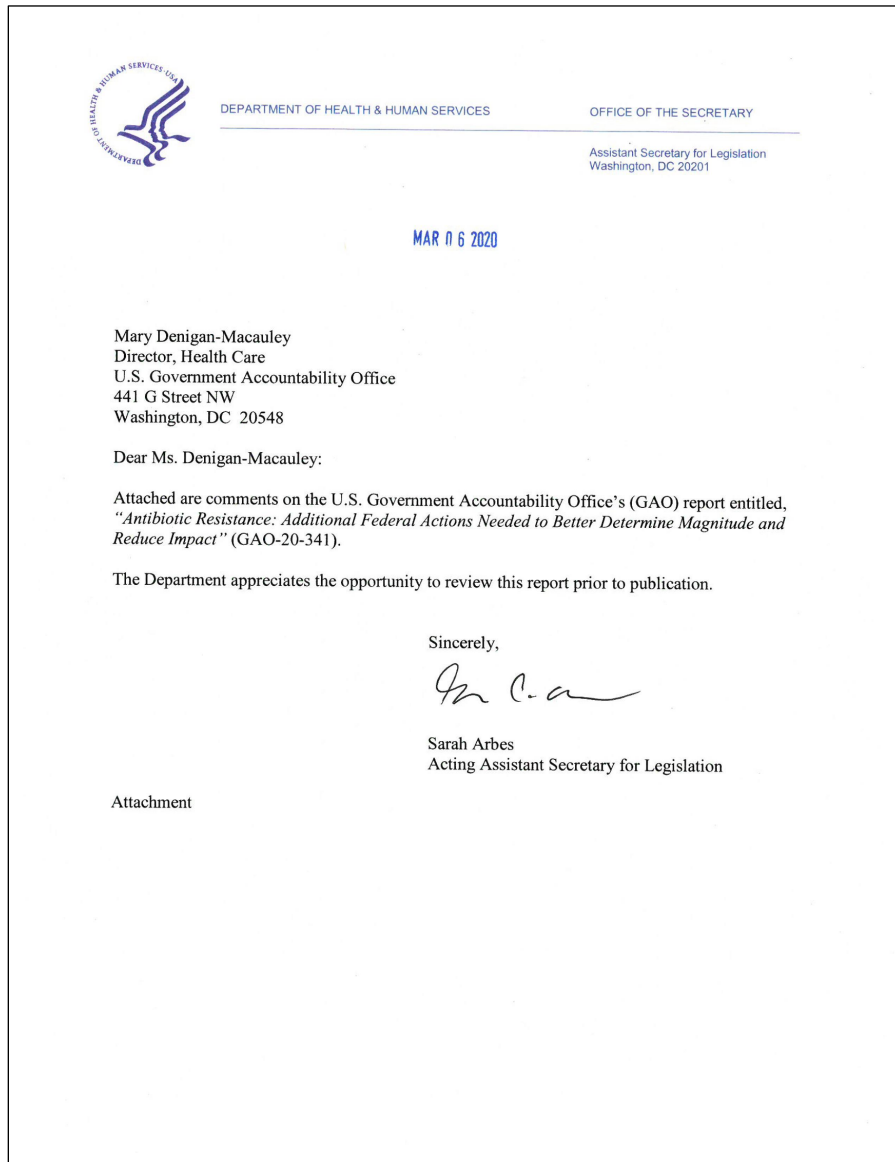
^gCenters for Medicare & Medicaid Services, *State Operations Manual Appendix PP – Guidance to Surveyors for Long-Term Care Facilities* (Nov. 22, 2017).

^hThe Medicare Access and CHIP Reauthorization Act of 2015 required CMS to implement an incentive program for clinicians participating in Medicare to receive higher payments based on their performance. Medicare Access and CHIP Reauthorization Act of 2015, Pub. L. No. 114-10, 129 Stat. 87, 92 (Apr. 16, 2015), codified at 42 U.S.C. § 1395w-4. In 2019, MIPS-eligible clinician types include physicians (doctors of medicine, which includes many specialties; doctors of dental surgery or dental medicine; and doctors of osteopathy), physician assistants, nurse practitioners, and others. In addition, to be eligible for MIPS in 2019, the clinician must (1) bill more than \$90,000 in allowed charges for professional services covered under the Medicare Physician Fee Schedule; (2) provide more than 200 covered professional services; and (3) furnish covered professional services to more than 200 Medicare beneficiaries. Eligible clinicians may participate in MIPS as individuals or as part of a group that includes one or more of the eligible clinician types.

