

SITUATION ANALYSIS AND RECOMMENDATIONS

Antibiotic Use and Resistance in Mozambique



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ABBREVIATIONS

APUA	Alliance for the Prudent Use of Antibiotics
CA	Centro de Abastecimento (Supply Center)
CDDEP	Center for Disease Dynamics, Economics & Policy
CISM	Centro de Investigação em Saúde de Manhiça (Manhiça Health Research Centre)
CIMed	Centro de Informação de Medicamento (Drug Information Center)
CMAM	Central de Medicamentos e Artigos Médicos
CMR	Chronic Malnutrition Rate
DAF	Direcção de Administração e Finanças
DNSV	Direcção Nacional de Serviços de Veterinária
DPS	Direcção Provincial de Saúde
DNAM	Direcção Nacional de Assistência Médica
DHS	Demographic and Health Survey
DDS	District Health Directorate
FBO	Faith-based Organizations
GARP	Global Antibiotic Resistance Partnership
GDP	Gross Domestic Product
HAI	Healthcare-Associated Infections
HCM	Hospital Central de Maputo (Maputo Central Hospital)
HIV	Human Immunodeficiency Virus
MDG	Millennium Development Goals
MICS	Multiple Indicator Cluster Survey
MoH	Ministry of Health
NGO	Non-governmental Organization
NHS	National Health System
PEPFAR	President's Emergency Plan for AIDS Relief
NCBI	National Center for Biotechnology Information
SITAN	Situation Analysis
TB	Tuberculosis
UEM	Universidade Eduardo Mondlane (Eduardo Mondlane University)
WHO	World Health Organization
WHO/AFRO	World Health Organization Regional Office for Africa
WHONET	Windows-based Database Software

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Foreword

Antibiotic resistance impairs our ability to treat common bacterial infections and is a major threat to public health, especially in developing countries where the burden of infectious diseases is enormous. Excessive use of the few available antibiotics adds to the antibiotic resistance problem, increasing morbidity and increasing costs to the National Health Service of treating resistant infections.

Although the problem of antibiotic resistance is global, and has been recognized in the scientific community and by many international organizations, there is still a lack of political commitment from most national governments, which have the primary responsibility for developing and implementing policies and action plans to mitigate antibiotic resistance.

In Mozambique the government is currently making a great effort to consolidate the pharmaceutical sector, with a focus on ensuring access to quality healthcare, strengthening regulation and inspection, and taking into account the challenge of significant growth in medicine imports, particularly antibiotics.

Increasing importation and easy access to medicines increases the pressure on government to improve management and inspection systems to protect human health. Counterfeit and substandard medicines, whether dispensed by a physician or purchased by a mother in an informal market, can put health at risk and must be factored into government programs.

In order to ascertain the extent of antibiotic resistance and use in the country, the Ministry of Health joined with a multidisciplinary working group, GARP-Mozambique, in August of 2012 to begin the hard task of developing national policy to protect Mozambique's citizens against the ravages of antibiotic resistance.

GARP-Mozambique objectives are:

1. To assess the current status of antibiotic use, quality and resistance levels in the country;
2. To review relevant research in order to identify and fill research gaps, as well as to obtain reliable data; and
3. Finally, to recommend national policies for the rational use of antibiotics and to prevent the emergence of antibiotic-resistant bacteria.

GARP-Mozambique was established in partnership with the Center for Disease Dynamics, Economics & Policy (CDDEP), based in the United States and India.

Today we have the honor and privilege of presenting this report, the Situation Analysis and Recommendations on Antibiotic Use and Resistance, produced by the GARP-Mozambique Working Group. This report is an important contribution to the country and the world, and will be instrumental in the development of strategies to strengthen the national health system and to ensure the rational use of antibiotics and the preservation their power.



