

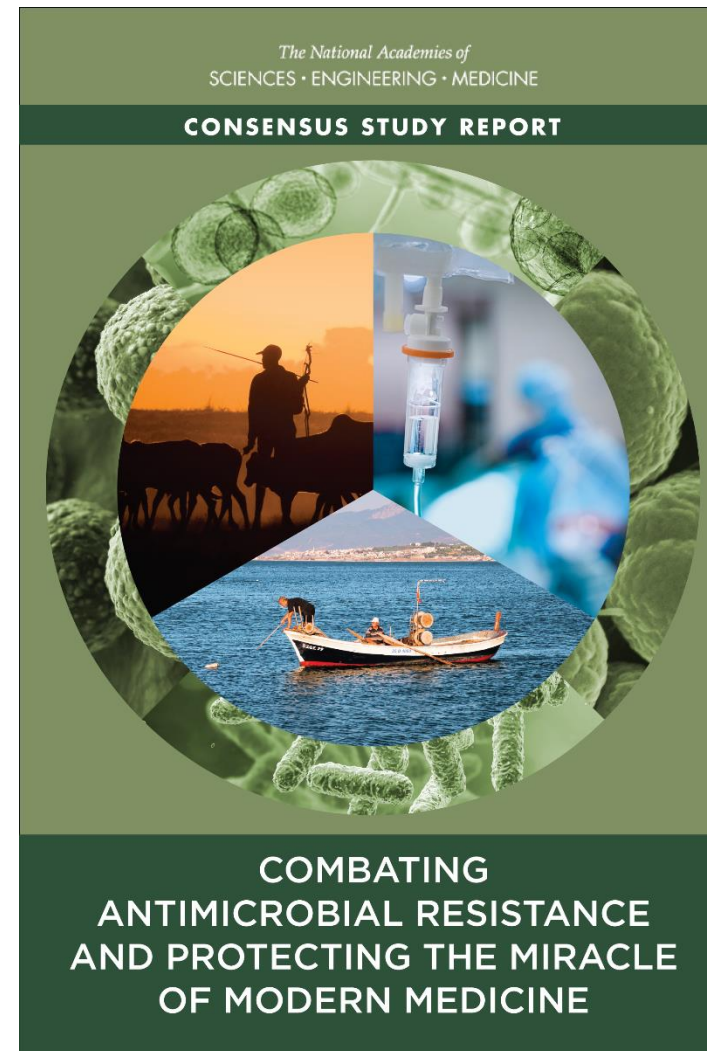


# Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine

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# Background

- Antimicrobial medicines have driven a century of progress in global health, progress that antimicrobial resistance could undermine.
- Response to antimicrobial resistance requires cooperation at many level of government and across sectors, as noted in the *National Strategy for Combating Antibiotic-Resistant Bacteria*.
- In 2019, Congress directed NIAID to support a National Academies consensus study on progress against the national strategy.
- The charge to the committee includes:
  - Effective surveillance
  - Measuring health and economic consequences
  - Interventions in animal health
  - Incentives for developing needed medical products



# Scope of the Problem

- Use of antimicrobial medicines drives resistance
- Human and animal medicine should aim for the most narrow, targeted agent, for the shortest effective duration
- Resistance is a web of related global health problems, sometimes related only loosely.
  - Urbanization, crowding, poor water and sanitation infrastructure, limited access to care, and unreliable medicines supply contribute to both a higher burden of disease and greater use, sometimes misuse of antimicrobials
- CDC *AR Threats*:
  - 2.8 million resistant infections a year in the United States, ~36,000 deaths
  - \$4.6 billion in direct medical costs, another \$1 billion from *C. difficile* and \$133.4 million from drug-resistant gonorrhea
- OECD
  - ~60,000 deaths a year in the US and Europe, 1.75 million DALYs lost, costing the countries involved \$3.5 billion a year



# Surveillance

- Surveillance is essential for understanding the burden of resistance
- WHO GLASS aims to build capacity for surveillance in LMIC, there is also considerable information collected by industry, academic researchers, and various disease-specific programs.
- Antibiograms are also useful and generated every day in the routine practice of clinical microbiology.
  - **The National Library of Medicine should establish an open-source, unified antimicrobial resistance database that integrates raw phenotypic data from national and international efforts. This database should support automatic importation from hospitals, laboratories, and surveillance networks and linking to genotypic data when available. The National Library of Medicine should engage the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, and other relevant stakeholders to determine the necessary data elements and confidentiality procedures.**
- Environmental monitoring of resistance is limited; a need to determine what factors amplify resistance traits in the environment and their health impact
- Wastewater treatment plants are an important bridge between human contamination and the natural environment
  - **The Environmental Protection Agency should provide guidance and funding to states for testing point source discharge at wastewater treatment plants for antimicrobial resistance traits and integrating these data with other surveillance networks.**



# Stewardship in Human Medicine

- There has been considerable progress in implementing ASP in hospitals since 2014
- There are still many practice settings where the need for stewardship is pronounced
  - **The Centers for Medicare and Medicaid Services should require nursing homes, long-term acute care hospitals, and dialysis centers to have antimicrobial stewardship programs and include that information on the Care Compare website. These programs should, at a minimum, designate key staff, a system for preauthorization of restricted antimicrobials, and a process for regular review of all antimicrobial prescriptions**