ⁱAgency for Healthcare Research and Quality, “Nursing Home Antimicrobial Stewardship Guide,” accessed December 17, 2019, <https://www.ahrq.gov/nhguide/index.html>.

^jHRSA is the primary federal agency for improving health care to people who are geographically isolated or economically or medically vulnerable, according to the agency’s website; tens of millions of Americans receive quality, affordable health care and other services through its 90-plus programs and more than 3,000 grantees.

Appendix V: Comments from the Department of Health and Human Services



GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED — ANTIBIOTIC RESISTANCE: ADDITIONAL FEDERAL ACTIONS NEEDED TO BETTER DETERMINE MAGNITUDE AND REDUCE IMPACT (GAO-20-341)

The U.S. Department of Health & Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

National Action Plan for Combating Antibiotic Resistant Bacteria (CARB) (NAP) Not Fully Addressed

Antibiotic resistance is a large scale and complex topic for which the United States Government has developed the National Action Plan for Combating Antibiotic Resistant Bacteria (CARB)(NAP) to address. HHS notes that the depth and breadth of current activities of agencies and departments under this comprehensive national plan are not fully reflected in this report, and actions to address these recommendations and other priorities would be necessary to fully achieve CARB goals.

There are two fundamental and important topics included in the USG CARB NAP that are not included in the GAO report that HHS finds important to highlight. Infection prevention and control is one of the foundational activities described under Goal 1 of the CARB NAP, and it is fundamentally needed to address the emergence of the spread of resistant pathogens in healthcare, food and the community. GAO's report provides limited information to highlight the importance of this topic, and HHS notes the importance of including the need for proper infection prevention and control in addressing the spread of antibiotic resistant infections. As highlighted in CDC's recent 2019 Antibiotic Resistance Threats Report, prevention efforts such as these have reduced deaths from antibiotic-resistant infections by 18 percent overall and by nearly 30 percent in hospitals since 2012. HHS views the discussion of infection prevention and control as on par with the other elements mentioned in the report (such as surveillance, stewardship, diagnostics, and drug development), and as essential to give a complete picture of the challenges, needs, and progress to date in this critically important area.

In addition, while HHS understands that the GAO's scope for this report was limited to antibacterial resistance, we note that the report excludes resistant fungal infections from its discussion and analysis. The pathogens covered under the US CARB National Action Plan are those identified by CDC as threats in its AR Threats Report. This includes bacterial and fungal pathogens, and importantly CDC's most recent Threats Report identified *Candida auris* as an urgent threat – the highest threat category – in the United States. The needs and actions to be taken to address fungal resistance are largely the same as those needed to address bacterial resistance and acknowledging the threat of fungal resistance is vital to fully reflecting the scope of the public health challenges that we face domestically and globally. . . When individuals become sick with bacterial or fungal infections, they want to be confident that an effective treatment exists or better yet to have effective prevention measures that ensure they do not get an infection in the first place.

The development of the CARB National Strategy and the CARB NAP brought together departments and agencies spanning the U.S. government to comprehensively articulate national goals, activities, and milestones and report on their progress regularly and transparently. This collaboration has built and continues to build programs and national infrastructure that now lead

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the world on many fronts and has transformed how the country responds to the threats of antibiotic resistance in every key area. While these activities are far from complete and in fact many efforts need to be scaled up considerably, CARB work has placed the U.S. government in a position where we have the potential -- through ongoing activities and resources -- to get ahead of one of the world's most challenging public health threats. The forthcoming update to the CARB NAP will build on the success of the first Action Plan and push the U.S. to make further progress domestically and globally.

Antimicrobial Susceptibility Test Devices

HHS recognizes that this report accurately discusses many of the historical challenges associated with updating antimicrobial susceptibility testing (AST) devices to reflect the most current susceptibility test interpretive criteria (STIC), also known as "breakpoints," for systemic antibacterial or antifungal drugs.

HHS commends the efforts of Congress to address these challenges through Section 511A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360a-2), as added by section 3044 of the 21st Century Cures Act (Cures Act) (Pub. L. 114-255), signed into law on December 13, 2016. This provision clarifies FDA's authority to identify and efficiently update susceptibility test interpretive criteria, including through the recognition by FDA of standards established by standard development organizations (SDOs). It also clarifies that manufacturers of AST devices may rely upon FDA-recognized breakpoints to support premarket authorization of their devices, provided they meet certain conditions, which provides for a more streamlined process for incorporating up-to-date information into such devices.