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Acknowledgments

The Global Antibiotic Resistance Partnership (GARP)-Mozambique team, in partnership with the Center for Disease Dynamics, Economics & Policy (CDDEP), has produced this report as part of a solid commitment to develop actionable policy proposals to tackle antibiotic resistance and improve appropriate antibiotic access. It is the result of a thorough review of published and unpublished data on antibiotic resistance and a long internal consultation effort that engaged academic scientists, health professionals and other stakeholders within Mozambique.

The preparation of this situation analysis (SITAN) on antibiotic resistance has involved many people and, as the authors are unable to thank everyone individually, the omission of their names should not be taken as an oversight of their contribution. However, the authors would specifically like to thank Dr. Nazira Valí Abdula and Dr. Mouzinho Saide, the Minister and Deputy Minister of Health in Mozambique, respectively, as well as Dr. Antonio Assane, Deputy National Director of Medical Assistance, for their immeasurable support for the formation and recognition of the GARP working group on antibiotic resistance in Mozambique.

Many thanks also to CDDEP for their financial and technical support, for helping GARP-Mozambique get off the ground and for bringing GARP-Mozambique into the larger GARP network.

We would like to extend a special thanks to all the national experts who participated in the inaugural GARP-Mozambique meeting, which took place on August 2-3, 2012 in Maputo, as well as to the participants of the second GARP working group meeting, on March 21, 2013, for their identification of research needs and gaps and recommendations of priorities to decelerate antibiotic resistance. Finally, special gratitude is also extended to all the investigators and co-authors who contributed to development of this SITAN.

Methods and Purpose of the Situation Analysis

This situation analysis on antibiotic resistance in Mozambique is based on a compilation of existing data, including peer-reviewed articles identified through web-based literature searches, policy documents, official reports and health facility log books. In addition, consultations were held with leaders of prominent institutions involved in antibiotic access and use, such as microbiology laboratories in hospitals and universities, the national veterinary school, research institutions, drug regulatory institutions and pharmacies. GARP-Mozambique is responsible for the contents of this situation analysis.

This document has three primary aims. First, to capture and document the available national data on antibiotic resistance with the goal of increasing awareness—among practitioners, researchers, policy makers and the public—about the importance of antibiotic resistance as both a national and global threat to human health. Second, to identify current knowledge gaps and corresponding research priorities. Finally, to draw upon local experience to develop evidence-based recommendations for consideration by policy makers.

Part I. Executive Summary

The discovery of antibiotics in the twentieth century has transformed the treatment of infectious diseases and the world's population structure by vanquishing deaths from common illnesses, especially in childhood. However, acute respiratory infections and diarrheal disease remain the leading causes of death for children under five worldwide because the benefit of antibiotics has not been shared universally. Antibiotic treatment can prevent most of these needless deaths, but only if antibiotics remain broadly effective. The potential for the growth of resistance to antibiotics has been known since Alexander Fleming first discovered penicillin in the 1920s.

Increased use of antibiotics in humans and animals has led to the development of resistance, reducing the effectiveness of drugs against common bacterial infections. Each time an antibiotic is used—both appropriately and inappropriately—resistance increases. When antibiotics are prescribed by health workers without a confirmed diagnosis or are purchased by patients without a prescription for an illness that does not require antibiotics, they can further increase the resistance burden without providing any benefit. The World Health Organization recently declared that the world is headed towards a post-antibiotic era, and the issue is now a major concern worldwide and for Mozambique.

While little information is available on resistance rates in Mozambique, the few studies that have been conducted have revealed high levels of resistance to the common drugs used to treat serious bacterial illnesses. To address the growing resistance burden, the Global Antibiotic Resistance Partnership (GARP)-Mozambique aims to improve knowledge on the current state of antibiotic use and resistance and to develop sustainable and actionable policies to reduce resistance rates. To achieve these goals, access to antibiotics must be increased while their inappropriate use is curbed, in order to ensure that these life-saving drugs maintain their ability to reduce human morbidity and mortality.