# Stewardship in Animal Medicine

- Tracking antimicrobial use is key to any stewardship program, but the U.S. does not have a strong system to track antimicrobial use in animals
  - **The Food and Drug Administration Center for Veterinary Medicine should establish a process and clear metrics to facilitate better tracking of antimicrobial consumption in animals. This information would support the design and implementation of stewardship programs.**
- Challenges in using diagnostic tests can also stand in the way of good stewardship.
- A lack of animal and pathogen-specific breakpoints also holds back stewardship, the time and expense of assembling the data needed to inform these breakpoints is a barrier.
  - **The Food and Drug Administration Center for Veterinary Medicine should convene an advisory committee to coordinate development of antimicrobial susceptibility test breakpoints in animals and identify priority animal, drug, and pathogen combinations. When necessary, the Center for Veterinary Medicine would fund the research needed to develop the priority breakpoints.**



# Diagnostic Stewardship

- Appropriate diagnostic testing could do much to reduce inappropriate antimicrobial use.
- The value of diagnostics, especially in terms of patient or financial outcomes is not usually readily apparent
  - **The Department of Health and Human Services agencies, including the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Centers for Medicare and Medicaid Services, and the Patient-Centered Outcomes Research Institute should support outcomes research in diagnostic testing to drive an iterative process of guidelines development and to influence reimbursement for diagnostic testing.**



# Prevention Strategies

- Vaccines have the potential to reduce the need for antimicrobials and to control the spread of resistance, but the relationship is not well studied.
- Incorporating questions about antimicrobial resistance into ongoing vaccine trials could yield information on this question with relatively little additional effort or expense.
  - **The National Institutes of Health and the Centers for Disease Control and Prevention should provide supplemental research funding to track antimicrobial use and antimicrobial resistance in immunization trials and large cohort studies to measure the indirect benefits vaccines provide and to provide evidence to enhance vaccine deployment as a tool to mitigate antimicrobial resistance.**





# Bringing New Products to Market

- Antimicrobials are complicated and expensive to develop and have a relatively small market
- There is a mismatch between society's need for the drug and industry's willingness to invest in them
- The package of push and pull incentives in place has modestly improved the antimicrobial pipeline, but most new products and those in the pipeline do not appear to be meaningfully different from existing drugs.
- Market entry rewards of between \$500 and \$2billion are often suggested as an incentive to bring a novel antimicrobial to market.
- Before funding any market entry reward the government should be clear that it is rewarding a truly novel and useful product.
  - **An HHS interagency committee should establish well-targeted, objective criteria to identify novel antimicrobials with high potential for filling a critical, unmet need. HHS should then support trials to establish the additional clinical benefit and optimal use of these drugs.**



# Ensuring the Reach of New Antimicrobials

- Integrating new medicines into automated susceptibility test panels is a major logistical barrier to the drugs' use.
- As resistance continues to emerge breakpoint changes will only be needed more frequently.
  - **To reduce regulatory hurdles in bringing automated susceptibility tests to market, the FDA should coordinate the review of new antimicrobials with the review of their automated susceptibility tests and work with the Clinical Laboratories Standards Institute (CLSI) to issue and update breakpoints for microbe-drug combinations.**
- FDA and drug manufacturers could find less restrictive methods for validation studies, and Congress could help defray the expense of these studies with tax credits.
  - **Congress should make automated susceptibility test manufacturers eligible for tax incentives to bring new automated susceptibility tests to market.**



# Ensuring the Reach of New Antimicrobials

- Some antimicrobials will simply never be candidates for inclusion on automated test devices.
- For such drugs, manual testing is necessary, but difficult for many laboratories.
  - **CDC should expand the capacity of the Antibiotic Resistance Laboratory Network by offering expedited, expanded susceptibility testing of all broad-spectrum antibiotics via certain CLIA-certified laboratories. CDC should also promote this service to clinical laboratories.**



# A One Health Approach to Product Development

- There is a need for a broad range of therapeutic and preventive products across human and animal health.
- The coordinated product development partnerships put in place for COVID-19 have transferable elements which could help coordinate investment in AMR across sectors.
  - **The Department of Health and Human Services (HHS) should establish a public-private partnership similar to ACTIV for antimicrobial resistance, bringing together BARDA, NIH, USDA, EPA, and DOD and interested academic, industry, and nonprofit organizations. The partnership would have working groups on diagnostics, alternatives to antibiotics, and prevention, with a goal of supporting a diversified and balanced portfolio of tools to reduce antimicrobial resistance using a One Health approach.**



# The National Action Plan

- The committee commissioned an analysis of agencies' progress against the goals of the 2015 action plan.
- CIDRAP investigators found the vast majority of milestones were completed on time and without serious duplication of effort.
- Process milestones are useful, but do not necessarily translate into meaningful improvements in antimicrobial use or the spread of resistant pathogens.
  - **Congress should direct the Government Accountability Office to conduct biennial evaluations of federal agencies' progress toward meeting the goals of the 2020-2025 National Action Plan for Combating Antibiotic-Resistant Bacteria to ensure objective assessment of agencies' activities. Congress and GAO should consider ways to use their evaluations to direct course corrections when necessary**



# A Role for the US in Coordinated, Global Action

- International investment in AMR is morally compelling and in the best interest of the United States.
- A program modelled on the PEPFAR program may be best suited to this problem.
  - **Congress should expand the United States global engagement on antimicrobial resistance by (1) strengthening surveillance of resistant pathogens both by supporting existing, multilateral surveillance systems and by expanding U.S. agencies' international surveillance programs; (2) reducing need for antimicrobials by broadening agencies' work on infection prevention and antimicrobial stewardship in humans and animals; and (3) ensuring sustained leadership and critical evaluation by creating a Global Coordinator for Antimicrobial Resistance similar to the Global AIDS Coordinator.**



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