U.S. Efforts to Curb Antibiotic Resistance — Are We Saving Lives?

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Antibiotic resistance represents a major crisis that limits the care of many patients. Demonstrating that large-scale efforts to control this problem have saved lives would help secure the ongoing and expanded funding and support needed to sustain action. However, data causally linking national and global efforts to the burden of antibiotic resistance and to outcomes are lacking. Existing antibiotic-resistance surveillance systems aren't designed to capture granular details on treatments and complications, and several countries suspected of having the highest rates of death attributable to antibiotic resistance don't conduct surveillance. Furthermore, patients infected with antibiotic-resistant pathogens are more likely to have coexisting conditions, to be critically ill, and to be immune suppressed than those with infections caused by susceptible pathogens. These factors make it difficult to accurately draw causal inferences between antibiotic resistance and mortality, let alone to quantify the lives saved by antibiotic-resistance countermeasures.

Using data from a point-prevalence survey and existing surveillance systems, the Centers for Disease Control and Prevention (CDC) estimated in 2013 that there were 2 million infections and 23,000 deaths attributable to antibiotic-resistant pathogens in the United States each year.[1] The CDC acknowledges that its estimates were limited by a lack of certain types and sources of contemporaneous data. Reporting on multidrug-resistant gram-negative pathogens was largely limited to health care–associated infections. Various pathogens and resistance phenotypes were treated as being equally lethal, which seemed biologically implausible. The report was therefore thought to substantially underestimate the number of deaths attributable to antibiotic resistance, and an estimate calculated using vital-statistics data was many times higher.[2] Nonetheless, the report elevated the issue of antibiotic resistance and catalyzed the deployment of important countermeasures by the U.S. government, with support from private companies and professional organizations.

Substantial strides have been made since then. The rate of overall health care–associated infections has decreased, thanks to boosted preventive efforts. Requiring hospitals to implement antibiotic-stewardship programs in order to be accredited by the Joint Commission and to participate in Medicare and Medicaid has contributed to a doubling in the proportion of hospitals with such programs (from 41% in 2014 to 85% in 2018). Push incentives offered by CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator), a nonprofit public–private partnership, have supported several candidate antimicrobial products through early-phase development, and legislation has enabled expedited approval of antibiotics addressing unmet needs. Among other recommendations, the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (of which one of us is a member) has suggested continuing existing efforts through 2025.[3]

In November 2019, the CDC released an updated version of its antibiotic-resistance report that overcomes some previous methodologic limitations and reflects collaboration with external partners.[4] The information it analyzed included electronic health record (EHR) data from a nationally weighted sample of more than 700 acute care hospitals. This approach improved generalizability and enabled reporting on community-onset infections and infections caused by certain noninvasive pathogens that weren't captured by traditional surveillance. Risk of death was reported by pathogen and individually for hospital- and community-acquired infections. The new report reveals reductions in the incidence of infections caused by carbapenem-resistant acinetobacter species, multidrug-resistant *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, and drug-resistant candida species. In addition, it identifies an increasing incidence of Enterobacterales that produce extended-spectrum beta-lactamase and drug-resistant *Neisseria gonorrhoeae* infections and the emergence of the multidrug-resistant yeast *Candida auris*. The CDC also looked back and determined that nearly twice as many Americans died from antibiotic-resistant infections in 2013 as was previously estimated (44,000, rather than 23,000).

The report revealed an 18% reduction in deaths attributable to antibiotic resistance since 2013 (with a current rate of 35,900 deaths per year), which suggests that some efforts are working. Understanding which big-ticket antibiotic-resistance countermeasures deployed over the past half-decade drove this success is crucial to optimizing ongoing resource allocation.

Any population-level reduction in deaths related to antibiotic resistance is likely to be caused by either a reduction in the number of antibiotic-resistant infections, improved survival rates among patients with these infections, or both. Various countermeasures differentially influence the incidence of infection and survival. Improved infection control, for example, generally reduces mortality by blocking transmission and thereby reducing the number of new infections. Improved antibiotic stewardship by health care facilities and stricter regulations against overuse of antibiotics in healthy food animals may reduce the proportion of bacteria that are resistant to antibiotics, which, in turn, could reduce deaths from antibiotic-resistant infections.

