Antimicrobial Resistance

Hilary D. Marston, MD, MPH; Dennis M. Dixon, PhD; Jane M. Knisely, PhD; Tara N. Palmore, MD; Anthony S. Fauci, MD

Antibiotics have revolutionized the practice of medicine by enabling breakthroughs across the spectrum of clinical medicine, including safer childbirth, surgical procedures, organ transplantation, and myeloablative chemotherapy regimens. However, antimicrobial resistance (AMR) threatens to impede and even reverse some of this progress. In the United States, AMR organisms cause more than 2 million infections and are associated with approximately 23,000 deaths each year (Table 1). In Europe, AMR is associated with approximately 25,000 deaths annually. The economic costs of AMR are substantial, estimated at $20 billion in excess medical spending each year in the United States. The full global effect of AMR is more difficult to quantify, as epidemiological data are sparse in many areas of the world. However, data that are available represent considerable concern. In this regard, the recent global emergence of resistance factors emanating from the United States (carbapenem-resistant Klebsiella pneumoniae), India (bacteria with the plasmid-mediated blaNDM-1 gene that confers resistance to carbapenems), and elsewhere (Escherichia coli with the plasmid-mediated mcr-1 gene that confers resistance to colistin, originally described in China) demonstrate the widespread nature of the problem and the importance of improved global surveillance.

The importance of AMR to human health is clear. In this Special Communication, we review the factors associated with AMR (and efforts to mitigate them), mechanisms of AMR and their influence on clinical practice, and the biomedical research response to the challenge.

Methods

The literature of international studies on AMR bacteria was reviewed by searching the PubMed database from January 2000 to June 2016. Priority for inclusion in further assessment was based...
Factors Associated With AMR and Key Response Strategies

To adequately address the threat posed by AMR, it is important to understand the factors driving its emergence. For example, bacterial replication cycles enable emergence of de novo mutations. A single Staphylococcus aureus bacterium can replicate through 10 generations in less than 12 hours, producing 1 million progeny. Each replication cycle offers the opportunity for mutation, allowing the emergence of genetic factors that contribute to resistance to antibiotics. Although de novo mutations can cause new problems, naturally occurring resistance factors appear to precede the antibiotic era. Permafrost samples from the Yukon revealed the presence of bacteria with resistance mutations 30,000 years before the discovery of penicillin. Resistance factors also were identified in samples drawn from a cave ecosystem that was isolated for more than 4 million years. Moreover, phylogenetic analyses of β-lactamases (enzymes that render penicillin consumption by animals ineffective) indicate their emergence 1 billion to 2 billion years ago.

Although naturally occurring resistance factors contribute to AMR, antibiotic use selects for their emergence; therefore, human activity plays an important role in the evolution of AMR. For example, consider the agricultural use of antibiotics for promotion of animal growth. In the United States, antibiotic use in animals raised for food represents 80% of total antibiotic consumption. The US Food and Drug Administration (FDA) estimates that 74% of these antibiotics are administered in feed, a method commonly used to promote animal growth, rather than to treat or prevent infection. Moreover, 62% of the antibiotics used in animals in this country represent “medically important” compounds, i.e., they have a role in treating human disease. Antibiotics used in the remaining 38% may influence human health as well. For example, bacitracin is commonly used topically on humans but not systemically administered as it is in animals. Although the direct influence of such practices on human health is difficult to quantify, reports of transmission of resistant bacteria via animal-to-human contact and consumption of animal products continue to emerge. Furthermore, an association has been demonstrated between antibiotic consumption by animals and the existence of humans of commensal organisms resistant to the same antibiotic classes. There also are reports of resistant pathogens passing from humans to animals. The potential influence of the agricultural use of antibiotics on human health has drawn a range of responses, including policies in Europe banning their use for purposes of animal growth, guidance from the FDA encouraging similar avoidance, and voluntary sourcing of antibiotic-free meat by a range of food providers.

In addition, the FDA recently published its Final Rule on Antimicrobial Animal Drug Sales and Distribution Reporting, requiring producers of animal drug products with antimicrobial activity to submit annual reports on the amount sold, to improve transparency of their use.

Human antibiotic use also contributes to the emergence of AMR (Figure 1). Substantial effort has addressed inappropriate antibiotic use within hospitals, including implementation of antimicrobial stewardship programs. Such programs involve collaborations among infectious diseases specialists and pharmacists with training in antimicrobial stewardship, supported by information management experts. The programs seek to optimize antibiotic selection and reduce the inappropriate use of broad-spectrum antibiotics (use of these agents applies selective pressure to bacteria and promotes emergence of AMR). Stewardship programs typically are empowered by hospital administrations to restrict the hospital formulary and require preauthorization for restricted antimicrobials or require audits of prescriptions paired with feedback to prescribers. Although the implementation of hospital antimicrobial stewardship programs has thus far been limited, the recent adoption by the Joint Commission (the primary accrediting body for hospitals) of an antimicrobial stewardship standard for health care facilities may encourage their use.

