Starter Resources on Antimicrobial Resistance

1. Overview Resources

Global Action Plan on Antimicrobial Resistance - resolution with amendments resulting from informal consultations | *World Health Organization (WHO)* | 2015
The Global Action Plan (GAP) sets out five objectives that seek to ensure an effective response to the challenge of antimicrobial resistance: increasing awareness and understanding of antimicrobial resistance (AMR); strengthening knowledge through surveillance and research; preventing infection; optimizing antimicrobial use for human and animal health; and developing the economic argument for sustainable investment in medicines, diagnostic tools, vaccines, and other interventions. National action plans aligned with the Global Action Plan should be put in place by the 70th World Health Assembly in 2017. -

WHO-NGO Dialogue on Antimicrobial Resistance | *World Health Organization* | 2015
Prior to the 68th World Health Assembly, the WHO invited over twenty civil society organizations to discuss the Global Action Plan (GAP) on AMR, in particular soliciting views on its implementation. These discussions focused on the technical and financial implementation of the GAP; issues of antibiotic access including rational use, restrictions on marketing, and the need for improved innovation through delinkage of R&D investment from sales; the need for One Health and multisectoral approaches; and the importance of accountability, monitoring, and evaluation to combat AMR.

Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations
| O'Neill | *Review on Antimicrobial Resistance* | 2014
This review is one in a series commissioned by the UK Government detailing the problems with AMR and studying ideas to combat these emerging threats. Among its findings are that resistant-infections could lead to 10 million deaths and a GDP reduction of 2 to 3.5 percent per year at current rates, costing society 100 trillion USD by 2050. Immediate concerted action can reduce the impact of the antimicrobial resistance crisis.

The Dangers of Hubris on Human Health | *World Economic Forum* | 2013
In a survey of the economic and social costs of antibiotic resistance, the World Economic Forum found that hospital-acquired antibiotic resistant infections have led to the deaths of 100,000 Americans, 80,000 Chinese, and 25,000 Europeans over a ten year timescale - a number that is likely to rise in the future. Antibiotics facilitate complex medical procedures, especially for an aging population likely to experience high rates of chronic disease. The report discusses why antibiotics are overused, why their R&D pipeline has slowed, and what can be done to tackle the complex issue.

Resistance | Graziano M and Park E | *Uji Films* | 2014
This documentary matches lost archival footage with candid stories of everyday people whose lives were upended by antibiotic-resistant infections to demonstrate that the risk of antibiotics becoming ineffective is greater than most may know. Using microscopic footage alongside personal narratives and expert opinions, this film discusses the history of antibiotic resistance and potential solutions.

2. Access to Antibiotics

The access and excess dilemma: Part 5 of Antibiotic resistance - the need for global solutions
| So, et al. | *Lancet Infectious Diseases* | 2013 (pp 15-19)
A challenge of antibiotic resistance is in ensuring access to these medicines when needed, but also the prevention of excessive use that may accelerate resistance, as outlined within the Lancet Infectious Diseases Commission on Antibiotic Resistance. This reading discusses strategic points of intervention from bench to bedside to address antibiotic resistance. These interventions must be focused on achieving access without excess, and include new treatment innovation, dissemination of effective antibiotic treatments, scale-up and implementation within the healthcare system through stewardship, and continued monitoring and assessment of these interventions with policy feedback and surveillance.

Access, excess, and ethics--towards a sustainable distribution model for antibiotics
| Heyman, et al. | *Upsala J of Med Sci* | 2014
A sustainable model for antibiotic distribution aimed to improve access in low- and middle- income countries (LMICs) could be constructed using systems thinking of the entire health system, as suggested in this article. Interviewing stakeholders in various LMICs, this reading provides four themes for such a model to consider, including the barriers to rational access, the balance of access and excess, drawing upon similarities of other communicable diseases, and addressing issues with a health system-wide approach.

3. Innovation of Antibiotics

Critical shortage of new antibiotics in development against multidrug-resistant bacteria - Time to react is now
| Freire-Moran et al. | *Drug Resistance Updates* | 2011
In this EMA-ECDC-ReAct analysis, a search of two commercial databases found that in 2011, of 90 possible antibacterial agents in clinical development, only 4 showed in-vitro action against Gram-negative bacteria, and none showed a novel mechanism of action. This result highlights an urgent unmet need to develop new treatments for multidrug-resistant bacterial infections, especially those caused by Gram-negative bacteria.