Since passage of the Cures Act, FDA has worked to implement section 511A of FD&C Act, and engaged in other efforts to promote the availability and updating of AST devices. In accordance with section 511A, FDA established in December 2017, within 1 year of enactment of the Cures Act, an Interpretative Criteria Website¹ (STIC website) that contains a list of FDA-recognized susceptibility test interpretive criteria standards (also referred to as breakpoints or STIC), as well as other susceptibility test interpretive criteria identified by FDA. This website identifies when FDA does or does not recognize breakpoints established by an SDO and lists breakpoints identified by FDA outside the SDO process. To ensure that the most up-to-date STIC information is available, holders of approved drug applications were required to remove STIC and related information from the labeling of approved systemic antibacterial and antifungal drugs and replace it with a reference to the STIC website.² AST device developers may rely upon the breakpoints listed on the FDA STIC website to support premarket submission of their devices. Further, in accordance with section 511A(c)(1) of the FD&C Act, at least every 6 months, FDA publishes on the website a notice recognizing new or updated susceptibility test interpretive criteria standards, or parts of standards; withdrawing recognition of susceptibility test interpretive criteria standards, or parts of standards; and making any other necessary updates to the lists published on the website. This makes up-to-date information about antimicrobial

¹ See <https://www.fda.gov/STIC>.

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**Appendix V: Comments from the Department
of Health and Human Services**

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susceptibility easily accessible by device manufacturers that are considering any changes to their devices and labeling.

In further efforts to promote the availability of up-to-date AST devices, FDA published draft guidance in early 2016 and, ultimately, finalized that guidance in February 2019, on use of a coordinated development process for new antimicrobial drugs and new or existing AST devices. Implementation of the final guidance, *Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices*,³ has drastically improved the time for AST device availability following new drug approval, with devices becoming available within weeks of drug approval in most cases.

Additionally, FDA has worked closely with AST device manufacturers and other stakeholders to understand the challenges associated with incorporating breakpoint updates applicable to their devices in a timely fashion. Through these discussions, FDA identified the opportunity to encourage the development of breakpoint change protocols for new and existing AST devices. AST device manufacturers can submit a breakpoint change protocol in their premarket submissions, outlining how they will validate breakpoint updates incorporated into their device when such updates are recognized by FDA and posted to the STIC website. Following change protocol submission and concurrence by FDA, AST device manufacturers may implement breakpoint changes to their devices and labeling to reflect the most current information without the need for a 510(k) submission, if certain conditions are met. This may be done when the inclusion and performance criteria outlined in the breakpoint change protocol are confirmed by the manufacturer. FDA reviewed and concurred with the first breakpoint change protocol in 2018, and FDA has continued to encourage manufacturers to use this approach. FDA expects that this approach will expedite updating of devices and assist in monitoring the status of these devices following FDA recognition of new or updated breakpoints.

Further, FDA intends to continue regular engagement with AST device manufacturers and related stakeholders to continue to improve these processes. While stakeholders can sign up for email updates when the STIC website is updated, FDA also intends to individually reach out to AST device manufacturers when breakpoint updates are made that could potentially affect their cleared devices. FDA hopes this additional outreach and coordination will lead to more rapid updates of AST devices.

While there is still much to be done, HHS is proud of how far we have come as a country and continues to look forward to how we can further address the ongoing threats of antibiotic resistance.

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Recommendation 1

The Director of CDC should take steps to determine participation rates and distribution needed in the AR Option of the National Healthcare Safety Network for conducting regional and national assessments of antibiotic resistance of public health importance.

HHS Response

HHS concurs with GAO's recommendation.

CDC recognizes the concerns of GAO and the Joint Public Health Informatics Task Force regarding the breadth of data currently available in the National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) Module's AR Option. NHSN's AUR module helps healthcare facilities to track antimicrobial resistance patterns for more than 20 different organisms. As there is currently no national requirement for facilities to report in the AR option, CDC is actively working with public health partners, including other federal agencies, health departments, health information technology vendors, and healthcare systems to promote the voluntary use of the AR option.

While NHSN has experienced vast expansion over time, appropriated resources have stayed largely stable with only modest increases. Since its creation in 2005, NHSN has grown from 300 hospitals reporting to more than 22,000 in 2020, an increase of approximately 7,300 percent. Over this same time, appropriated resources for NHSN have only increased by 40 percent.