Although individual studies and programs have demonstrated the potential importance of antimicrobial stewardship in hospitals, limited implementation and acceptance continues to hamper sustainable change. However, inpatient antibiotic usage represents only 38.5% of the total antibiotic market. A recent analysis revealed that 12.6% of outpatient visits in the United States resulted in the prescribing of an antibiotic, and 30% of those prescriptions may have been inappropriate. Direct-to-consumer sales compound the problem of inappropriate use in many areas of the world. Outside of the United States and Europe, such purchases account for one-fifth to nearly all antibiotic use, depending on peer-reviewed articles and studies that focused on the epidemiology, microbiology, genomics, and clinical effects of AMR, development of vaccines and other therapies to prevent and treat AMR infections, diagnostic tests to identify AMR and refine use of antimicrobial drugs, discovery of novel agents to fight AMR bacterial infections, and nonpharmacological strategies to eliminate or modify AMR bacteria. In addition to articles found in PubMed, selected media reports, public health guidance documents, health policy reports, and NIH REPORTER and ClinicalTrials.gov database entries were identified and reviewed because they described recent trends in AMR. Among 217 identified sources, 103 were selected for inclusion as references on the basis of quality and relevance to understanding the problem and consequences of AMR, recent key trends and current events in AMR, and efforts under way to address AMR.
on location. Worldwide, antibiotics dispensed directly to the consumer are more likely to be inappropriately selected, taken at doses below standard of care, or both. All of these factors contribute to the emergence of AMR.

Public education campaigns have exerted a positive influence on inappropriate prescribing in countries such as Belgium and France. For example, a national media campaign in Belgium coincided with a 36% reduction in antibiotic prescriptions over 7 years (although other factors likely contributed as well). Other countries, including the United States, have launched education campaigns (eg, the Centers for Disease Control and Prevention’s [CDC’s] “Get Smart About Antibiotics Week” or the “Medicines With the Red Line” public awareness campaign in India). Importantly, these programs are still relatively new and conclusive evidence of their effectiveness is not yet available. Efforts targeting primary care clinicians also can change practice: a recent randomized clinical trial of behavioral interventions (eg, lists comparing levels of inappropriate prescribing among peers) demonstrated statistically significant decreases in inappropriate prescribing. Similarly, in a cluster randomized trial in which investigators offered an educational module and personalized feedback designed to reduce broad-spectrum antibiotic prescriptions for acute respiratory tract infections in children, intervention sites demonstrated a 12.5% decline in prescriptions for broad-spectrum agents compared with a 5.8% decline in control settings.

While human behavior contributes to AMR, another human endeavor—research innovation—provides a means to respond, for example, through the development of new antibiotics. The pace at which new antibiotics have been introduced has slowed considerably. For example, 16 antibiotics were approved by the FDA between 1983 and 1987, whereas only 2 were approved between 2008 and 2012, and a total of 5 new antimicrobials have been approved since the end of 2012. This slowdown is not unique to antibiotics; similar trends were observed for cardiovascular drugs and other agents. Nevertheless, certain characteristics of the antibiotic market likely hinder pharmaceutical industry investment in new drug development. Limited duration of treatment, relatively low prices per dose, the potential for the rapid emergence of resistance (and resulting uncertain market longevity), and antimicrobial stewardship efforts that limit access to new compounds all may curtail revenue prospects for a new antimicrobial agent. Clinical trials of new therapeutic candidates for drug-resistant infections pose their own unique challenges; for example, the sporadic incidence of infections and likelihood of antecedent antibiotic exposure in hospitals complicate enrollment into clinical trials. Antibiotic development for gram-negative infections is particularly difficult due to low permeability of the

Table 1. Annual Cases and Deaths for Selected Antimicrobial-Resistant Organisms and Clostridium difficile Infection in the United States, 2008-2011

<table>
<thead>
<tr>
<th>Year of Approval</th>
<th>Year Approval</th>
<th>Deaths per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>or Introduction</td>
<td>(resistant to clinically relevant drugs)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1.2 million</td>
<td>7000</td>
</tr>
<tr>
<td>Drug-resistant Campylobacter</td>
<td>310 000</td>
<td>28</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>250 000</td>
<td>14 000</td>
</tr>
<tr>
<td>Drug-resistant Neisseria gonorrhoeae</td>
<td>246 000</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Drug-resistant nontyphoidal Salmonella</td>
<td>100 000</td>
<td>38</td>
</tr>
<tr>
<td>Methicillin-resistant Staphylococcus aureus</td>
<td>80 461</td>
<td>11 285</td>
</tr>
<tr>
<td>Drug-resistant Shigella</td>
<td>27 000</td>
<td>40</td>
</tr>
<tr>
<td>Extended spectrum β-lactamase-producing Enterobacteriaceae</td>
<td>26 000</td>
<td>1700</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae</td>
<td>9300</td>
<td>610</td>
</tr>
<tr>
<td>Clostridium-resistant group B Streptococcus</td>
<td>7600</td>
<td>440</td>
</tr>
<tr>
<td>Drug-resistant Acinetobacter</td>
<td>7300</td>
<td>500</td>
</tr>
<tr>
<td>Multidrug-resistant Pseudomonas aeruginosa (≥3 drug classes)</td>
<td>6700</td>
<td>440</td>
</tr>
</tbody>
</table>

*Organisms ordered by number of cases. Methods describing figure derivation are described in the technical appendix of the Centers for Disease Control and Prevention’s Antibiotic Resistance Threats in the United States, 2013.