The Drugs Don't Work | Davies | *Penguin* | 2013
This book by the Chief Medical Officer of the United Kingdom sketches an apocalyptic future in which people who contract everyday infections are locked into isolation until they recover or die. The book discusses the familiarity of antibiotics as "wonder drugs" which may lead to taking their effect for granted. It also details the dwindling range of effective antibiotics as "the new inconvenient truth," and how it poses health risks for generations to come.

Securing New Drugs for Future Generations: The Pipeline of Antibiotics
| O'Neill | *Review on Antimicrobial Resistance* | 2015
The current antibiotics R&D pipeline is insufficient to supply clinical needs. Out of 41 recently licensed drugs, no approved compounds and only 3 candidates currently in clinical trials meet high-priority needs, defined as effective against 90% or more highly-resistant (in this case, carbapenemase-producing) bacteria. It typically takes 15 years for a drug to come to market, and the success rate for antibiotics is between 1.5 and 3.5%. Unlike development of new drugs to improve on old ones, the commercial returns for new antibiotics is uncertain until resistance has emerged against a previous generation of drugs.

3Rs for innovating novel antibiotics: sharing resources, risks, and rewards | So, et al. | *BMJ* | 2012
Sharing resources, risks, and rewards (3Rs) along the value chain of new drugs can reduce barriers to antibiotic innovation. Sharing resources can improve the availability of the building blocks of scientific research, such as compound libraries and natural products as candidates for drug development. Sharing risks seeks to leverage public sector financing to enable greater innovation. Sharing rewards can help ensure fair returns on public investment and affordable end products for those in need. In concert, the 3Rs offer useful benchmarks to evaluate how public investments and incentives might shape the enabling conditions for innovation of novel antibiotics and health technologies to tackle antibiotic resistance.

New Business Models for Sustainable Antibiotics | Outterson | *Chatham House* | 2014
Antibiotics should be treated as a public good as they are a common pool resource that are exhaustible due to resistance. In traditional models of pharmaceutical research and development, price and volume-based sales determine return on investment. However, prioritizing quantity conflicts with the public health goal of regulating antibiotic use. Delinkage of revenue from sales volume encourages long-term coordination among stakeholders and enhances access among those in need.

Towards new business models for R&D for antibiotics | So et al. | *Drug Resistance Updates* | 2011
Bottlenecks at points along the pharmaceutical value chain must be addressed for antibiotic innovation. These include hit identification during drug discovery, lead optimization in pre-clinical testing, and then crossing the "valley of death" into clinical development. This conference proceeding recognized that "strategies that delink product sales from the firms' return on investment can help ensure that the twin goals of innovation and access are met." South-South innovation platforms alongside product development development partnerships may be particularly useful and are currently underutilized to develop and produce needed innovations.

4. Conservation, Rational Use & Stewardship in Humans

Antimicrobial Resistance Global Report on Surveillance | *World Health Organization* | 2014
This report shows global trends in antibiotic resistance, highlighting specific bacteria of international concern. It examines country- and regional-level data on nine bacterial strains, including common hospital- and community-acquired infections such as methicillin-resistant *S. aureus* (MRSA) and *E. coli*. The report describes health and economic burdens attributable to resistance and the emergence of resistance within WHO programs for tuberculosis, malaria, HIV, and influenza. The report is limited by the present gaps in worldwide surveillance. Tools and standards need to be developed and integrated for observation of AMR and its impacts on humans and the food chain.

Worldwide country situation analysis: response to antimicrobial resistance | *World Health Organization* | 2015
A questionnaire-based analytic tool was used to survey national leaders (with 133 responses out of 194 countries) within the six WHO regions on their national AMR plans, laboratory capacity to track resistance trends, access to medicines, prevention of antibiotic misuse, and general public awareness. Few countries had comprehensive, well-financed plans to monitor and combat antibiotic resistance, with only 34 out of 133 participating countries reporting comprehensive AMR plans. High-income regions reported higher rates of access to quality antimicrobials, and regions with concerns over counterfeit and low-quality medicines reported weaker regulatory authority or capacity to enforce national standards. All six regions reported overuse of antimicrobials as a problem, with several regions noting concerns over lack of prescription requirements or regulation of antimicrobials. Public awareness was also low, raising concerns that adequate standards will be ineffective without improved awareness.