CDC also provides technical support to states that may be considering a state or local mandate to require AR/ AU reporting. To date, two states have implemented a local mandate that requires AR/AU reporting, and one state is considering implementation of a mandate.

With the current level of reporting, CDC is developing pilot programs to assess AR option data and other data sources for determining the landscape for regional and national extended-spectrum beta-lactamases (ESBLs). The goal of this analysis will be to improve our understanding of community transmission and amplification in healthcare settings in order to have greater impact on preventing ESBLs. This work is still in the early development phase; however, CDC believes it will be a valuable initial analysis of the use of AR option data beyond the hospital facility-level.

Recommendation 2

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HHS Response

HHS concurs with this recommendation.

CDC concurs with the recommendation to assess the representativeness of GISP. It should be noted, however, that GISP, as a sentinel surveillance system, was not designed to be representative of the U.S. population with gonorrhea (GC) but, rather to identify new trends in resistance before they become generalized across the entire population with GC. Historically, CDC has successfully used this approach to anticipate emerging trends and inform changes in the CDC's STD Treatment Guidelines to ensure patients are treated with the most effective antibiotic available.

Through eGISP and SURRG, CDC has taken steps to examine the representativeness of GISP as mentioned in the report. By testing women with gonorrhea, extragenital sites of men with gonorrhea, and men and women from non-sexually transmitted disease clinic sites, results can be compared with those from GISP. It is currently necessary to obtain cultured isolates for these laboratory analyses. This is more difficult in women, and from extra-genital sites in men in whom infections are usually asymptomatic, than it is in symptomatic men included in GISP. To overcome this, CDC is currently working to develop laboratory methods to examine genetic markers for GC resistance in swab specimens and urine without the need for cultured isolates. Although this would not replace culture-based surveillance, this would allow CDC to obtain a larger number of samples from non-GISP populations and to compare the genetic markers in those populations with ones from GISP patients. Since culture is now rarely used outside of CDC sponsored projects, this approach could provide samples that are more representative of the overall U.S. population infected with GC. However, additional resources are needed for developing and validating these methods and applying them to different populations.

In FY 2016, CDC requested \$264 million annually to support full implementation of all of its activities under the CARB Action Plan including the expansion of GC testing nationwide. Ultimately, Congress supported funding for the overall CARB budget initiative of \$160 million in FY 16 and has provided small increases since then. With available resources, CDC has supported an expansion of GC testing under the ARLN compared to pre-CARB levels, however, additional work to further refine and improve on the collection of AR data for GC cannot be completed with existing resources.

Recommendation 3

The Director of CDC should provide information on uncertainties for antibiotic resistance estimates in its consolidated Threats Reports, including standard errors or confidence intervals, as appropriate.

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HHS Response

HHS generally concurs with GAO's recommendation. CDC believes that information on uncertainties including standard errors or confidence intervals should be accessible within the public domain and is committed to doing so. Given that many of the new estimates provided in the 2019 AR Threats Report were based on new methodologies that aggregated data across three electronic health databases, CDC felt that it was critical to have the analysis peer reviewed by external experts and published in the scientific literature for wider reference and dissemination. CDC feels that publishing these data in a way that it is most helpful for the scientific community is critical, and multiple publications are pending. Once published in the scientific literature, CDC will link these publications back to online resources of the 2019 AR Threats Report for awareness and understanding of the connection between the report and the contributing peer reviewed material.

Recommendation 4

The Director of CDC should develop a plan for timely, consolidated reports of antibiotic resistance in priority pathogens at regular intervals.

HHS Response

HHS concurs with GAO's recommendation. The GAO report appears to imply that the AR Threats Report is the only report released by the agency that provides information on priority pathogens at regular intervals. To clarify, CDC already provides timely, consolidated updates of antibiotic resistance in priority pathogens at regular intervals through the following:

- NARMS Now (Updated Daily): CDC updates the latest approved resistance data for enteric pathogens nightly.
- AR & Patient Safety Portal (Updated Bi-annually): CDC updates resistance data for healthcare infections twice annually in the spring and fall.
- Active Bacterial Core surveillance (ABC) Bact Facts interactive (Updated annually): CDC includes resistance data for Streptococcus in annual updates.
- STD Surveillance Report & GISP (Updated Annually): Antibiotic resistant data for gonorrhea is released annually in the STD Surveillance Report and GISP Profiles with site-specific data.
- Reported Tuberculosis in the United States (annual surveillance report): Includes data on drug-resistant TB.