About GARP:

The Global Antibiotic Resistance Partnership (GARP) is a project of the Center for Disease Dynamics, Economics & Policy (CDDEP) that facilitates the development of actionable policy proposals on antibiotic resistance by and for low- and middle-income countries (LMICs). With a grant from the Bill & Melinda Gates Foundation (BMGF), GARP supports the creation of multi-sectorial national-level working groups whose mandate is to stimulate specific research and develop evidence-based proposals to encourage the introduction of measures to preserve antibiotic effectiveness, slow the spread of antibiotic resistance and improve antibiotic access.

The first phase of GARP took place from 2009 to 2011 and involved four countries: India, Kenya, South Africa and Vietnam. Phase one culminated in the 1st Global Forum on Bacterial Infections, held in October 2011 in New Delhi, India. In 2012, phase two of GARP was initiated with the addition of working groups in Mozambique, Tanzania, Nepal and Uganda.

The GARP-Mozambique working group is the first multi-disciplinary, multi-sectoral group in the country to consider the problem of antibiotic resistance and to prioritize recommendations for public health policies.

National Burden of Disease and Resistance Rates

Mozambique has experienced strong economic growth in recent years, accompanied by a drop in maternal and under five mortality rates. However, life expectancy at birth remains low, in part due to the large burden of infectious diseases. The under-five mortality rate is largely driven by malaria, acute respiratory infections (ARIs), meningitis, sepsis and HIV/AIDS, several of which can be successfully treated with antibiotics.

Major contributors to the burden of disease include acute lower respiratory tract infections such as pneumonia; meningitis and bacteremia; and enteric infections such as *Escherichia coli*, non-typhoidal *Salmonella*, *Shigella* and *Vibrio cholerae*. The true burden of these diseases and their resistance rates remains largely unknown, but the available evidence points to high rates of resistance for all these diseases to first-line treatments. Improving surveillance and diagnostics for these diseases would help to provide an improved evidence base for the development of policies addressing resistance. The following section presents an outline of the research on antibiotic resistance that has been conducted in Mozambique. Complete details can be found in Section III.

Respiratory Tract Infections and Invasive Bacterial Diseases

Many Bacterial infections are a leading cause of death in young children in Mozambique. Among neonates, severe infections such as pneumonia, sepsis and diarrheal diseases are among the leading causes of death, and pneumonia is the third-largest cause of death of children under five. Common invasive bacterial diseases include bacteremia, pneumonia, meningitis and sepsis.

Many respiratory tract infections are caused by viral diseases and are resolved without any type of medical treatment. Pneumonia is a serious and often fatal lower respiratory tract infection that can be caused by many pathogens, including viruses and bacteria. Bacterial pneumonia is appropriately treated with antibiotics.

Studies have found high levels of resistance of bacterial pneumonia pathogens to penicillin and cotrimoxazole, the most commonly used first-line antibiotics for these infections. In published studies, resistance ranged from 37 to 89 percent for cotrimoxazole and from fully susceptible to more than 50 percent resistant for penicillin. The widespread use of cotrimoxazole as a first-line treatment for acute respiratory infections as well as to prevent opportunistic infections in people with HIV/AIDS also contributes to high rates of resistance.

Bloodstream infections, where bacteria enter the blood, include bacteremia and sepsis. These conditions are major contributors to the under-five mortality burden. The main pathogens responsible for bloodstream infections are *Haemophilus influenzae type b* (Hib) and *Streptococcus pneumoniae*, though vaccines for these diseases have been recently introduced.

Community-acquired bacteremia is a major contributor to the neonatal health burden, and studies have revealed increasing rates of resistance of various bacteria to chloramphenicol, the first-line treatment, between 2001 and 2006, reaching 92 percent of *E. coli* isolates and 94 percent of *H. influenzae* isolates. High rates of multi-drug resistance were also observed in many pathogens, ranging from 5 to 92 percent.

Bacterial meningitis is another major contributor to under-five mortality in Mozambique. Bacterial meningitis is treatable with antibiotics such as chloramphenicol and penicillin G with gentamicin, but high rates of resistance have been reported to all these drugs. Resistance ranged from 39 percent to chloramphenicol to 52 percent to ampicillin or penicillin. A study focusing on *H. influenzae* isolates found that resistance had increased to both chloramphenicol and ampicillin between 2001 and 2005, and that resistance to

cotrimoxazole was also high during this period. Mortality rates were much higher for those with resistant compared to susceptible strains.

