A Conversation with Dr. Steve Solomon and Dr. Jean Patel on Antimicrobial Resistance
June 18th, 2013

Participant List

- Dr. Steve Solomon, Director, Office of Antimicrobial Resistance, Division of Healthcare Quality Promotion (DHQP) and The National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) in the Centers for Disease Control and Prevention (CDC).
- Dr. Jean Patel, Deputy Director, Office of Antimicrobial Resistance, DHQP/NCEZID in the CDC.
- Alexander Berger, Senior Research Analyst, GiveWell.

Note: This set of notes was compiled by GiveWell and gives an overview of the major points made by Dr. Solomon and Dr. Patel.

Summary

GiveWell spoke with Dr. Jean Patel and Dr. Steve Solomon as part of our shallow investigation of antimicrobial resistance. The conversation focused on: identifying the magnitude of the risk of drug resistant microorganisms, understanding the factors that are shaping the development of resistance, how our scientific and political institutions are responding or could respond to this issue, and offering potential philanthropic responses to these risks.

Changing Nature of the Problem of Antibiotic Resistance

For approximately the first 60 years of the "Antibiotic era", which effectively began 75 years ago with the introduction of clinical antibiotics, drug innovation had outpaced the development of antimicrobial resistance. More recently, the spread of drug resistance has outpaced the development of new drugs for two primary reasons:

1) Most of the "easy to identify" antibiotic agents have already been developed. It is becoming increasingly difficult from a scientific point of view to develop new drugs for the same diseases.
2) The economic incentives that face the pharmaceutical industry do not favor the development of new antibiotics. It is not considered profitable to invest in research and development of new antibiotics.

Drug resistance, especially pan-drug resistance, is an issue that was previously a major consideration only in a hospital setting but is increasingly becoming a community-level concern as well; its existence outside of a clinical setting has made it more unpredictable and harder to control. Although the number of individuals infected with multi-drug resistant infections in the United States is relatively

small—depending on one's definition it is estimated in the thousands—there may be the potential for rapid spread.

Additionally, the widespread use of antibiotics to increase livestock output has increased. Approximately 80% of antibiotics sold in the U.S. are sold to farms. Reducing antimicrobial use in this industry is a significant challenge. Although there is some academic disagreement on this question, both Dr. Solomon and Dr. Patel believe that there is a significant risk that antibiotic resistance developed on farms could spread to humans.

Time Frame for Risk

The public health impact of antimicrobial resistance is a reality today. Within the year CDC is expected to publish a report with estimates of the number of serious infections caused by the most important antimicrobial resistant pathogens. The impact can be reduced by preventing transmission of resistant pathogens, improving antimicrobial use, and developing new antimicrobial agents.

Developing new antimicrobial agents is critically important but there will never be enough new drugs because resistance always emerges and the public heath impact of new resistant pathogens can occur quickly. Dr. Solomon and Dr. Patel roughly estimated that the timeframe between the first identification of a new antimicrobial resistant pathogen and a significant impact of that pathogen on national health may be on the order of 5 years.

It can take ten years or more to develop a new antimicrobial drug and bring it to market, and there is only so much you can do to speed up the development cycle. Therefore, it is unlikely scientists would be able to decrease this time span significantly in the case of an emergency. However, there are some new antibiotics already under development, so it is not the case that we are currently 10 years from any new antibiotics coming onto the market.

Examples of Pathogens that Exhibit Drug Resistance

***Tuberculosis* –** Although it is a critical threat internationally, due to significant infrastructure investment and over 60 years of experience treating tuberculosis with antimicrobial drugs, the U.S. has reduced the number of cases of TB, including multidrug-resistant tuberculosis (MDR-TB), to extremely low levels.

Gonorrhea – Although it does not present a major risk in terms of mortality, the rate at which resistance can spread in cases of gonorrhea makes it an urgent threat. Until recently, the CDC recommended treatment of gonorrhea with fluoroquinolone antimicrobial drugs, primarily ciprofloxacin ("Cipro"). However, resistance rates increased from near 0% to 20-30% in less than a decade, forcing the CDC to recommend the use of "last-line" antibiotics for patients with drug resistant gonorrhea. These drugs, cephalosporin antibiotics, are indeed the "last-line" drugs

available to treat this disease. In the case of gonorrhea, if complete resistance emerges, treatment options would be virtually absent and this inability to treat patients could lead to increased transmission and a rise in potentially debilitating co-morbidity (though would likely have a limited effect on mortality). In contrast, there are not even comparable "last-line" drugs left for certain other antimicrobial resistant threats like CRE (see below).