Figure 1. Time From Antibiotic Approval or Introduction to Detection of Resistance in Clinical Samples

The bars represent the years elapsed between regulatory approval or introduction of an antibiotic to the pharmaceutical market and the first report of resistance in a clinical sample. Displayed antibiotics represent either first member or representative member of the drug class. Adapted from Schmieder and Edwards, additions from Ayliffe, and Drugs@FDA.
gram-negative cell wall, a variety of efflux pumps (which actively transport drugs out of the cell), and an array of enzymes capable of inactivating all known β-lactam drugs (eg, penicillins and cephalosporins).

Policy interventions offer an important strategy to encourage drug development. For example, 6 new antibacterial drugs have been approved since 2010 under the “Generating Antibiotic Incentives Now” law in the United States, which grants extended patent exclusivity and expedited regulatory review for qualifying compounds. As of March 2016, 37 distinct systemic antibacterial drugs were reported to be in clinical development for bacterial infections (excluding mycobacterial infections). However, it is noteworthy that drug candidates for gram-negative infections are scarce, and this gap merits further policy discussion. For example, at a time when several new gram-negative resistance factors are being identified, drugs with activity against one or more of the gram-negative ESKAPE pathogens (Enterococcus faecium, S aureus, K pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacter species) represent only one-third of the antibiotics in clinical development.

While new antibiotic options are critically needed, other approaches also have an important role. Both ensuring judicious use and shortening the duration of treatment can reduce antimicrobial use and reduce the development of AMR. Similarly, proven public health interventions such as access to clean water and sanitation and hospital infection control can prevent bacterial infections and obviate the need for some antibiotic use. In addition, vaccines may have a role: Laxminarayan and colleagues estimated that improved vaccination coverage for Streptococcus pneumoniae could avert 11.4 million antibiotic days per year in children under 5 years of age worldwide.

Mechanisms of AMR and Their Influence on Clinical Practice

While numerous strategies are available to curtail antibiotic demand, an expanding array of resistant organisms poses an immediate concern for human health. The organisms and resistance mechanisms of greatest concern are detailed below.

Organisms Resistant to Carbapenems

β-Lactamases are a family of AMR enzymes that hydrolyze β-lactam rings, structures present in common antibiotics such as penicillins, cephalosporins, and aztreonam. Some are considered “extended-spectrum β-lactamases” because they can inactivate a wide range of β-lactam antibiotics. Carbapenemases are even more versatile members of the β-lactamase family due to their ability to hydrolyze both traditional β-lactam antibiotics and carbapenems, the latter representing the broadest-spectrum antibiotics available for treatment of gram-negative bacterial infections. Although many β-lactamase genes are encoded in the bacterial chromosome, extended-spectrum β-lactamase and carbapenemase genes, which render gram-negative bacteria resistant to important antibiotic classes, are usually plasmid mediated.

Plasmids are typically circular pieces of DNA that are considered mobile because they can be passed between bacteria via conjugation, a process that briefly connects the cytoplasm of 2 bacteria allowing horizontal gene transfer (Figure 2). Antimicrobial resistance genes encoded in bacterial chromosomes, such as multidrug efflux pumps in P aeruginosa, are usually not mobile, whereas those that are carried in plasmids can disseminate rapidly among bacteria of the same or different species. Moreover, plasmids often carry multiple AMR genes. At times, these additional genes are acquired through transposable elements, or transposons. Transposons are mobile DNA sequences that can integrate either into the bacterial chromosome or a plasmid, often carrying AMR genes.

Chromosomally encoded carbapenemases have been recognized for decades; however, only within the past 15 years have plasmid-mediated carbapenemases become clinically significant. Enteric bacteria carrying the K pneumoniae carbapenemase gene (blaKPC) were first reported in the United States in the early 2000s. They became widespread in health care facilities in the northeastern states and then in Israel. Within a decade, blaKPC variants and several additional plasmid-carried carbapenemases were identified in other regions of the world, typically in health care-associated gram-negative bacteria. It soon became apparent that infections with these multidrug-resistant organisms were associated with mortality rates of 40% to 80%.

The New Delhi metallo-β-lactamase (NDM-1)–containing bacteria were identified in India in 2009 and rapidly became endemic throughout South Asia and the Balkan states. The blaNDM-1 gene
has now been implicated in nosocomial infections and outbreaks on every inhabited continent.\textsuperscript{41-43} Bacteria containing the \textit{bla}\textsuperscript{NDM-1}, gene are so widespread on the Indian subcontinent that they have been cultured from runoff water on the streets,\textsuperscript{44} in newborns delivered in hospitals,\textsuperscript{45} and in community-acquired infections.\textsuperscript{46} The \textit{bla}\textsuperscript{NDM-1} gene has been identified in a broad range of gram-negative bacteria beyond enteric flora, including \textit{Acinetobacter} and \textit{Pseudomonas}.\textsuperscript{41}

The plasmid-carried OXA-48 family of carbapenemases first appeared in 2001 and have spread around the globe over the past 15 years. Organisms with these enzymes caused at least 2 clusters of nosocomial infection in the United States in 2015, as well as dozens of sporadic cases of colonization or infection.\textsuperscript{47} Other clinically significant carbapenemase enzymes include imipenemase-1 and the Verona integrin metallo-β-lactamase (VIM).