Enteric Infections

Diarrheal diseases are the second leading cause of death in children under five worldwide. They are caused by a variety of pathogens, including bacteria, and detecting the source of the infection requires good diagnostic facilities. While most diarrheal diseases can be treated with simple oral rehydration therapy, severe infections can be fatal and require antibiotic treatment. The primary bacterial infectious agents in Mozambique include *E. coli*, non-typhoidal *Salmonella*, *Shigella* spp. and *V. cholerae*. Non-typhoidal *Salmonella* is highly prevalent in children presenting with bacteremia.

Resistance of all these pathogens to first-line antibiotics, including chloramphenicol and ampicillin, was found to be high across all studies. Multi-drug resistance was also detected in a high percentage of isolates.

In one study, 96 percent of *E. coli* isolates were resistant to ampicillin. Non-typhoidal *Salmonella* showed high rates of resistance to chloramphenicol and ampicillin. Similarly, *Shigella* spp. showed resistance of over 50 percent to both ampicillin and chloramphenicol, with a high level of multi-drug resistance. Resistance rates of *V. cholerae* isolates to chloramphenicol, cotrimoxazole and tetracycline ranged from 58 to 97 percent in one study.

Overall, quinolones, 3rd generation cephalosporins and fluoroquinolones were found to be effective against most pathogens, but these drugs are more expensive and may not be an accessible treatment option for all patients.

Antibiotic Use and Resistance in Animals

Very limited information is available on the use of antibiotics and related resistance patterns in animals in Mozambique. Antibiotics for food-producing animals are generally used for disease prevention and treatment, in addition to for growth promotion, particularly in chickens. A variety of antibiotics are available for use in animals but no pharmacovigilance is currently conducted. A National Veterinary Council is being established to regulate the Vet Act, and a draft document regulating the registration of veterinary medical products was recently submitted to the Ministry of Health (MoH). Use of antibiotics in aquaculture is regulated by the Ministry of Fisheries and the National Plan for the Control of Veterinary Antibiotic Residues and Environmental Contaminants.

Strategies to Reduce Antibiotic Resistance

Reducing resistance requires limiting antibiotic use while ensuring access for those who need treatment. The six primary strategies to improve antibiotic use at the national level are:

1. Reduce the need for antibiotics through public health measures;
2. Improve hospital infection control and antibiotic stewardship;
3. Rationalize antibiotic use in the community;
4. Reduce antibiotic use in agriculture;
5. Educate health professionals, policy makers and the public on sustainable antibiotic use; and
6. Ensure political commitment to meet the threat of antibiotic resistance.

At the global level, the development of new antibiotics, alternatives to antibiotics and new diagnostics for bacterial and other infectious diseases is an important aspect of curbing antibiotic resistance, and these efforts should be increased.

Reduce the need for antibiotics through public health measures

Reducing the burden of disease can reduce the need for antibiotics. Every episode of infection averted equals a savings of antibiotic treatment. Decreasing both the viral and the bacterial disease burden can have an impact, as many viral diseases are mistakenly treated with antibiotics and some, especially influenza, predispose to secondary bacterial infections. Increasing immunization coverage and improving access to clean water, food, nutrition and sanitation are the most obvious routes to disease reduction.

While vaccination coverage for many childhood diseases is relatively high in Mozambique, at 74 percent, one-fourth of the population is still not receiving protection against preventable infections. Recently, both Hib and pneumococcal vaccines have been introduced but national coverage rates are still below 80 percent. Increasing vaccine coverage should reduce the disease burden, particularly for children under five. Rotavirus vaccination to prevent diarrhea is scheduled to start in 2015.

GARP-Mozambique will not specifically target the important public health improvements in water, food, nutrition and sanitation that are critical for better health, because they have their own constituencies and programs. They are, however, high priorities.

