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Antibiotic Resistance Threats in the United States: Stepping Back from the Brink

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In a recently issued report, the Centers for Disease Control and Prevention (CDC) estimated the national burden of illnesses and deaths caused by the most common and most worrisome antibiotic-resistant pathogens.[1] The report focused on 16 antimicrobial-resistant bacterial pathogens, as well as *Candida* infections, which together account for more than 2 million illnesses and at least 23,000 deaths every year in the United States.[1] The report also included information on *Clostridium difficile* infections, which, like antibiotic resistance, are driven by antibiotic use. *C. difficile* causes more than 250,000 clinical infections annually and is associated with more than 14,000 deaths every year in the United States.[1]

In this report, the CDC categorized 18 pathogens *(eTable A)* into three groups (urgent, serious, and concerning) based on seven criteria: clinical impact, economic impact, incidence, 10-year projection of incidence, transmissibility, availability of effective antibiotics, and barriers to prevention.[1] Three types of bacteria were included in the urgent category: carbapenem-resistant Enterobacteriaceae, drug-resistant *Neisseria gonorrhoeae*, and *C. difficile*. In the past, drug-resistant strains of Enterobacteriaceae and *N. gonorrhoeae* have shown a propensity to spread rapidly in the United States and around the world. Some strains of carbapenem-resistant Enterobacteriaceae are currently untreatable with available antibiotics, and the cephalosporin agents to which some gonococci are now showing emerging resistance are the last available drugs to effectively treat this infection. Thus, further spread of these strains constitutes a public health crisis. *C. difficile* infections already cause significant morbidity and mortality, and a recently emerging epidemic strain, BI/NAP1/027, appears to be more virulent.

Prevention strategies can be effective, but the major goals of the CDC report are to (1) increase awareness of the magnitude and looming risk of untreatable infections, and (2) spur concerted action, both to prevent further spread of resistant pathogens and to preserve the effectiveness of existing antibiotics. Thinking of antibiotics as a precious and diminishing resource has engendered the concept of antimicrobial stewardship, a defined set of practices designed to improve the appropriate use of antimicrobial agents.[2] *Table 1* lists steps to help implement resistance prevention strategies. Family physicians have an important role in combating antibiotic resistance through carefully prescribing antibiotics, educating patients, and identifying and reporting unexpected treatment failures and suspected resistance.

There are three main elements of preventing and controlling antibiotic resistance that are most applicable to outpatient practice. First, physicians must improve their antibiotic prescribing. Antibiotic use is the principal driver of antibacterial resistance. A considerable proportion of antibiotics in inpatient and outpatient settings are prescribed in cases when they are not needed or in which the choice of antibiotic, the dose, or the duration of therapy is inappropriate.[3,4] Rates of outpatient antibiotic prescribing vary widely by region and state—a much greater variation than is likely explained by differences in patient populations or rates of bacterial diseases.[5] It has been documented that inappropriate antibiotic prescribing, especially for viral upper respiratory tract infections, is common in ambulatory care.[6] These illnesses are the most common reason for seeking medical attention in the United States and are associated with up to 75% of total antibiotic prescriptions each year.[7] The causes of the overuse of antibiotics, which is a problem throughout the world, are complex and well described.[8,9] ▶

