Antimicrobial Resistance
in Developing Countries
Antimicrobial Resistance in Developing Countries

Foreword by Thomas F. O’Brien
Introductory Preface by the Editors
Guest Preface by Stuart B. Levy
Avoiding infection has always been expensive. Some human populations escaped tropical infections by migrating into cold climates but then had to procure fuel, warm clothing, durable housing, and crops from a short growing season. Waterborne infections were averted by owning your own well or supporting a community reservoir. Everyone got vaccines in rich countries, while people in others got them later if at all.

Antimicrobial agents seemed at first to be an exception. They did not need to be delivered through a cold chain and to everyone, as vaccines did. They had to be given only to infected patients and often then as relatively cheap injectables or pills off a shelf for only a few days to get astonishing cures. Antimicrobials not only were better than most other innovations but also reached more of the world’s people sooner.

The problem appeared later. After each new antimicrobial became widely used, genes expressing resistance to it began to emerge and spread through bacterial populations. Patients infected with bacteria expressing such resistance genes then failed treatment and remained infected or died. Growing resistance to antimicrobial agents began to take away more and more of the cures that the agents had brought.

It then proved to be much more resource-intensive to keep patients from becoming infected with and failing treatment for drug-resistant bacteria than it had been to deliver the drugs that had caused the problem. Resource-limited countries that had managed to make antimicrobials available to their infected patients could not afford to do all the things that were then needed to manage the antimicrobial resistance that resulted.

Antimicrobial resistance seems a function of how many bacteria have been exposed to antimicrobials, for example, so treat only infections that antimicrobials cure for as long, but only as long, as needed. Treating an infecting germ with a drug it resists not only fails but also makes that resistant germ spread, so treat only with the drug that can still kill it. Resistant germs spread to others, so identify them and interrupt their spread.

Each of these ways to control resistance costs much more than it had cost to distribute the boxes of pills and injectables that had begun the resistance. Expensive microbiology laboratories in rich countries test whether the germ
infecting any patient is of a kind that antimicrobial agents kill, and if so which agent could still kill it. Those countries then make that agent promptly available by keeping ubiquitous costly stocks of all agents.

Adequate housing and support for personal hygiene may also minimize interpersonal exchange of resistant bacteria in communities of developed countries, and clean water limits their ingestion. Many developed countries feed large amounts of resistance-selecting antimicrobials to food animals, however, but they do ban their residuals in food or their use to preserve food. Less is known about these in developing countries.

In both rich and poor nations, resistant bacteria cause their most frequent, costly, and deadly infections in hospitals and intensive care units. In the rich nations, however, disposable items come in truckloads from warehouses to help nurses, and well-organized infection control teams slow the spread of resistant bacteria between private rooms, while the poorer struggle with shortages of reusable items and one hand-washing sink for an open ward.

Further promoting resistance in resource-limited countries is a cruel underlying inequity. They have more of the infections that richer countries have, e.g., pneumococcal, AIDS, meningococcal, trauma-related, tuberculosis, shigellosis, plus many they do not have, such as typhoid, malaria, and cholera. These require more valid antimicrobial use and also elicit more inadvertent misuse by complicating diagnosis, thus making resistance worse.

In a developed country, a sick febrile patient has prompt laboratory testing and compiled local test results to predict diagnosis and best therapy immediately, with confirmation or adjustment in a few days. In an undeveloped country, there will be fewer or no tests or compiled results, fewer antimicrobials available for often blind therapy of more possible diagnoses and so more chance of treatment failure and further spread of resistance.

For all of these reasons, the management of antimicrobial resistance in the resource-limited world faces special challenges and appears to need tools that are less resource-intensive than those that have evolved in the developed world. Affordable strategies and tools to manage antimicrobial resistance in less-resourced regions may need special effort to develop, but possible examples can be considered.