For all of these pathogens, other publications highlighting antibiotic resistance (MMWR, peer review publications) are issued ad hoc depending on new findings. Finally, CDC has plans to update its enterprise-wide AR Threats Report every three years.

Recommendation 5

The Secretary of HHS should identify leadership and clarify roles and responsibilities among HHS agencies to assess the clinical outcomes of diagnostic testing for identifying antibiotic-resistant bacteria.

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HHS Response

HHS concurs with GAO's recommendation.

As part of the development of the next National Action Plan for CARB (2020-2025), CARB Task Force leadership will work with relevant HHS agencies to clarify roles and responsibilities for supporting research on clinical outcomes related to diagnostic tests. These discussions will include identifying leadership for this work, if such a strategy would be appropriate. The next Plan will maintain the goal of advancing the development and use of diagnostic tests (Goal 3).

Recommendation 6

The Commissioner of FDA should direct the Center for Devices and Radiological Health to conduct additional monitoring and evaluation of the status of commercial tests that rely on breakpoints, on a regular basis, to determine whether test manufacturers are updating breakpoints, seeking additional resources as needed.

HHS Response

HHS concurs with GAO's recommendation.

FDA concurs with GAO's recommendation to conduct additional monitoring and evaluation of AST devices to determine whether device manufacturers are making updates, where appropriate, when FDA identifies or recognizes new breakpoints.

FDA agrees with GAO that it is important that AST devices reflect the most current information as one aspect in improving patient care and antimicrobial stewardship, and combating antimicrobial resistance. Although FDA agrees that in the past there have been significant challenges associated with updating AST devices to reflect the most current breakpoints, FDA believes it is important to understand that many of the concerns raised in the report have been resolved by recent FDA actions and the passage and implementation of section 511A of the FD&C Act. As described above, FDA has taken major steps in the implementation of the new statutory provision, and has engaged in other activities to promote the availability and updating of AST devices.

Recommendation 7

The Secretary of HHS should develop a strategic framework to further incentivize the development of new treatments for antibiotic-resistant infections, including through the use of postmark financial incentives, and, if appropriate, make recommendations to Congress for necessary authority.

HHS Response

HHS non-concurs with GAO's recommendation because it is still unclear whether post-market financial incentives should necessarily be part of HHS's forthcoming strategic framework to further incentivize the development of new treatments to combat antibiotic resistance.

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED – ANTIBIOTIC RESISTANCE: ADDITIONAL FEDERAL ACTIONS NEEDED TO BETTER DETERMINE MAGNITUDE AND REDUCE IMPACT (GAO-20-341)

HHS agrees with GAO that additional incentives are needed to address the limited pipeline for novel and innovative treatments to combat antibiotic resistance. As noted by GAO, HHS convened a workgroup in March 2019 to analyze existing incentives, proposals for new incentives as raised by non-governmental, industry, and international groups, and other options to address this need. This analysis has included consideration of the current and future burden of AMR on both public health and the economy, the dynamics of drug development that specifically impact relevant antibacterial and related products, and the statutory, regulatory, and budgetary feasibility of any incentive strategy. Based on this work, the group is developing a strategic framework that includes specific proposals to address a variety of scientific and market challenges facing antibiotic product developers. ASPE and HHS are still conducting analyses to understand whether post-market financial incentives should be included in this framework as a solution among a range of potential solutions.

Recommendation 8

The Secretary of HHS should direct the CARB Task Force to include in its annual updates to the President plans for addressing any barriers preventing full implementation of the National Action Plan and, as appropriate, make recommendations for new or modified actions. Specifically, the CARB Task Force should identify plans to address barriers, such as those related to expanding (1) a CDC program designed to strengthen the U.S. response to resistant gonorrhea, (2) antibiotic stewardship programs across health care settings, and (3) antibiotic use data collection across health care settings, to the extent feasible

HHS Response

HHS concurs with GAO's recommendation.

Beginning in 2020 with the Annual Report for Year 5 of the first CARB National Action Plan, and continuing thereafter in the annual reports for the next iteration of the plan, HHS will include discussion of any barriers preventing full implementation of these activities, including any barriers that GAO has included in the recommendation where appropriate.