Interventions to improve antibiotic prescribing practices for hospital inpatients
| Davey, et al. | *Cochrane Database Syst Rev* | 2013
The effectiveness of restrictive versus persuasive interventions on antibiotic prescribing practices in hospital care was studied in a review of 89 studies. The analysis supported the use of restrictive interventions in the setting of urgent need, but found both persuasive and restrictive interventions to be equally effective after six months. Few of these studies (<6%) were conducted in low- and middle-income country settings.

5. Responsible Use of Antibiotics in Animal Agriculture

Global Antimicrobial Use in the Livestock Sector
| *OECD Working Party on Agricultural Policies and Markets (APM)* | 2015
Widespread antimicrobial use in human medicine and agriculture to the emergence of resistant pathogens that circulate among humans, animals, food, and the environment. Unchecked, global use of antimicrobials in animal agriculture will increase 67% by 2030. Countries such as Denmark and Sweden, which have better hygiene and nutrition conditions for animal husbandry, have not experienced negative effects on productivity following antimicrobial bans. The report suggests that restricting subtherapeutic antimicrobial animal use would have disparate economic impacts, affecting countries differently based on their agricultural production systems.

The interface between people and animals: Part 4 of Antibiotic resistance - the need for global solutions
| Greko | *Lancet Infectious Diseases* | 2013 (pg 12-15)
Local and global partnerships among all sectors are needed to improve health systems, especially to phase out growth promotion and routine preventive uses of antimicrobials intended to increase productivity. The EU banned antimicrobials for growth promotion in 2006, while in many other countries, several antibiotic growth promoters remain legal and available over the counter. Various pathways likely transfer resistant bacteria from animals to humans, including exposure through food, spread through international trade, and run-off from fertilized land or sewage. Resistance reduces antibiotic effectiveness in not only animals, but also humans. This public health concern warrants stewardship that acknowledges the links among human, animal, and environmental health.

Germination | *National Geographic Phenomena*
Germination is a blog that explores public health, global health, and food production and policy. In the blog, Maryn McKenna discusses antibiotic resistance, including numerous articles on antibiotics in the food and agriculture system. Selected stories include a study that suggests drug-resistant staph A poses a work hazard to farm workers, as reflected in the higher likelihood for people working with swine to carry and be infected by drug-resistant staph. She also discusses the FDA's finding that antibiotic use in US animals increased despite restrictions on antibiotics in human medicine. McKenna additionally writes about alerts from the US Centers for Disease Control and Prevention that drug-resistant foodborne illness is spreading in the US.

6. Selected Multilateral Efforts to Tackle Antimicrobial Resistance

Declaration on Antibiotic Resistance | *Antibiotic Resistance Coalition (ARC)* | 2014
Launched at the World Health Assembly in 2014, the Declaration on Antibiotic Resistance lays out principles and policy concerns endorsed by twenty civil society organizations as well as the South Centre. The Declaration touches on key concerns over the need for access to antibiotics without excessive use; non-therapeutic use of antibiotics in agriculture; effective innovation of novel antibiotics; and future steps in international cooperation and action.

Strategic Research Agenda | *Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)* | 2013
Key stakeholders from nineteen countries participating in the JPIAMR laid out a strategic research agenda to tackle AMR. This agenda covers the development of therapeutics, antibiotics and alternatives to antibiotics, new diagnostic tools, surveillance systems, and interventions to influence the transmission dynamics of infections.

Leader's Declaration G7 Summit--Antimicrobial Resistances | 2015 (pg 11)
Convening in June 2015, the G7 leaders pledged to develop national action plans on antimicrobial resistance and commit to a One Health approach. Detailed in the summit's annex on Joint Efforts to Combat Antimicrobial Resistance (beginning on page 2), G7 leaders committed to a two-fold approach to addressing AMR by conserving the effectiveness of current and future treatments while innovating new drugs, vaccines, and rapid diagnostic tools.

Jaipur Declaration on Antimicrobial Resistance | *WHO South-East Asia Regional Office (SEARO)*| 2011
The health ministers of the member states of WHO SEARO collectively affirmed their commitment to adopt "a holistic and multidisciplinary approach towards prevention and containment of antimicrobial resistance to improve public health." The Jaipur Declaration highlights a range of measures that would strengthen local infrastructure in tackling this inter-sectoral challenge.