In the United States and Europe, carbapenemase-producing isolates have been identified predominantly in health care facilities, with rare cases seen in community-acquired infections.\textsuperscript{48,49} Several outbreaks related to contaminated duodenoscopes have occurred,\textsuperscript{50,51} forcing new methods of scope reprocessing and reconsideration of scope design. The potential for spread of carbapenemase-containing plasmids to community-acquired bacterial strains, such as \textit{E coli} ST131, is a concerning prospect. Although little evidence exists for extensive community spread outside Asia, the isolation of carbapenemase-producing organisms from wild birds and other animals demonstrates that the bacteria have disseminated to some degree from health care settings to the environment.\textsuperscript{52}

Carbapenemase-producing organisms are typically resistant to all β-lactam drugs, although NDM-1-producing bacteria may retain susceptibility to aztreonam. In addition, these bacteria often simultaneously carry other plasmid-mediated resistance factors. In such cases, tigecycline, polymyxins, and aminoglycosides are often the only drugs with activity against these microbes; among these, tigecycline has limited efficacy and its use has been associated with poor clinical outcomes in serious infections.\textsuperscript{53} Thus, the limited therapeutic options and the toxicity of the few active drugs are largely responsible for the high mortality rates associated with these infections.\textsuperscript{37-44} Infections with highly resistant carbapenemase-producing organisms are usually treated with combination antibiotic therapy in an attempt to achieve better microbial killing and preserve susceptibility to the few remaining antibiotic options.\textsuperscript{54} However, repeated exposure to suboptimal antibiotics and inadequate dosing fosters further resistance and can result in recrudescence infection due to extremely drug-resistant bacteria. Newer antimicrobial options, such as the β-lactam and β-lactamase-inhibitor combinations ceftazidime-avibactam and cefotaxime-tazobactam offer promise for treatment of some carbapenemase-producing organisms. Their utility may be limited because they are expensive (approximately $1100 and $315 per day of treatment, respectively).\textsuperscript{55} Ceftazidime-avibactam lacks activity against metallobetalactama- ses (eg, NDM-1 and VIM), and bacterial resistance to ceftazidime-avibactam has already been reported among \textit{bla}\textsuperscript{KPC}-containing bacteria.\textsuperscript{56}

Thus, a wide array of carbapenemase-carrying plasmids have appeared with differing effects on clinical practice. This group of resistant organisms has been dubbed “carbapenem-resistant Enterobacteriaceae” (CRE). However, as noted above, the plasmids are often also carried by bacteria outside of the Enterobacteriaceae family, and clinicians must be aware of this possibility.

\textit{Acinetobacter baumannii}, a common and tenacious nosocomial pathogen, is more frequently carbapenem resistant than Enterobacteriaceae. Although its carbapenem resistance is typically chromosomally encoded, \textit{A baumannii} can also carry plasmid-mediated carbapenemases. Nosocomial strains of \textit{A baumannii} are minimally susceptible to newly developed combination antibiotics such as ceftolozane-tazobactam, and the antibiotic pipeline does not appear to offer more effective options,\textsuperscript{59,60} making \textit{A baumannii} a continued major concern for hospitalized patients.

**Organisms Resistant to Colistin**

In 2015, scientists in China identified a plasmid-carried gene conferring resistance to polymyxins such as colistin.\textsuperscript{5} The gene, \textit{mcr-1}, has been found in human and animal isolates of Enterobacteriaceae and represents the first known plasmid-mediated resistance to polymyxins, which are antibiotics of last resort for gram-negative bacteria. Although colistin resistance among gram-negative bacteria is not new, the potential epidemiological consequences of rapid interspecies spread of plasmid-carried colistin resistance are concerning. Since its discovery, \textit{mcr-1} has been identified in Enterobacteriaceae cultured from humans, animals, and meat in at least 5 continents, including North America (Figure 3).\textsuperscript{57,58,60} As evidenced by an isolate reported from Germany, when this gene finds its way to a highly resistant carbapenemase-producing organism, the result would be a pan-resistant organism that is potentially untreatable with any existing antimicrobial drugs.\textsuperscript{61}

**Consequences of Empirical Antibiotic Treatment**

Other patterns of AMR can have serious consequences, even when resistance is limited to a single class of drugs. Resistance may complicate early treatment of infection before culture results are known, such as with empirical therapy for community-acquired pneumonia or urinary tract infections, as well as for surgical prophylaxis. For example, fluoroquinolones have long been used as perioperative prophylaxis for patients undergoing transrectal prostate biopsies. In the past decade, increasing reports of postprocedure sepsis with fluoroquinolone-resistant \textit{E coli} have led to new preprocedure selective rectal cultures for such strains, which require an additional visit to the urologist and specialized microbiology testing.\textsuperscript{62} Alternatively, some hospitals have broadened surgical prophylaxis to drug combinations such as ceftriaxone and gentamicin that cover fluoroquinolone-resistant \textit{E coli}. However, this approach may select for different resistant strains because of the broad-spectrum coverage, thereby delaying the clinical consequences of resistance until a later date.