Table 1. Steps to Combat Antimicrobial Resistance in Outpatient Settings

Steps	*Suggestions for implementation*
Improve antibiotic prescribing	
Use current clinical guidelines to support rational and appropriate antibiotic prescribing	Share unremarkable findings during the examination (e.g., "no inflammation" or "normal breathing"), while acknowledging the patient is sick
	Determine the likelihood of a bacterial infection, especially for upper respiratory tract infections
	Provide a specific diagnosis (e.g., "viral bronchitis" vs. "virus")
	Weigh benefits vs. harms of antibiotics
	Implement judicious prescribing strategies
Communicate with patients about when and why antibiotics may not be necessary	Explain that unnecessary antibiotic use can be harmful (e.g., adverse effects associated with antibiotic use, potential resistance development)
	Explain that treating viral infections with antibiotics does not work
	Explicitly plan treatment of symptoms by describing the expected normal course of the illness, and instruct patients to call or come back if symptoms persist or worsen; consider providing care packages with nonantibiotic therapies
Educate patients if an antibiotic is needed	Encourage adherence
	Discuss potential adverse effects
Create an office environment that promotes a reduction in antibiotic use	Start the process in the waiting room with videos, posters, and other materials
	Hang posters in examination rooms to display a commitment to not prescribe antibiotics for viral infections
	Involve office personnel in the reinforcement of the physician's messages
Prevent infections and the spread of resistant bacteria	
Ensure that all patients get recommended vaccinations	Provide pneumococcal and influenza vaccines (to help avoid secondary bacterial infections), which are particularly important
Prevent cross-transmission	Counsel patients on how to avoid spreading or becoming infected with resistant pathogens in the community (e.g., methicillin-resistant *Staphylococcus aureus*)
	Follow recommendations for infection control in outpatient settings (http://www.cdc.gov/hai/settings/outpatient/outpatient-care-guidelines.html)
Monitor antibiotic-resistant infections	
Report notifiable diseases	When appropriate, report to the health department any diseases caused by bacteria on the Centers for Disease Control and Prevention's list of urgent and serious pathogens (reporting requirements differ by U.S. state and Canadian province); antibiotic-resistant strains of some bacteria (e.g., methicillin-resistant *S. aureus*) are reportable in some states
Be alert for treatment failures	Consider the possibility of antibiotic resistance in cases of treatment failure; obtain laboratory confirmation and notify local public health authorities in cases of unusual or unexpected treatment failure

The second main element is preventing infections and the spread of resistance. Preventing an infection eliminates the possibility that the infection could be drug resistant. Immunization and rigorous infection control, including hand washing, clearly reduce the likelihood of infection. On its website, the CDC provides information for patients on how to protect themselves from many types of infections, such as by ensuring safe food handling to prevent *Salmonella* and *Campylobacter* infections[10] and by avoiding gonorrhea and other sexually transmitted infections.[11] Counseling patients on how to avoid spreading or becoming infected with resistant pathogens in the community is an important role for physicians. For example, if an athlete is diagnosed with a methicillin-resistant *Staphylococcus aureus* infection, he or she should keep the wound properly covered, avoid whirlpools or therapy pools, shower after participation, clean uniforms and equipment after each use, and report infection to coaches and trainers.

The third main element is public health reporting. Gathering, analyzing, and disseminating information on resistant infections and the prevalence of resistant microorganisms is a critical strategy that informs clinical and public health decision making. A key component of detecting emerging and spreading resistance is identifying the cause of unexpected treatment failures. Patients who return with persistent or recurrent symptoms shortly after treatment should be retested by culture, and isolates should be submitted for antimicrobial susceptibility testing. Any case of unexplained treatment failure or a positive culture result after appropriate empiric treatment should be reported promptly to local or state health departments.[12] Ultimately, public health surveillance is dependent on reporting by physicians and laboratories.

The nightmare scenario of the spread of pan-resistant bacteria is a real and frightening possibility. Cases of untreatable infections are already occurring. Preventing and controlling resistance requires the engagement of many different sectors of society. However, the physician's role in this effort is singularly important.[12] As the threat becomes more urgent, the leadership of the medical community is the most critical factor to ensure a successful response.

The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. Mention of trade names or commercial products does not constitute endorsement or recommendation for use by the U.S. government.

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eTable A. Antibiotic-Resistant Microorganism Threats

