Emergence of Global Antibiotic Resistance

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KEYWORDS

• Antibiotic resistance • Global health • Antibiotic stewardship • CDC bacterial threats
• Gram-positive bacteria • Gram-negative bacteria • WHO global action plan

KEY POINTS

- Antibiotic resistance is a worldwide phenomenon and a global public health crisis.
- The overuse and misuse of antibiotics in the human sector as well as the animal, food, and agricultural arenas have contributed to the current dilemma.
- Both gram-positive and gram-negative resistant bacteria have been deemed serious and urgent threats by the Centers for Disease Control and Prevention.
- The World Health Organization has created a 5-objective global action plan to address antimicrobial resistance and to coordinate numerous international sectors.
- Antibiotic resistance affects both this generation and the next; thus, related ethical challenges such as patient autonomy and justice have yet to be fully understood.

INTRODUCTION

The World Health Organization (WHO) has warned that unless the issue of antibiotic resistance is effectively addressed and contained, the phenomenon has the capacity to fundamentally change health care systems as we know them. The potential for a multiplicity of infectious diseases to have no viable antibiotic therapy is an imposing and impending reality. The complexity of the resistance problem must be confronted on multiple levels, from individual practitioners and patients, to community and national hospital systems, from local to global public health organizations, and via global surveillance and collaboration structures. Only a comprehensive paradigm shift, from

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both public and private sectors, can stem the advancing tide of antimicrobial resistance (AMR) and its consequences for current and future generations.[1]

EPIDEMIOLOGY: ANTIBIOTIC USE AND RESISTANCE

- The Centers for Disease Control and Prevention (CDC) estimates 30% to 50% of all antibiotics prescribed in outpatient clinics are unnecessary.[2]
- Approximately 269 million antibiotic prescriptions were dispensed in the United States in 2015, enough for 5 of every 6 people to receive 1 antibiotic prescription.[2]
- Excess prescriptions put patients at risk for drug reactions or other complications, including *Clostridium difficile.*
- One-third of the ~500,000 *C difficile* infections in the United States in 2011 were community-associated.[2]
- Approximately 250,000 people each year require hospitalization for *C difficile* infections.[3]
- In the United States, ≥14,000 people die each year from *C difficile* infections, many preventable.[3]
- Eleven percent of nursing home residents take antibiotics on any single day, according to a small CDC study, yet many of these prescriptions were for the wrong drug, dose, or duration.[2]
- Overall rates of antibiotic use in US hospitals were stable in 2006 to 2012, but use of high-powered antibiotics increased by ~40% for carbapenems and 30% for vancomycin.[3]
- The CDC estimates ~30% of antibiotics used in hospitals are unnecessary or prescribed incorrectly.[2]
- The CDC estimates antibiotic-resistant bacteria cause more than 2 million illnesses and 23,000 deaths per year in the United States.[3]
- The European Center for Disease Prevention and Control estimates antibiotic-resistant bacteria cause ~25,000 deaths and €1.5 billion in health expenditures per year in Europe.[4]

Antibiotic resistance is a threat to individuals, health care and veterinary systems, and agricultural industries. The total economic cost of antibiotic resistance could be as high as $20 billion in excess of direct health care costs, with additional costs for lost productivity of $35 billion.[3] Estimates from the UK government project the cost of drug resistance to be US $100 trillion worldwide by 2050, with a death toll up to 10 million per year.[5]

BACKGROUND: HISTORY OF ANTIBIOTIC DEVELOPMENT AND RESISTANCE

The emergence of antibiotic resistance is a complex, multifactorial issue.[6] Soon after antibiotic discovery, the identification of resistance was not far behind (**Table 1**). *Staphylococcus* resistance to penicillin was identified even before widespread production of the first antibiotic in 1943.[6] Research shows that the genetic diversity required for this type of resistance to develop could not have come about in the time frame since the introduction of penicillin. This discovery indicates that bacteria likely have an intrinsic predilection for resistance stored within their genome that has been advancing over thousands of years.[6] The development of bacterial resistance to antibiotics is therefore a natural process and would exist with or without human intervention.[7]

However, since the introduction of penicillin, selection pressure from the use of antibiotics allows these bacterial adaptive mechanisms to further accelerate the selection of naturally resistant or more virulent bacteria. The inappropriate use of antibiotics