**The Special Problem of \textit{Clostridium difficile}**

\textit{Clostridium difficile} is the leading cause of health care–associated infections in the United States and is a cause of epidemics of nosocomial infections.\textsuperscript{164} The bacterium’s resistance to multiple antibiotics allows its selection for overgrowth in the gut when the gut microbiome is disrupted by antibiotic drugs. \textit{Clostridium difficile} spores shed by infected or colonized patients persist on the surfaces of objects in hospitals and may be ingested by patients receiving antibiotics and other therapies. In addition, the
hypervirulent strain BI/NAP1/027 possesses increased resistance

to fluoroquinolones,\textsuperscript{65} giving it a selective advantage in patients
treated with that class of antimicrobials. \textit{Clostridium difficile}

bacteria are generally not invasive; however, these organisms elab-
orate exotoxins (toxins A and B) that cause mucosal damage in
the colon leading to the morbidity of the infection. The disease
manifests as colitis with diarrhea and classically a colonic pseudo-
membrane; in a recent multicenter study, 8% of patients with \textit{C difficile}
infection developed severe complications such as toxic megacolon.\textsuperscript{66}

The rate of \textit{C difficile} infection among hospitalized patients in the United States nearly doubled from 2001 to 2010,\textsuperscript{67} peaked in 2011 at roughly 147 cases per 100 000 population, and has declined slightly since.\textsuperscript{68} The United Kingdom, in contrast, has seen a decline in \textit{C difficile} infection rates of more than 75% since 2007 (from 108 to 26 cases per 100 000),\textsuperscript{69} likely attributable to successful preventive measures including antimicrobial stewardship, strict mandatory infection control precautions, environmental cleaning to eliminate spores, and patient-level analysis of the failures and factors precipitating individual cases of \textit{C difficile} infection.\textsuperscript{70}

\textit{Clostridium difficile} infection is usually treatable with antimi-
crobials, such as oral metronidazole for mild to moderate infection and oral vancomycin for more severe infection.\textsuperscript{71} Recurrent dis-
ease occurs in approximately 20% of patients.\textsuperscript{68,71} underscoring the

importance of prevention. Newer antimicrobials, such as fidaxomi-
cin, have some efficacy both in treatment of infection and preven-
tion of relapse. Severe or fulminating disease that does not respond to vancomycin or fidaxomicin may be treated surgically. Fecal mi-
crobiota transplant (FMT), or transfer of stool from an individual with a healthy fecal microbiome, is an evidence-based and highly effec-
tive treatment, with success rates of 81% to 94%.\textsuperscript{72} The high effi-
cacy of FMT has made it a standard approach and an often wel-
come intervention for patients with recurrent relapses or refractory disease.\textsuperscript{72} A variety of preventive agents for \textit{C difficile} are in clinical trials, including vaccines, monoclonal antibodies, therapeutic agents such as nontoxicigenic strains (to prevent recurrence),\textsuperscript{73} and toxin-
binding compounds.

\textbf{Neisseria gonorrhoeae}

Another resistant organism causing increasing concern is \textit{Neisse-
ria gonorrhoeae}. Gonorrhea is the second most common report-
able communicable disease in the United States (after chlamydial disease).\textsuperscript{74} \textit{Neisseria gonorrhoeae} has developed increasing resis-
tance to oral antibiotics (eg, azithromycin, fluoroquinolones, and the oral cephalosporin cefixime) previously used to treat this infection; in 2014, 37% of \textit{N gonorrhoeae} isolates in the United States were resistant to at least 1 antibiotic.\textsuperscript{75} Although cefixime resistance in the United States has declined in recent years,\textsuperscript{76} the slow, inexorable rise in resistance of \textit{N gonorrhoeae} has resulted

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Figure 3. Recovery of \textit{mcr-1}-Expressing Resistant Enterobacteriaceae Isolates as of June 21, 2016}
\end{figure}

The figure depicts the identification of \textit{mcr-1}-expressing isolates from various specimen types (human, animals used for food, food, environment) by country. Data from the European Centre for Disease Prevention and Control,\textsuperscript{57} updated from Skov and Monnet\textsuperscript{58} and the US Department of Health and Human Services\textsuperscript{59} and adapted under a Creative Commons Attribution (CC BY) license.
in increasingly narrow treatment options and has led the CDC to
declare drug-resistant *N gonorrhoeae* one of the leading microbial
threats to public health.1

Increasing rates of resistance to oral agents have left ceftriaxone
as the last remaining reliable treatment for gonorrhea.74 Resistance
to ceftriaxone has been reported,77,78 foreshadowing the need
for escalation of doses and new drug combinations to overcome resis-
tance. Treatment guidelines reflect these changes as they move
toward use of drug combinations.74 Current recommended first-
line therapy for gonorrhea in the United States is ceftriaxone plus
azithromycin, even if nucleic acid testing is negative for *Chlamydia
trachomatis*.74 Recent clinical studies have identified drug combina-
tions that could be used for salvage treatment of nonresponders,
such as azithromycin in combination with either gentamicin or
gemifloxacin.79 Although treating on the basis of antimicrobial sus-
ceptibility of *N gonorrhoeae* in individual patients might help pre-
serve the long-term effectiveness of the remaining antimicrobial
armamentarium,80 rapid molecular detection of resistance is not
available for this organism. Treatment for *N gonorrhoeae* must be pro-
vided promptly at the point of care to ensure adherence and mini-
mize transmission.