Improve hospital infection control and antibiotic stewardship

Hospitals are notoriously dangerous places for the spread of infections, including multi-drug resistant infections. Often these infections are transmitted inadvertently through health care providers as they move from patient to patient. Infection prevention and control (IPC) programs in hospitals can decrease transmission through simple interventions such as promoting hand washing with soap or the use of alcohol hand sanitizer between patients. Creating antibiotic stewardship programs in hospitals can also improve practices. Finally, the establishment of sentinel surveillance or point prevalence systems for antibiotic resistance can provide data to guide clinical decisions and policies at the hospital level.

The MoH currently has an IPC program in place in several hospitals but the program lacks consistency in quality between sites.

Antibiotic stewardship programs (ASPs) in hospitals aim to improve the correct treatment of bacterial infections with appropriate antibiotics, improving patient outcomes and reducing overall antibiotic use. ASPs also have the potential to reduce rates of antibiotic resistance. The components of ASPs vary, including the use of formularies, prescription reviews, pharmacist consultations and others. An additional measure to improve rational antibiotic use in hospitals is the development of prescribing guidelines for common bacterial diseases, taking local resistance patterns into account.

Increased surveillance of antibiotic use and resistance in hospitals is needed to inform interventions and policies at the hospital and higher levels. The implementation of surveillance systems will require increased microbiological lab capacity and facilities as well as standardized lab methods and procedures.

The establishment of point prevalence surveillance in some hospitals is planned, and Maputo Central Hospital is currently working with WHONET to begin monitoring resistance in their laboratory.

Rationalize antibiotic use in the community

Unnecessary antibiotic use can be defined as the administration of antibiotics for viral or other non-bacterial infections. Antibiotics may be unnecessarily prescribed by health care providers or unnecessarily purchased directly by consumers. Studies in Mozambique have shown that health practitioners are liable to misuse their status to profit from antibiotic prescription sales. Informal sales of antibiotics overall are estimated to be quite high, in part because antibiotics are not subsidized the way other medications are. Another study found that 14 percent of university students had purchased antibiotics without a prescription.

The recognition of infectious diseases as a public health problem by the MoH and subsequent government subsidization of antibiotics would lower costs and reduce incentives for resale. In addition, conducting regular reviews of prescriptions written by health care providers at the district and provincial levels and assessing the clinical and laboratory basis of those prescriptions would help provide feedback to reduce irrational prescribing in communities.

Although the levels of antibiotic use at the community level are likely to be high, there is limited information on resistance patterns in communities. While surveillance has been initiated at the hospital level, this should eventually be expanded to communities. Studies to assess the magnitude of antibiotic consumption at the community level and to understand health-seeking behavior are urgently needed to guide community interventions to improve the rational use of antibiotics. These strategies would ultimately reduce the sale of antibiotics without a prescription and reduce the self-administration or healthcare provider prescription of antibiotics for most acute respiratory illnesses and diarrhea.

Reduce antibiotic use in agriculture

Because so little is currently known about antibiotic use in animals in Mozambique, it will be important to quantify the amount of antibiotics currently in use to fully understand the situation. The establishment of studies and sentinel veterinary surveillance systems to document the current disease burden, levels of antibiotic use and resistance levels is an important first step in deciding on policies to limit the impact of drug use in animals. There is also a need to update and enforce current regulations and policies relating to antibiotic use in animals and to raise awareness about the issue in all sectors.

For disease prevention, the Direção Nacional de Serviços de Veterinária (DNSV) runs a vaccination program that includes the strategic compulsory immunization of animals, including the bacterial diseases bovine brucellosis, anthrax and blackleg. Other compulsory immunizations are administered against viral diseases including Newcastle disease in poultry, foot and mouth disease in cattle and rabies in dogs and cats. Immunization of animals against vector-borne diseases such as the Rift Valley fever, African horse sickness and lumpy skin disease is also recommended by the DNSV.