Beginning in 2020 with the Annual Report for Year 5 of the first CARB National Action Plan, and continuing thereafter in the annual reports for the next iteration of the plan, the CARB Task Force will include discussion of any barriers preventing full implementation of these activities, including the barriers that GAO has included in this recommendation where appropriate

Text of Appendix V: Comments from the Department of Health and
Human Services

Page 1

Mary Denigan-Macauley Director, Health Care

U.S. Government Accountability Office

441 G Street NW

Washington, DC 20548

Dear Ms. Denigan-Macauley:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "Antibiotic Resistance: Additional Federal Actions Needed to Better Determine Magnitude and Reduce Impact" (GAO-20-341).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Sarah Arbes

Acting Assistant Secretary for Legislation

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GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED — ANTIBIOTIC RESISTANCE: ADDITIONAL FEDERAL ACTIONS NEEDED TO BETTER DETERMINE MAGNITUDE AND REDUCE IMPACT (GAO-20-341)

The U.S. Department of Health & Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

National Action Plan for Combating Antibiotic Resistant Bacteria (CARB) (NAP) Not Fully Addressed

Antibiotic resistance is a large scale and complex topic for which the United States Government has developed the National Action Plan for Combating Antibiotic Resistant Bacteria (CARB)(NAP) to address. HHS notes that the depth and breadth of current activities of agencies and departments under this comprehensive national plan are not fully reflected in this report, and actions to address these recommendations and other priorities would be necessary to fully achieve CARB goals.

There are two fundamental and important topics included in the USG CARB NAP that are not included in the GAO report that HHS finds important to highlight. Infection prevention and control is one of the foundational activities described under Goal 1 of the CARB NAP, and it is fundamentally needed to address the emergence of the spread of resistant pathogens in healthcare, food and the community. GAO's report provides limited information to highlight the importance of this topic, and HHS notes the importance of including the need for proper infection prevention and control in addressing the spread of antibiotic resistant infections. As highlighted in CDC's recent 2019 Antibiotic Resistance Threats Report, prevention efforts such as these have reduced deaths from antibiotic-resistant infections by 18 percent overall and by nearly 30 percent in hospitals since 2012. HHS views the discussion of infection prevention and control as on par with the other elements mentioned in the report (such as surveillance, stewardship, diagnostics, and drug development), and as essential to give a complete picture of the challenges, needs, and progress to date in this critically important area.

In addition, while HHS understands that the GAO's scope for this report was limited to antibacterial resistance, we note that the report excludes resistant fungal infections from its discussion and analysis. The pathogens covered under the US CARB National Action Plan are those identified by CDC as threats in its AR Threats Report. This includes bacterial and fungal pathogens, and importantly CDC's most recent Threats Report identified *Candida auris* as an urgent threat – the highest threat category – in the United States. The needs and actions to be taken to address fungal resistance are largely the same as those needed to address bacterial resistance and acknowledging the threat of fungal resistance is vital to fully reflecting the scope of the public health challenges that we face domestically and globally. . When individuals become sick with bacterial or fungal infections, they want to be confident that an effective treatment exists or better yet to have effective prevention measures that ensure they do not get an infection in the first place.

The development of the CARB National Strategy and the CARB NAP brought together departments and agencies spanning the U.S. government to comprehensively articulate national goals, activities, and milestones and report on their progress regularly and transparently. This collaboration has built and continues to build programs and national infrastructure that now lead

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susceptibility easily accessible by device manufacturers that are considering any changes to their devices and labeling.

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Report were based on new methodologies that aggregated data across three electronic health databases, CDC felt that it was critical to have the analysis peer reviewed by external experts and published in the scientific literature for wider reference and dissemination. CDC feels that publishing these data in a way that it is most helpful for the scientific community is critical, and multiple publications are pending. Once published in the scientific literature, CDC will link these publications back to online resources of the 2019 AR Threats Report for awareness and understanding of the connection between the report and the contributing peer reviewed material.

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- AR & Patient Safety Portal (Updated Bi-annually): CDC updates resistance data for healthcare infections twice annually in the spring and fall.
- Active Bacterial Core surveillance (ABC) Bact Facts interactive (Updated annually): CDC includes resistance data for Streptococcus in annual updates.
- STD Surveillance Report & GISP (Updated Annually): Antibiotic resistant data for gonorrhea is released annually in the STD Surveillance Report and GISP Profiles with site- specific data.
- Reported Tuberculosis in the United States (annual surveillance report): Includes data on drug-resistant TB.