**Staphylococcus aureus**

For the past 2 decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has been a leading public health concern. MRSA is second
only to *C difficile* as a cause of health care–associated infections.64 In the early 2000s, the community-acquired strain USA300 be-
came the dominant etiology of skin and soft tissue infections in com-
unity settings. Methicillin resistance is conferred by the meca
gene; many MRSA isolates also contain β-lactamases and genes con-
ferring resistance to clindamycin.

For decades, vancomycin was the only available, effective in-
travenous therapy for MRSA infections. Isolates of MRSA with re-
duced susceptibility to vancomycin, known as vancomycin-
intermediate *S aureus*, have been identified infrequently in clinical infections. Vancomycin-intermediate *S aureus* strains have thick-
ened cell walls that contain vancomycin-binding dipeptides, which
detain the drug and lead to reduced drug at the target.81

The identification of vancomycin-resistant *S aureus* in clinical isolates in the early 2000s was not entirely unexpected: the plasmid-mediated vancomycin-resistance gene, *vanA*, is regularly
found in health care–associated isolates of vancomycin-resistant
enterococci. Therefore, ample opportunity exists for gene transfer
from vancomycin-resistant enterococci to *S aureus* in patients or
settings where the organisms coexist. While this intergenus trans-
fer has occurred, it has been documented thus far in only a handful
of identified cases.82 Given the mobility of plasmid DNA, it is
unclear why vancomycin-resistant *S aureus* infections have
remained so uncommon.

Multiple drugs are available to treat MRSA; however, few are rec-
commended for treatment of deep-seated infections involving interi-
or bodily structures such as endocarditis and osteomyelitis.83 Over
the past 15 years, new drugs such as daptomycin, linezolid, and ori-
tavancin have become available for treatment of serious resistant
gram-positive infections, offering alternatives to vancomycin (in
countries where these newer, expensive drugs are obtainable). Al-
though resistance to the newer drugs has been reported, they re-
tain considerable activity against MRSA and have the potential to
treat vancomycin-resistant *S aureus* if it becomes a more wide-
spread challenge.

#### The Scientific Pathway Forward

Since bacterial resistance to antibiotics is inevitable, researchers must
respond with innovative strategies to identify and develop new drug
candidates, vaccines, and other prophylactic immune interven-
tions and create novel treatment methods that are less likely than
typical antibiotics to result in resistance (Table 2).

#### Technologies to Facilitate Drug Discovery and Development

One reason for the limited number of new antibiotics is that tradi-
tional sources of these products have been carefully evaluated to
the point that virtually all promising antibacterial compounds have
been identified. These sources include chemical libraries used by
pharmaceutical companies and the small proportion of antibiotic-
yielding bacteria and fungi that can be easily cultured. To improve
this situation, investigators are developing new tools to identify novel

<table>
<thead>
<tr>
<th>Table 2. Novel Approaches to Address Antimicrobial Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Approach</strong></td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Antibiotic Discovery</strong></td>
</tr>
<tr>
<td>New ways to identify natural antibiotics</td>
</tr>
<tr>
<td>Untapped sources of natural products</td>
</tr>
<tr>
<td>Antimicrobial peptides</td>
</tr>
<tr>
<td><strong>Harnessing the Immune System</strong></td>
</tr>
<tr>
<td>Vaccines</td>
</tr>
<tr>
<td>Monoclonal antibody development</td>
</tr>
<tr>
<td>Innate immune modulators</td>
</tr>
<tr>
<td><strong>Manipulating Microbial Communities</strong></td>
</tr>
<tr>
<td>Fecal microbiota transplant</td>
</tr>
<tr>
<td>Live biotherapeutics</td>
</tr>
<tr>
<td>Bacteriophages</td>
</tr>
<tr>
<td><strong>Antivirulence Strategies</strong></td>
</tr>
<tr>
<td>Toxins</td>
</tr>
<tr>
<td>Secretion systems</td>
</tr>
<tr>
<td>Biofilm formation</td>
</tr>
<tr>
<td><strong>Rapid Diagnostics</strong></td>
</tr>
<tr>
<td>Point of care</td>
</tr>
<tr>
<td>Culture independent</td>
</tr>
<tr>
<td>Biomarkers</td>
</tr>
</tbody>
</table>
sources of naturally occurring antibiotics, such as the iChip platform that facilitates screening of natural products from previously unculturable soil organisms by mimicking their native environment. Using this technology, researchers identified teixobactin, an antibiotic compound with a novel mechanism of action. Although teixobactin is still in the early stages of development, this experience suggests that the iChip technology could prove an effective way to identify new classes of antibiotics. Investigators are also exploring other untapped sources of products such as marine microbes and bacteria living in extreme conditions. Furthermore, antimicrobial peptides known as bacteriocins, produced by bacteria, are being evaluated for activity and feasibility as products. Although these new approaches to drug therapy hold promise, drug screening also could be improved with methods that better model physiologic conditions.