Improving regulation and registration of veterinary products is a much needed first step in reducing antibiotic use. The importation, commercialization, distribution and use of antibiotics in animals and aquaculture are currently controlled through policies and regulations that are obsolete and poorly enforced. The DNSV has drafted regulations for veterinary medicines and a Veterinary Council is to be established to implement a Vet Act that may facilitate the incorporation of new policies and regulations for antibiotic use in animals. Finally, eliminating the use of antibiotics as growth promoters in food producing animals and reducing their use for disease prevention would have a significant impact on the levels of antibiotics being used.

Educate health professionals, policy makers and the public on sustainable antibiotic use

In spite of the seriousness of the issue, antibiotic resistance is still not widely recognized as a problem, even within the health community. Raising awareness about resistance and educating health professionals, policy makers and the public on the diverse roots of resistance will support efforts to improve practices and build policies that improve rational antibiotic use.

Health professionals can be targeted through updates to curricula and treatment guidelines, as well as through the implementation of hospital antibiotic stewardship programs, as mentioned previously. Policy makers can be engaged through the dissemination of relevant research and by fostering dialogue at national and regional meetings. Finally, the public can be educated through awareness campaigns and events coinciding with international activities. Effective education should have an impact on many other areas, including improving rational use at the hospital and community level, reducing use in agriculture and building political commitment for the issue.

Current educational activities targeting healthcare workers include a yearly course on rational drug use given to doctors at Eduardo Mondlane University. It will be important to review and revise curricula and training materials on antibiotic prescribing practices for all levels of health care workers, including clinicians, nurses, pharmacists, community health workers, veterinarians and other allied health sciences.

Ensure political commitment to meet the threat of antibiotic resistance

GARP-Mozambique is the first multi-sectoral group working on antibiotic resistance in the country, and has engaged with key stakeholders from human, animal and environmental health. Further efforts to raise awareness and build cooperation between experts have the potential to improve antibiotic use as they engage in advocacy and take action in their respective sectors. In addition, increasing collaborative research will strengthen the knowledge base on which policies can be built. Creating national policies and action plans to guide antibiotic use is the most sustainable way to ensure that changes are implemented and maintained. At present, though there are laws that guide drug purchasing, distribution and use, and a national formulary that outlines essential medicines and the type of health providers that may prescribe them, no national policies are in place to guide antibiotic use.

Ensuring Access to Effective Antibiotics

Improving access to drugs for those who need them will be another important component of policies aiming to rationalize the use of antibiotics. Only half the population of Mozambique currently has access to a primary health care facility, and shortages of doctors and drugs are common in the health facilities that do exist. The government is currently seeking to expand access to health workers and pharmacies outside of the capital.

Ensuring that the antibiotics being accessed are effective requires strong supply chains and quality assurance measures at the hospital and community level. Antibiotics may be substandard as manufactured, or may degrade during transport and storage, a particular risk for drugs sold in informal markets. Quality assurance methods include conducting spot checks for drug quality on imports and at the point of sale, which need to be carried out on a consistent basis. Currently the Pharmaceutical Department of the MoH is responsible for monitoring drug quality. An analysis of the current supply chain is needed to identify factors contributing to stock outs of antibiotics and to address them.

Recommendations

This situation analysis aims to provide a solid scientific basis for future interventions to improve the sustainable use of antibiotics in Mozambique, presenting all the available information and highlighting research and policy gaps. Based on the findings of this analysis and the urgent global need to confront the threat of antibiotic resistance, GARP-Mozambique recommends the following priority action:

The development and implementation of a national strategic plan for antibiotic resistance, preserving the effectiveness of antibiotics while ensuring their effective use against disease.

To achieve this ambitious goal, GARP-Mozambique will work with a broad range of external stakeholders from relevant sectors. Priority activities will be determined by their potential impact, the feasibility of their implementation, and the costs, expertise and time required for their design and execution. GARP-Mozambique will focus on interventions that are likely to have significant benefits for antibiotic effectiveness but are unlikely to be addressed by other constituencies, with a focus on those outlined in the six strategies to reduce antibiotic resistance presented above.