Microorganism	*Notable information*
Urgent	
Clostridium difficile[A1,A2]	Deaths related to *C. difficile* increased 400% between 2000 and 2007, in part because of a stronger strain Most infections are connected to receiving medical care Hand sanitizer does not kill *C. difficile*, and hand washing may not be sufficient
Carbapenem-resistant Enterobacteriaceae[A3]	Difficult to treat and, in some cases, untreatable Kills up to one-half of patients who get bloodstream infections Easily spreads antibiotic resistance to other bacteria
Drug-resistant *Neisseria gonorrhoeae*[A4]	Cases in the United States are more prevalent in the West and among men who have sex with men All patients treated for gonorrhea should routinely be offered condoms, referred for risk-reduction counseling, and retested for gonorrhea three months later
Serious	
Multidrug-resistant *Acinetobacter*[A5]	Increasingly common in U.S. health care facilities; hard to treat Noted in U.S. service members wounded in Iraq and Afghanistan
Drug-resistant *Campylobacter*[A6]	Most cases are sporadic and not part of outbreaks Ciprofloxacin (Cipro) resistance to *Campylobacter* increased from 12% in 1997 to 24% in 2011
Fluconazole- (Diflucan-) resistant *Candida* (fungus)[A7-A9]	Antifungal resistance in mucosal candidiasis varies by species
Extended spectrum β-lactamase–producing Enterobacteriaceae[A10,A11]	Infections have become more common in recent years Once confined largely to hospitals, these bacteria, especially *Escherichia coli*, are increasingly common in community-acquired infections, particularly urinary tract infections
Vancomycin-resistant *Enterococcus*[A12-A14]	Enterococci are the fifth most common cause of health care–associated infections Most likely to be found in urine and in wounds; may pose a risk for spreading in the outpatient setting
Multidrug-resistant *Pseudomonas aeruginosa*[A15,A16]	About 8% of all health care–associated infections are caused by *P. aeruginosa*; about 13% of severe *P. aeruginosa* health care–associated infections are multidrug resistant *P. aeruginosa* may be isolated from outpatients with otitis, skin rash, and urinary tract infections
Drug-resistant non-typhoidal *Salmonella*[A17,A18]	Estimated 1.2 million cases occur each year in the United States; most go unreported About 100,000 cases (8%) are caused by drug-resistant *Salmonella* Outbreaks occur each year; some involve multiple states and/or national distribution
Drug-resistant *Salmonella* serotype Typhi[A19]	Estimated 5,700 cases annually in the United States Most (up to 75%) are acquired during international travel Increasing resistance to antibiotics, especially fluoroquinolones
Drug-resistant *Shigella*[A20]	High-risk groups include children in day care centers (younger than five years) and their caregivers, men who have sex with men, international travelers, and persons in custodial institutions Increasing resistance to ciprofloxacin and azithromycin (Zithromax) is of particular concern
Methicillin-resistant *Staphylococcus aureus*[A21-A23]	Although overall cases of invasive methicillin-resistant *S. aureus* are declining, the proportion of community-associated infections has increased Should be considered in the differential diagnosis of skin and soft tissue infections

continued

eTable A. Antibiotic-Resistant Microorganism Threats *(continued)*

Microorganism	*Notable information*
Serious *(continued)*	
Drug-resistant *Streptococcus pneumoniae*[A24]	Increasing threat of antibiotic resistance makes vaccination according to the Advisory Committee on Immunization Practices recommendations for children and adults more important
Drug-resistant tuberculosis[A25,A26]	Number of tuberculosis cases is declining in the United States 63% of tuberculosis cases in the United States occur among foreign-born persons Proportion of primary multidrug-resistant tuberculosis cases occurring among foreign-born persons has been increasing
Concerning	
Vancomycin-resistant *S. aureus*[A27]	Rare; 13 cases have been identified in the United States since 2002 Severity of the consequences of *S. aureus* resistance to vancomycin require continued vigilance for this pathogen
Erythromycin-resistant group A *Streptococcus*[A28]	Penicillin remains the drug of choice, but the resistance to other drugs needed for patients allergic to penicillin is worrisome Of samples tested by the Centers for Disease Control and Prevention, 10% were erythromycin resistant and 3.4% were clindamycin resistant
Clindamycin-resistant group B *Streptococcus*[A29]	Neonates, pregnant women, and persons older than 65 years with underlying conditions are at highest risk Penicillin remains the drug of choice, but the resistance to other drugs needed for patients allergic to penicillin is worrisome

NOTE: *Additional information on the microorganisms in this table can be found in the Centers for Disease Control and Prevention's antibiotic threats report at http://www.cdc.gov/drugresistance/threat-report-2013/index.html (accessed March 27, 2014).*

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