Harnessing the Immune System

Vaccines capable of preventing bacterial infection, disease, or both circumvent the problem of AMR and have been successfully developed for several bacterial pathogens. However, the development of vaccines for health care–associated bacterial pathogens has been challenging, due to inadequate understanding of immune correlates of protection, complex pathogenic mechanisms, and extensive strain and antigenic variability. In this regard, several staphylococcal vaccine development programs have failed at the phase 3 stage of clinical trials, despite promising preclinical and early clinical data. However, a number of vaccine candidates for health care–associated infections remain in clinical development and, if successful, would likely be deployed in targeted populations of at-risk individuals.

Passive infusion of monoclonal antibodies provides additional options for treatment and prevention. Monoclonal antibodies are being developed for use in combination with antibiotics in severely ill patients with certain bacterial infections (eg, S aureus and P aeruginosa), as well as for prophylactic use. The low toxicity and long serum half-lives of certain monoclonal antibodies as well as the absence of conventional, drug-mediated selective pressure when they are used as antimicrobials make them attractive options, especially for prophylaxis. Monoclonal antibodies are particularly promising for patient populations with suboptimal responses to vaccination because of immune compromise, immune senescence, or other conditions. In addition, bispecific antibodies that can simultaneously bind pathogens and activate T cells have been developed for use against tumors and virus-infected cells. In the future, such innovations could be adapted to target bacterial infections.

Furthermore, considerable progress has been made in identifying the signaling pathways and receptors of the innate immune system. Investigators have identified new potentiators of innate immunity that may be effective as vaccine adjuvants or directly as therapeutic modalities. Such immune enhancements could lessen the required antibiotic dose, treatment duration, or both, thereby decreasing selective pressure toward resistance. Some prospects include broadly active innate immune–based strategies such as defensins, bactericidal/permeability–inducing protein, engineered γ-core motif peptides or peptidomimetics, complement, components of mucosal secretions including surfactant, and inflammation resolving mediators.

Manipulating Microbial Communities to Counteract Resistant Infections

The diverse communities of microbes that inhabit the human body (the microbiota) support human health in multiple ways and play crucial roles in protection against infectious diseases. The elements of the microbiota are diverse and include bacteria, fungi, and viruses. The potential to manipulate the microbiota to treat infection has already been demonstrated with the successful use of FMTs for treatment of C difficile infections. Use of this procedure to decolonize patients with multidrug-resistant organisms is the subject of active investigation. For example, researchers are working to translate the therapeutic potential of FMT into live biotherapeutic products, or drug products composed of specific and characterized live organisms.

Although the gut microbiome is the farthest along as a target for prevention and treatment of infection, there is potential in expanding these approaches to treat infections at other colonized sites, such as the skin or respiratory tract. Other types of innovative live biotherapeutic concepts are also being explored, such as exploiting Bdellovibrio and Micavibrio bacteria that parasitize gram-negative pathogens.

Bacteriophages, viruses that infect and kill bacteria with high specificity, also represent a promising tool for addressing AMR. Clinicians have sought to exploit the potential of bacteriophages to treat bacterial infections since their discovery in the early 1900s. From the early 1920s through the 1930s, phages were pursued as medical interventions for wound infection, dysentery, cholera, and plague. With the introduction of broad-spectrum antibacterial drugs, phage therapy fell out of favor in the United States and Western Europe but continued to be used in Russia and Eastern Europe. However, most studies using phage therapy were not done in accordance with modern clinical trial standards, raising questions about efficacy. Nevertheless, the clinical results were promising, particularly with antibiotic-resistant supplicative infections. The potential application of phage therapy to drug-resistant infections, as well as its pathogen specificity, has led to a resurgence of efforts to evaluate this approach for the prevention and treatment of bacterial infections. Recent randomized, double-blind, placebo-controlled studies of phage therapy in patients in the United Kingdom with chronic, antibiotic-resistant P aeruginosa infections have shown significant clinical benefit and an ongoing clinical trial in Europe is evaluating the effectiveness of phage therapy to treat burns and wounds.

Innovative phage-derived modalities also are being developed and evaluated. Lysins are lytic enzymes produced by phages that selectively destroy specific gram-positive pathogens with high specificity and disperse biofilms. The first commercially developed therapeutic product of this type, which targets S aureus, is currently in phase 1 clinical trials. Investigators are also using phages as a starting point to develop engineered products that can modulate bacterial cells, including their antibiotic-resistance mechanisms and virulence factors.