The realization of a national strategy will be a long and collaborative process, and many of these initiatives can and should be initiated while the process is ongoing. GARP-Mozambique has identified several priority activities, including:

- Improving infection control in hospitals,
- Gathering better information on antibiotic use in the community and formulating interventions to rationalize it,
- Gathering data on antibiotic use in animals and initiating discussions about how to control antibiotic use in food animals, and
- Building political support for a national plan.

With the publication of this situation analysis, GARP-Mozambique is well placed to contribute to the growing knowledge base on antibiotic resistance, inform stakeholders, increase collaboration and initiate change to confront the challenge of antibiotic resistance.

Part II. Health and Economic Context

Geographic and Demographic Context

Mozambique is located on the southeastern coast of Africa, bordered by Tanzania to the north, Malawi, Zambia, Zimbabwe and Swaziland to the west, South Africa to the south and the Indian Ocean to the east. It is divided into eleven provinces, with one capital city, Maputo. Portuguese is the country's only official language, though for most Mozambicans it is a second language, while common native languages include 43 indigenous languages ("Portal do Governo de Moçambique," 2014).

Covering 799,380 square kilometers (km), Mozambique has an estimated population of 23.9 million people (with an average growth rate of 2.7 percent in 2007) (Instituto Nacional de Estatística, 2007), of which 38 percent reside in urban areas. Almost half of the Mozambican population is under 15 years of age, a typical age structure in developing countries (Figure 1). Approximately 29 percent of people living in rural areas have access to an improved water source such as a household connection, public standpipe, borehole, protected well or spring and rainwater collection. The rest rely primarily on unprotected wells, springs and rivers. More than half of Mozambicans have received some education, with a 71 percent literacy

rate among the 15- to 24-year-old population (64 percent for females and 78 percent for males) (Instituto Nacional de Estatística, 2007).

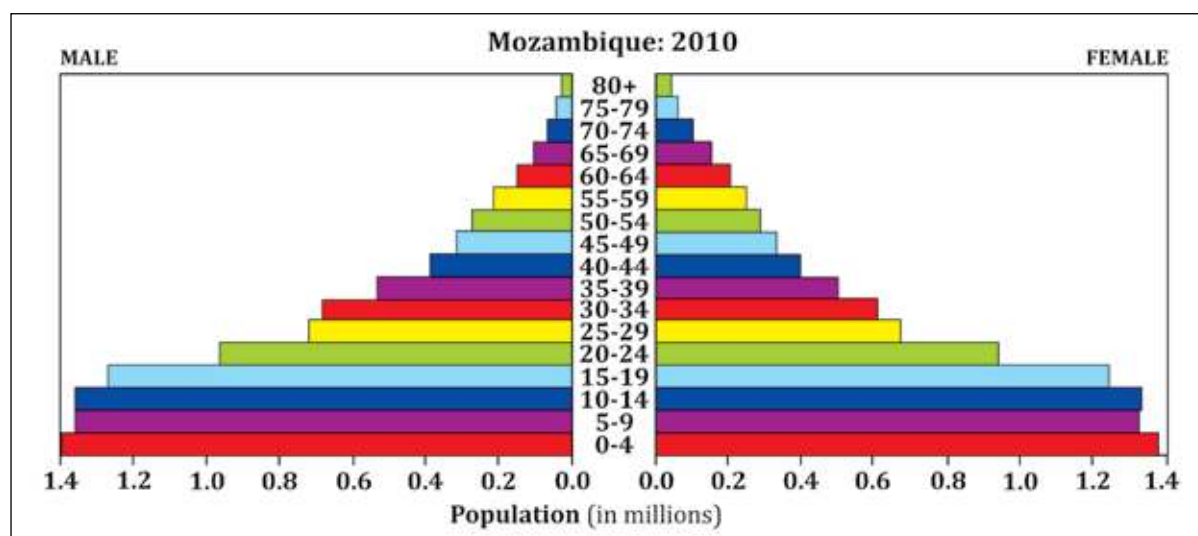
Economic Context

Civil war tore Mozambique apart immediately following the country's independence from Portugal in 1975. Devastated by 16 years of civil war, Mozambique was the poorest country in the world in 1990. Despite the achievement of political stability since 1992, economic development continues to be challenged by the loss of infrastructure and human resources. Recurrent natural disasters, in particular cyclones and flooding, have further contributed to economic insecurity.