Carbapenem-resistant Enterobacteriaceae (CRE) – CREs are nearly pan-resistant pathogens that include *E. coli* and *K. pneumoiae*. While CRE infections occur most commonly in healthcare settings, these pathogens also circulate in community settings raising the concern that these resistant infections could be transmitted outside of hospitals as well. Because CRE infects the GI tract and does not always manifest symptoms, silent carriers can spread CRE once they are hospitalized. Mortality rates of serious infections in a hospital setting are between 30% and 50%.

Who works on this?

The Centers for Disease Control and Prevention (CDC)

The CDC is working in many areas to address emerging problems in antimicrobial resistance, including increasing laboratory capacity to detect resistance, expanding surveillance programs, deploying effective prevention interventions to limit the spread of AR infections, and better communicating surveillance data to the public to ensure it is adequately informed. In the past, the public health threat of drug resistance was mitigated by the availability of new antibiotics. More recently, increases in the number and types of bacteria demonstrating high-level resistance and the marked decline in the availability of new antibiotics requires that drug resistance be addressed through comprehensive programs. Four of CDC's eight National Centers conduct work related to antimicrobial resistance; these activities fall within a number of different budget lines.

The Interagency Taskforce on Antimicrobial Resistance

The Interagency Taskforce, on which Dr. Patel and Dr. Solomon serve, is co-chaired by the Food and Drug Administration (FDA) and the National Institute of Health (NIH) as well as the CDC, and has members from several other government agencies. Each agency has a broad portfolio of activities addressing public health needs in antimicrobial resistance. For example, the FDA is streamlining the process for drug development and acting to limit antimicrobial use in the food supply. The NIH is establishing a new clinical trials network to evaluate and identify how drugs we do have can be used effectively while preventing resistance from emerging. CDC is working in many areas to address emerging problems in antimicrobial resistance, including increasing laboratory capacity to detect resistance, expanding surveillance programs, and better communicating surveillance data to the public to ensure it is adequately informed.

Activities focused on combating the spread of antimicrobial resistance are embedded within a wide variety of programs and initiatives within the many Federal agencies addressing this complex problem.

Other groups

There are a significant number of nonprofit advocacy organizations, NGOs, and professional organizations that deal with these issues. Some specific organizations that were mentioned during this discussion were:

- Infectious Disease Society of America (IDSA)
- Alliance for Prudent Use of Antibiotics (APUA)
- Pew Charitable Trusts' Antibiotics and Innovation Project
- Keep Antibiotics Working

Challenges

The public does not currently perceive antibiotic resistant pathogens as a major threat to the extent of some other public health problems, so there is not presently a sufficient sense of urgency around this issue. This lack of popular support is compounded by a lack of political support among governments who are often not tuned to the urgency of the problem. Recently, the chief medical officer in the United Kingdom issued a report in which she emphasized the role that a lack of political attention plays in sustaining this unprecedented public health challenge. "Political support" means not only adequate funding, but also prioritizing the threat of antimicrobial resistance within the context of other public health priorities.

Solutions

Extraordinary work on the prevention side is necessary, including significant investment in infrastructure before emergency strikes. Potential philanthropic opportunities in this area may involve supporting studies to determine the most cost-effective strategies for prevention, which could then be applied to save resources in the long run. Prevention is effectively local, and because of the risk of resistance developing in one region before spilling over to another, the local level is essential for broader safety.

One particularly important prevention strategy is to ensure that antibiotics are used only when necessary, and, when necessary, are used appropriately, in order to slow the development of AR. Another response focuses on measures to prevent spread of the antimicrobial resistant diseases from one individual to another. In hospitals, this means infection control; in other contexts, it may be accomplished by using immunizations or good personal hygiene. The interventions in these areas would be education campaigns in the community around better hygiene and awareness of the risks of antibiotics.

Although drug development alone cannot fully address the problem of AR, developing new models for investment and development of new antimicrobials is essential. There are some drugs in the pipeline right now, but that pipeline needs to be fully re-stocked for the long term.

Although not a solution in the short-term, vaccines could be highly impactful interventions. For instance, the introduction of a vaccine for the bacteria causing pneumococcal pneumonia has helped reduce the incidence of AR in those infections.

Other organizations and individuals to speak with

The Infectious Disease Society of America (IDSA)- **Amanda Jezek**

Alliance for Prudent Use of Antibiotics (APUA) – **Stuart Levy** is a globally recognized expert on this issue.

Pew Charitable Trusts' Antibiotics and Innovation Project– **Allan Coukell**

Center for Disease Dynamics, Economics, and Policy - **Ramanan Laxminarayan**

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