Other innovative tools being explored for their ability to target resistant bacteria are systems that likely evolved to protect bacteria from phages: CRISPR (clustered regularly interspaced short palindromic repeats)-Cas systems, capable of precise genome editing. For instance, in enterococci, multidrug-resistant phenotypes seem to be correlated with the loss of functional CRISPR systems.
suggesting that some bacteria may trade their CRISPR defense system for enhanced ability to acquire new resistance traits through horizontal gene transfer. Some investigators have proposed taking advantage of this observation by using phages to specifically deliver CRISPR systems to target resistance genes, ensuring that only resistant strains are targeted.101

Antivirulence Strategies
Factors that contribute to pathogen virulence—such as toxins, iron acquisition systems, secretion systems, quorum-sensing pathways, adhesins, and biofilm formation—have the potential to be exploited as novel therapeutic targets. Selectively targeting virulence factors is attractive because this strategy does not affect microbe viability and thus does not exert the selective pressure associated with conventional antimicrobials. The goal of antivirulence therapeutics is to reduce pathogenicity while allowing the host to clear the bacterial infection. This approach has the added benefit of preserving the host microbiota. However, new preclinical testing approaches and models will need to be developed if antivirulence therapeutics are to be advanced to the clinic. For example, animal efficacy models will need to more accurately reflect clinical progression of disease and new in vitro assays will need to be developed.

Diagnostics
In addressing the problem of AMR, the importance of rapid diagnostics for optimal stewardship of antibiotics cannot be overstated. Although mass spectrometry has sped identification of bacteria and fungi, this technology as well as antimicrobial susceptibility testing are still largely dependent on culture. Therefore, empirical therapy with broad-spectrum antibiotics is often initiated before this critical information is available. Requirements for an optimal diagnostic test differ depending on the clinical setting. In an inpatient setting, a test with a turnaround time of several hours may be sufficient, whereas outpatient settings may require a simple point-of-care test that can provide results while the patient waits—ideally for less than 30 minutes. Differences also exist in the technical challenges for typically sterile vs nonsterile clinical specimens. For example, bacterial bloodstream infections can be difficult to detect due to the low number of organisms present in the blood; all currently FDA-cleared tests for this indication require some culture prior to identification. However, several companies are exploiting new sensitive technologies, such as magnetic resonance technology, fluorescence in situ hybridization, and transcriptional profiling to enable pathogen detection directly from a blood sample and eliminate the need for a culture step. In addition, distinguishing between colonization and infection at nonsterile sites presents a distinct technical challenge. For example, in respiratory tract infections, detected organisms may not be the cause of the patient’s symptoms. To circumvent these issues, researchers are developing tests based on host response expression signatures, which could help distinguish colonization from infection and bacterial from viral infections.102 Biomarkers, such as procalcitonin, are used in some countries as surrogates of infection to support microbial diagnosis, and they are also being explored as tools to help guide initiation of empirical therapy.103

Commercial developers of rapid diagnostics also encounter practical challenges with clinical validation of their tests, such as access to clinical isolates for test validation. Recently, resources such as the CDC-FDA Isolate Bank and the Antibiotic Resistance Leadership Group Virtual Repository have been established to provide well-characterized panels of clinical isolates. Furthermore, the Antibiotic Resistance Leadership Group plans to develop master protocols for diagnostics in which the same group of patients can be used to validate multiple diagnostic tests simultaneously.

Looking Ahead
Although advances in biomedical research hold promise for efforts to prevent and treat AMR, many of these technologies are in the earliest stages of discovery. Meanwhile, effective action can slow the spread and mitigate the negative effects of resistant bacteria today. Medical professionals and facilities have an important role to play, through implementation of antimicrobial stewardship programs, reduction in inappropriate prescribing, immunization against bacterial and viral pathogens, and robust infection control measures including enhanced surveillance for resistant organisms. National plans, such as the President’s National Strategy for Combating Antibiotic Resistant Bacteria, lay out more comprehensive approaches, drawing on contributions from health care practitioners, biomedical researchers, and the pharmaceutical and agricultural sectors (among others).2 Analogous international efforts, overseen by the World Health Organization, are also under way. These programs require committed and concerted implementation to realize their promise. Without a coordinated response, the postantibiotic age presaged by so many is a distinct and unwelcome possibility.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: We thank the following individuals for their helpful input in the preparation of this manuscript: Gregory K. Follers, MS, MPH, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Baoying Liu, PhD, MHS, Bacteriology and Mycology Branch of the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Stephanie M. Coomes, PhD, and Christina McCormick, MA, both of the Office of Scientific Coordination and Program Operations, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health. François Franceschi, PhD, Therapeutics Development, Bacteriology and Mycology Branch of the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

REFERENCES
2. President’s Council of Advisors on Science and Technology. Report to the President on combating...
50. Epstein L, Hunter JC, Arwady MA, et al. New Delhi metallo-

β-lactamase–producing carbapenem-resistant Escherichia coli associated with exposure to dengue vectors. 
52. Guerra B, Fischer J, Helmuth R. An emerging public health problem: acquired carbapenemase-producing microorganisms are present in food-producing animals, their environment, companion animals and wild birds. 
53. Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. 