7. Select National Reports on Antimicrobial Resistance

Report to the President on Combating Antibiotic Resistance
| *President's Council of Advisors on Science and Technology (PCAST)* | 2014
PCAST recommended that the United States government combat antibiotic resistance as a national priority through coordinated federal leadership, with strengthened public health infrastructure needs to conduct surveillance and response. To facilitate antibiotic development, they proposed that the US find new approaches to developing antibiotics for human and alternatives to antibiotics in agriculture. The recommendations for new antibiotics included changes in clinical trials, such as national testing networks and drug approval based on clinical trials in limited patient populations. It also discusses the need for new commercial models for R&D, including both push and pull mechanisms, such as direct federal partnerships and changed economic incentives. The report highlights the need for stewardship in human healthcare, including rapid-point-of-care diagnostics, and animal agriculture. PCAST also advises cooperation with international partners to advance efforts to address antibiotic resistance around the world.

National Strategy on Combating Antibiotic-Resistant Bacteria | *The White House* | 2014
This report by the US government details five goals to tackle the challenge of antibiotic resistance, which include slowing the development of resistance bacteria and preventing the spread of resistant infections; strengthening national one-health surveillance efforts to combat resistance; advancing the innovation and use of rapid diagnostic tests for resistant bacteria; accelerating research on new antibiotic compounds as well as complementary therapies and vaccines, and improving the international collaboration for prevention, surveillance, control and R&D efforts. The report also details next steps, and the US becomes one of many countries with national action plans including: United Kingdom, Australia, Ethiopia, France, Germany, India, Ireland, Norway, Sweden, and Switzerland.

The Chennai Declaration: a roadmap to tackle the challenge of antimicrobial resistance
| Ghafur, et al. | *Indian Journal of Cancer* | 2013
The 2012 Clinical Infectious Disease Society Conference at Chennai created a roadmap and commitments for tackling antibiotic resistance through antimicrobial stewardship, prevention, education, and innovation. The stakeholders included the Indian Ministry of Health, the Drug Controller General, the State Departments of Health, the Medical Council of India, the National Accreditation Board of Hospitals, the Indian Council of Medical Research, and the WHO India Office. Together, these forces agreed to develop a national action plan to phase out over-the-counter antibiotic sales, standardize microbiology laboratories, institute hospital and veterinary antibiotic monitoring, teach medical students, and increase public awareness.

8. Additional Resources

ReAct Toolbox
The ReAct Toolbox provides educational materials to empower individuals, educators, health professionals, and policymakers with an understanding of antibiotic resistance and ways to raise awareness. The Toolbox offers guidance on how to encourage rational antibiotic use, control infections in communities and clinics, create national policies that take into account all stakeholders, and conduct empirical studies to monitor antibiotic resistance.

Upsala Journal of Medical Sciences Issue on Antibiotic Resistance, Volume 119, Number 2
In this online journal issue dedicated to antibiotic resistance, a comprehensive range of articles focusing on causes and effects of antibiotic resistance and a diverse range of perspectives on antibiotics. It discusses possible new treatment approaches, including combination therapies, phage therapies, antimicrobial peptides, and microwave irradiation. Also discussed is stewardship in the health system, structural and scientific bottlenecks in drug R&D, and new business models for antibiotic innovation.

Imagining the Post-Antibiotics Future | McKenna | *Medium* | 2013
Opening with the narrative of a great-uncle who died in New York from a routine infection five years before the advent of antibiotics, Maryn McKenna explains the history and consequences of antibiotic resistance. She discusses how losing antibiotics would undermine, not only medicine, but the food supply, our daily lives, and much of what holds modern society together.

Superbug: The Fatal Menace of MRSA | McKenna | 2011
This book covers the historical narrative of one of the most highly publicized strains of drug-resistant bacteria--methicillin-resistant *Staphylococcus aureus*, also called MRSA. Tracing MRSA's historical development of drug-resistance and spread throughout many regions of the world and levels of society provides context to the problem that growing antibiotic resistance poses to society now and in the future.

Prepared by *ReAct--Action on Antibiotic Resistance's* Strategic Policy Program within the Duke University Program on Global Health and Technology Access.

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