Microbiology laboratories in developed countries, for example, using supply-intensive instruments and highly trained and salaried staff for a huge menu of tests, become the model of excellence. Attempts to duplicate them in a developing country, however, may deplete the pool of trained professionals, outrun supply sources, and price tests so high that few patients can afford them and they become, after all, largely unused.

An alternative model might be developed in which a limited set of inexpensive essential tests using a common list of supplies could be performed by less-extensively but specifically trained workers supported by a web-based support and oversight system. This would not replace any currently functioning laboratories but supplement them at the next lower tier of medical facilities that now have no laboratories.
Similarly, growth of the Internet may provide cheap ways to provide updated information on currently prevalent infections and their drug resistances, as locally compiled data now do in developed countries, and use it to update and disseminate treatment guidelines. Every microbial test result that can be produced in a resource-limited country should be captured and analyzed to help overview its problems and update responses to them.

Each of the tools now used to control antimicrobial resistance might thus be reviewed with developing world caregivers to explore ways in which they could be modified to be cost-effective in their circumstances. Might not hospitals that cannot afford a team of infection control nurses, for example, have access to special training materials and information support to help their existing nursing staff carry out some of their functions?

Such a rethinking of the tools and strategies for controlling antimicrobial resistance to improve their application in the resource-limited world will not happen spontaneously. It will require concerted and funded effort by specialists from both worlds. Gaining support for it may prove difficult, moreover, since the whole problem of antimicrobial resistance has repeatedly slipped from the attention of public health and other funding agencies.

The first step in such a needed initiative is to recognize that antimicrobial resistance is a different and more deadly problem in the developing world and to elaborate in detail all of the aspects of that problem. That is what this book does and why it is important. It can be seen as both an informative work and a basis for action.

Boston, Massachusetts

Thomas F. O'Brien
Introduction

This book was mainly compiled while we quietly celebrated the 80th anniversary of the discovery of penicillin, a fact that formally inaugurated the “era of antibiotics” and it will become available during the celebration of the 150th anniversary of Darwin’s *On the Origin of Species* (and the 200th anniversary of Darwin himself). These two milestones remind us, on the one hand, that we have been witnesses to the evolution of bacteria and other microorganisms from mostly susceptible to mostly resistant to drugs and, on the other, how little to heart even those of us who are not blinded by superstition have taken the basic notions of genetic change and selection. But in addition to the formidable evolutionary forces behind resistance, and the equally formidable neglect in putting our knowledge of it to work, developing countries have to deal with a wide variety of peculiar conditions that foster the emergence and spread of resistant germs. These aggravating factors range from malnutrition to lack of medical services and inadequate medical training and then to counterfeit drugs and incompetent governments. These traits are not exclusive to poor countries, but coalesce in the worst possible ways here. There is an exceptional need for rigorous data on the scale and spread of antimicrobial resistance, as well as for effective means for sharing the data and using it as an evidence base for effective containment strategies. In developing countries where resistance is a prime issue, data are least available, evidence is rarely collated, and containment interventions have been poorly implemented. Indeed, the validity of many proposed interventions in developing countries remains untested.

In putting together this book, we tried to assemble an overview of the magnitude, causes, consequences, and possible actions on microbial resistance in developing countries. If the book appears brief, it is because we know little about this particular side of the problem, as one of the main features of poor countries is insufficient scientific and medical research, and of opportunities to publish the scarce findings in “international” scientific journals, which routinely dismiss papers from developing countries because results are “only of local interest”. Therefore, in addition to presenting information and ideas, the book explicitly highlights gaps that represent opportunities for research and policy innovation. High among our priorities has been to obtain data and critique
from scholars who work not on but in developing countries and to include input from a variety of geographic regions. The picture that emerges, although incomplete, allows the reader to assess the current and emerging threats, the distinct issues that influence the evolution of resistance, the main problems caused by resistance, and the potential avenues to tackle at least some of this complex panorama.
Preface