For all of these pathogens, other publications highlighting antibiotic resistance (MMWR, peer review publications) are issued ad hoc depending on new findings. Finally, CDC has plans to update its enterprise-wide AR Threats Report every three years.

Recommendation 5

The Secretary of HHS should identify leadership and clarify roles and responsibilities among HHS agencies to assess the clinical outcomes of diagnostic testing for identifying antibiotic-resistant bacteria.

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HHS Response

HHS concurs with GAO's recommendation.

As part of the development of the next National Action Plan for CARB (2020-2025), CARB Task Force leadership will work with relevant HHS agencies to clarify roles and responsibilities for supporting research on clinical outcomes related to diagnostic tests. These discussions will include identifying leadership for this work, if such a strategy would be appropriate. The next Plan will maintain the goal of advancing the development and use of diagnostic tests (Goal 3).

Recommendation 6

The Commissioner of FDA should direct the Center for Devices and Radiological Health to conduct additional monitoring and evaluation of the status of commercial tests that rely on breakpoints, on a regular basis, to determine whether test manufacturers are updating breakpoints, seeking additional resources as needed.

HHS Response

HHS concurs with GAO's recommendation.

FDA concurs with GAO's recommendation to conduct additional monitoring and evaluation of AST devices to determine whether device manufacturers are making updates, where appropriate, when FDA identifies or recognizes new breakpoints.

FDA agrees with GAO that it is important that AST devices reflect the most current information as one aspect in improving patient care and antimicrobial stewardship, and combating antimicrobial resistance. Although FDA agrees that in the past there have been significant challenges associated with updating AST devices to reflect the most current breakpoints, FDA believes it is important to understand that many of the concerns raised in the report have been resolved by recent FDA actions and the passage and implementation of section 511A of the FD&C Act. As described above, FDA has taken major steps in the implementation of the new statutory provision, and

has engaged in other activities to promote the availability and updating of AST devices.

Recommendation 7

The Secretary of HHS should develop a strategic framework to further incentivize the development of new treatments for antibiotic-resistant infections, including through the use of postmarket financial incentives, and, if appropriate, make recommendations to Congress for necessary authority.

HHS Response

HHS non-concurs with GAO's recommendation because it is still unclear whether post-market financial incentives should necessarily be part of HHS's forthcoming strategic framework to further incentivize the development of new treatments to combat antibiotic resistance.

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HHS agrees with GAO that additional incentives are needed to address the limited pipeline for novel and innovative treatments to combat antibiotic resistance. As noted by GAO, HHS convened a workgroup in March 2019 to analyze existing incentives, proposals for new incentives as raised by non-governmental, industry, and international groups, and other options to address this need.

This analysis has included consideration of the current and future burden of AMR on both public health and the economy, the dynamics of drug development that specifically impact relevant antibacterial and related products, and the statutory, regulatory, and budgetary feasibility of any incentive strategy. Based on this work, the group is developing a strategic framework that includes specific proposals to address a variety of scientific and market challenges facing antibiotic product developers. ASPE and HHS are still conducting analyses to understand whether post-market financial incentives should be included in this framework as a solution among a range of potential solutions.

Recommendation 8

The Secretary of HHS should direct the CARB Task Force to include in its annual updates to the President plans for addressing any barriers preventing full implementation of the National Action Plan and, as appropriate, make recommendations for new or modified actions. Specifically, the CARB Task Force should identify plans to address barriers, such as those related to expanding

(1) a CDC program designed to strengthen the U.S. response to resistant gonorrhea, (2) antibiotic stewardship programs across health care settings, and (3) antibiotic use data collection across health care settings, to the extent feasible

HHS Response

HHS concurs with GAO's recommendation.

Beginning in 2020 with the Annual Report for Year 5 of the first CARB National Action Plan, and continuing thereafter in the annual reports for the next iteration of the plan, HHS will include discussion of any barriers preventing full implementation of these activities, including any barriers that GAO has included in the recommendation where appropriate.

Beginning in 2020 with the Annual Report for Year 5 of the first CARB National Action Plan, and continuing thereafter in the annual reports for the next iteration of the plan, the CARB Task Force will include discussion of any barriers preventing full implementation of these activities, including the barriers that GAO has included in this recommendation where appropriate

Appendix VI: GAO Contacts and Staff Acknowledgments

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