

Part I. The Global Antibiotic Resistance Partnership (GARP)

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The global problem of antimicrobial resistance is particularly pressing in developing countries, where the infectious disease burden is high and cost constrains the replacement of ineffective antibiotics with newer, more expensive ones. Gastro-intestinal, respiratory, sexually transmitted and hospital-acquired infections are leading causes of disease and death in the developing world; their management is compromised by the appearance and spread of resistance. Actions taken now can slow the spread of resistance without impairing access to antibiotics when they are appropriate. These, as well as extending access where it is currently inadequate, are the ultimate aims of the Global Antibiotic Resistance Partnership (GARP).

Drug resistance is usually viewed as a medical problem, but the causes of resistance – at least the pace of escalation – are also cultural and economic. Patients, physicians, veterinarians and medicine retailers have little motivation to weigh up the negative impact of their use of antibiotics on others. This is especially the case where alternative treatments are few or non-existent and the consequences of inappropriate use are likely to occur in the future. Standard government responses, such as increasing surveillance and launching public information campaigns on the hazards of resistance, while a necessary part of an overall policy response, are unlikely to work on their own. To be effective, policy solutions must alter incentives for patients, physicians and others in the health care system to act in society's best interests. Evaluating policy solutions involves understanding the epidemiology of infectious diseases in populations and making sure that changes are beneficial, or at least not detrimental, immediately *and* in the longer term. Research evaluating focused, context-specific policy solutions is a first step. Translating these policy solutions to policy action is the second.

Antibiotic resistance does not top any list of national problems, and the strategies proposed should not drain resources from more pressing concerns. At its best, controlling antibiotic resistance should not involve extra cost. In the long run, and maybe even in the shorter term, it is likely to save money and save lives.

Country-specific goals

Drivers of antibiotic resistance are multifaceted and measures to address them must consider the specific conditions of a country, including the health care system, the socio-economics of the populace, the strength and reach of regulatory authorities, and even geography. GARP, funded through a grant from the Bill & Melinda Gates Foundation, aims to define policy solutions and opportunities by investigating the particular contexts of four target countries: India, South Africa, Kenya and Vietnam. In each country, national working groups, with support from the Center for Disease Dynamics, Economics & Policy (CDDEP), have developed a set of strategies tailored to local conditions, based on the information compiled and analysed in this report. The strategies encompass two basic approaches: first, to target the use of antibiotics in human health and livestock production better; and second, to reduce the demand for antibiotics by reducing the incidence of infections in the hospital and community, and on the farm. The strategies will be discussed and debated by a wide range of interested parties from government and civil society near the end of the process. A subsequent phase will involve implementation of the agreed-upon policy strategies in the four countries, and extension to other countries.

GARP inaugural meeting

GARP-South Africa was launched at the Spier Estate in Stellenbosch on 8 - 9 February 2010. Professor Adriano Duse, Chair of the GARP-SA Working Group and Director of the Department of Clinical Microbiology of the University of the Witwatersrand, led a gathering of 40 experts from the clinical, research, pharmaceutical, veterinary and policy spheres, all with an interest in preserving the effectiveness of antibiotics for the greater good. Professor Keith Klugman of Emory University, chair of the GARP International Advisory Group, outlined the scope of the problem of antibiotic resistance globally and in sub-Saharan Africa, while the remaining sessions focused on levels of antibiotic resistance at particular sites, national surveillance efforts, and interventions aimed at promoting rational antibiotic use.

Drs Adrian Brink and Colleen Bamford described strong initiatives aimed at curbing antibiotic resistance in both the public and private sectors. Dr Anne von Gottberg presented on surveillance for meningitis and respiratory pathogens, Dr Karen Keddy on enteric pathogens, and Professors Anwar Hoosen and David Lewis on antibiotic resistance in patients with sexually transmitted infections. Mr Andy Zoepke, from the South African medical device company, Smith & Nephew, took the meeting in a different direction, exploring the role of topical antibiotic preparations for wound care and burns. These products provide substitutes for systemic antibiotics, reducing exposure of commensals and thus the unnecessary spread of resistance elements. A national surveillance system, the fate of which is not yet known, was proposed and described by Dr Olga Perovic. Professor Sabiha Essack described her work documenting increasing levels of antibiotic resistance from district to regional to tertiary hospitals in KwaZulu-Natal. These findings are discussed in part IV of this report.

The importance of antibiotic use in animals in the development and spread of antibiotic resistance in humans is a perennial topic for debate. Dr James Oguttu reported relatively high levels of resistance to a range of antibiotics (including quinolones not used in poultry) in *Escherichia coli* organisms from the gastro-intestinal tracts of slaughtered broilers raised in factory farm conditions that included antibiotic use. Dr Maryke Henton expanded on antibiotic use in other farm animals (and provided evidence to dismiss aquaculture use as a problem), and Dr Jackie Picard ended the veterinary session with a look at 2 years of recent surveillance data, showing high levels of resistance to a variety of antibiotics of human significance. The data from this session are presented in part VI of the report.

Presenters also discussed the pharmaceutical industry and interventions to reduce bacterial disease and resistance. A window into the antibiotic market was opened by Mr Deon Benjamin from Sanofi-Aventis, the largest seller of these products in South Africa by sales value. Sales appear to be increasing for both patented and some generic antibiotics, with more detail promised to separate out effects of price and volume. Vaccines that prevent infectious diseases clearly save antibiotics, and the status of vaccines deployed, on the shelf and in development, was reviewed by Professor Anwar Hoosen. Dr Gary Kantor spoke about Best Care...Always! (BCA), a national campaign recently begun by Discovery Health, and its emphasis on infection-control practices and 'antibiotic stewardship' by hospital physicians as elements of the campaign. Completely voluntarily, 137 hospitals have signed on for at least one intervention. If successful, BCA can provide

a platform for extending work on reducing antibiotic resistance. Parts III and VII review information from these discussions.

Finally, the meeting reviewed the work of other GARP (India, Vietnam, Kenya) and sub-Saharan African (Ghana, Uganda) countries, as well as activities of the Alliance for the Prudent Use of Antibiotics (APUA) and ReAct, represented by Drs Anibal Sosa and Otto Cars, respectively. In most respects, South Africa has a head start, at least in information.

The meeting closed with a discussion on the next steps, concluding that the first priority was consolidating what is and is not known about antibiotic resistance. The importance of forming a GARP-SA Working Group was also highlighted. The product of these decisions is found in this report – a situation analysis on antibiotic use and resistance in South Africa, authored by the GARP-SA working group.

Global efforts

In addition to country-specific work, GARP is developing tools and conducting research in support of a global effort to understand,

quantify and address antibiotic resistance. With collaborators, CDDEP is working on methodology to estimate the health and economic burden of disease, including mortality, attributable to antibiotic resistance. Surprisingly, the required methods do not yet exist. The aim is to develop an approach that can be used in all countries of the world with a minimal amount of information.

A second major thrust is developing a mathematical model of pneumococcal disease – ‘PneuMOD’ – that can be used to examine strategies for curbing the evolution and spread of antibiotic resistance and to compare modalities. At the heart of most ideas for controlling antibiotic resistance is the notion that the way antibiotics are used and their level of use in a population drive the development and spread of antibiotic-resistant organisms. Mathematical models play a useful role in highlighting policies that offer the greatest potential, even where information is insufficient to complete the analyses. At a minimum, the information needed can be identified and the necessary mechanisms set in motion.