The problem of antimicrobial resistance knows no boundaries. Drug-resistant microbes of all kinds can move among people and animals, from one country to another—without notice. From the early stages of identifying and discovering antibiotic resistance, the problem was clearly severe in developing countries where drug availability was limited and resistance was high. However, it has been in the developed world, with its abundant resources, where resistance has been more vigorously studied. Therefore, it is of some interest that out of a 1981 meeting in the Dominican Republic, where representatives from developing as well as industrialized countries assembled, came an Antibiotic Misuse Statement declaring the consequences of inappropriate use of antibiotics, namely the emergence and spread of antibiotic resistance. The response to the wide circulation of the statement led to the establishment of the Alliance for the Prudent Use of Antibiotics (APUA). This international organization continues today, 27 years later, to champion increased awareness and appropriate antimicrobial use so as to curtail drug resistance and “preserve the power of antibiotics.” APUA fosters partnerships and communications among people in both developed and developing countries to improve antibiotic accessibility and reverse resistance.

This book, edited by Drs. Anibal Sosa and Denis Byarugaba and their associate editors, is unique in focusing on antimicrobial resistance as it relates to and threatens developing countries. It is curious that it has taken this long to produce a book dedicated to antibiotic resistance in developing parts of the world. One can ask “why?” since resistance is and has been so common there. In fact, whereas resistance has been addressed for the past four decades by experts in the industrialized world, studies describing the problem and the public health situation in the developing world have lagged behind. Although we have learned much from studies of the genetics and molecular biology of the problem from investigations in industrialized countries, it is in developing countries where more studies and efforts are needed. With travel encouraging the transport of microbes, the information in this book will have wide-sweeping benefit, not only for developing countries but also for the world at large. Surveillance of resistance and the prevention of resistance need attention on a worldwide basis. Improving antibiotic use requires a global effort.
One hopes that bringing an organized focus to the problem in developing nations will help efforts to improve accessibility to effective antibiotics and reduce resistance in previously neglected regions and countries of the globe. And so it is relevant that there are chapters in this book devoted to a particular country or region in which resistance poses a life-threatening challenge. We read about treatment failures and resistance challenges in Asia, Africa, and Latin America. The microbes under discussion in the book are not confined to bacteria, but encompass HIV, fungi, and parasites, including the agents of malaria and trypanosomiasis.

Lessons learned in one country can help others. What is needed is a clear idea of what the magnitude of the problem is and what efforts are being made to address it. The focus needs to be on the antimicrobial—its use and its availability—as well as the presence of resistant organisms and their resistance genes. Spread of resistance traits and resistant organisms is a further complicating feature of the resistance problem.

The chapter on the economics of resistance opens the potential for important cost analysis comparisons in this part of the world with studies in hospitals and health-care systems in industrialized countries. Cost is an important obstacle to change but needs to be assessed if we are to see change. Other chapters include discussions of the pivotal positive and negative roles of the pharmaceutical industry in delivering and marketing drugs in the developing world. Quite clearly, greater recognition of the needs and objectives of the stakeholders is critical to an understanding of and a cooperation in improving antibiotic availability and the decreasing frequency of resistance in these parts of the world.

The authors of these chapters are each distinguished in their own right and internationally recognized. The subjects are broadly inclusive of different infectious diseases, including those of the respiratory, urinary, and gastrointestinal tracts. The role of vaccines in helping to control organisms and avoid the overuse of antibiotics is critically important and discussed.

It is time, and timely, to focus attention on the developing countries in terms of helping people understand their role in reversing the global resistance problem. This book is an important step and will join other efforts, at both the government and nongovernment levels, including those of such organizations as the Alliance for Prudent Use of Antibiotics, the World Health Organization, the Pan American Health Organization, and others, to bring attention and potential solutions to the antimicrobial resistance problem as it presents in developing countries. The book shows how the problem has similar causes and the solution has similar goals as those in the industrialized countries. Drug resistance has no geographic preference—it compromises infectious disease treatments in countries throughout the world.

Boston, Massachusetts

Stuart B. Levy
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