On the other hand, rapid and reliable pathogen identification and the use of safer and more effective antibiotics probably reduces deaths by improving survival rates among infected people. In addition, countermeasures that lead to earlier diagnoses and the development of better antibiotics will often have collateral benefits for patients with infections caused by antibiotic-susceptible bacteria, which are far more common than antibiotic-resistant infections and can pose serious risks. Any attempts to use antibiotic-resistance surveillance to optimize resource allocation should therefore capture changing trends in outcomes of infections caused by antibiotic-resistant bacteria and the indirect effect of interventions on overall infection-related deaths. Furthermore, such efforts should make use of knowledge gained from smaller-scale investigations assessing the clinical-effectiveness and cost-effectiveness of individual interventions.

There is no single national data source capable of tracking changes in survival among people with antibiotic-resistant infections over time. Although deidentified aggregate EHR data can provide granular within-encounter information, tracking of postdischarge deaths (which aren't uncommon among these patients) generally requires personal identifiers. The CDC addressed this limitation in its 2019 report by leveraging an external source — the Veterans Health Administration database, in which patients can be tracked after discharge — to model excess 90-day mortality attributable to antibiotic resistance for various pathogens.

Several concerns remain, however. First, whether mortality risks observed among veterans and their families are broadly generalizable is unclear. Second, the report didn't account for receipt of appropriate antibiotic therapy, an important determinant of survival. Third, for each pathogen, the same attributable mortality was applied to each year's infection counts, but survival rates for antibiotic-resistant infections have probably changed. In the United States, mortality from most infectious diseases has decreased considerably over time. As the practice of supportive care and empirical prescribing and the uptake of rapid diagnostics and newer antibiotics continue to evolve, so might their effect on survival. Hence, the actual drop in antibiotic-resistance–associated deaths may be greater than the report suggests.

The CDC findings offer a conservative, best-available estimate and represent an important step forward. The framework incorporating data from multiple sources created for the report could provide a foundation for future work, bolstered by data from additional EHR systems. Associating resistant pathogens with deaths, however, requires better data on both infections and patients.

Efforts to generate such data are under way. The CDC's antibiotic-use and antibiotic-resistance modules help health care facilities track their own trends in these areas; bolstering participation in these modules will improve estimates of the national antibiotic-resistance burden. The Centers for Medicare and Medicaid Services may mandate such participation in the future, which could bring us closer to having comprehensive national data. Incorporating laboratory and physiological data and diagnosis codes into these modules and focusing on definitions with more prognostic value (e.g., difficult-to-treat resistance)[5] could help identify patients with antibiotic-resistant infections in near-real time and could facilitate population-level assessments of appropriateness of antibiotic therapy. Such efforts could soon enable periodic appraisals of national antibiotic-resistance initiatives. Business models need reform; some CARB-X–supported companies that developed recently approved antibiotics have gone bankrupt or are on the verge of bankruptcy. Instability in the antibiotic industry and the unclear potential of resistant bacteria to complicate treatment of patients with Covid-19 are examples of changing conditions that make near–real-time assessments important.

Efforts to curb antibiotic resistance have saved lives. As mortality associated with antibiotic resistance decreases, however, margins for further improvement will narrow, making the use of appropriately calibrated metrics especially important. Deaths associated with antibiotic resistance are unlikely to fall to zero in the United States. But we can strive to optimize efforts that we know are effective and continue our quest to better understand what is unknown.

The opinions expressed in this article are those of the authors and do not represent any position or policy of the National Institutes of Health, the U.S. Department of Health and Human Services, or the U.S. government.

Disclosure forms provided by the authors are available at NEJM.org.

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DOI: 10.1056/NEJMp2004743