Mozambique has a per capita gross domestic product (GDP) of US\$510, which is lower than the average GDP per capita for low-income countries (US\$578). More than half of Mozambicans live on less than one dollar a day; these individuals make up 50 percent of the urban population and 57 percent of the rural population (Ministry of Planning and Development, 2010).

Recently Mozambique has been showing signs of stronger economic growth. The GDP growth rate in 2010 was 7 percent, up from 6 percent in 2009,

Figure 1: The Mozambican Population Pyramid in 2010



SOURCE: (U.S. Census Bureau), International Data Base

which compares favorably with the 6 percent average growth rate among all low-income countries. The number of people living under the poverty line dropped from 70 percent in 1997 to the current 55 percent. This progress is credited to the growth of the agricultural, manufacturing, trade and transport sectors (Instituto Nacional de Estatística, 2007). Agriculture continues to be a major source of livelihood in Mozambique, with 63 percent of the country's land serving as agricultural land in 2009 and 81 percent of jobs relating to the agricultural sector in 2003. In 2010, agriculture alone accounted for 32 percent of GDP (World Bank, 2012). In summary, the political stability and evidence of economic growth constitute the optimal environment for businesses in areas such as agriculture and fisheries, as well as in new emerging areas.

Health System Context

Health Indicators

Up to 2013, the average life expectancy at birth in Mozambique was still low, at 52 years, though higher among females ("Instituto Nacional de Estatística," n.d.), primarily as a result of high rates of infant mortality and excess mortality due HIV/

AIDS among young adults. As a signatory to the Millennium Declaration, Mozambique has adopted and strives to achieve the health-related Millennium Development Goals (MDGs). Mortality rates for women and children (MDGs 4 and 5) have decreased substantially over the past two decades. Between 1995 and 2008, maternal mortality nearly halved, dropping from 980 to 500 deaths per 100,000 live births (Ministry of Planning and Development, 2010). Similarly, under-five mortality decreased from 135 to 97 per 1,000 live births between 2010 and 2011. These reductions have been credited to the implementation of the National Strategy for the Reduction of Maternal and Newborn Mortality from 2000, which was developed with the goal of increasing access to maternal and child health services across the country.

Despite these tremendous gains, under-five mortality in Mozambique is still high relative to the world average of 57.9 deaths per 1,000 live births in 2010 (Instituto Nacional de Estatística, 2007). Most under-five deaths are caused by infectious diseases (Table 1) including malaria, acute respiratory infections, meningitis and sepsis as well as HIV/AIDS.

Other major indicators related to child health include vaccination coverage and the prevalence of malnutrition in children under-five. In 2010,

Table 1: Percentage of cause-specific mortality by main causes of death

Cause of death	Under five (percent)	Neonatal (percent)
Malaria	33.2	4.8
Acute LRTI	10.1	2.2
HIV/AIDS	9.8	1.4
Prematurity	7.6	34.9
Acute and severe diarrhea	6.7	N/A
Other infectious diseases	5.3	3.9
Birth asphyxia	4.9	24.3
Malnutrition	3.8	N/A
Sepsis of newborn	3.4	16.7
Meningitis	2.3	N/A
Other causes	12.9	11.9

SOURCE: (Ministry of Health, 2009)

74 percent of Mozambican children were fully immunized, having received one dose of the Bacillus Calmette–Guérin and measles vaccines and three doses of the pentavalent (diphtheria, tetanus, and pertussis + Hepatitis B + *Haemophilus influenzae* type b) and polio vaccines (UNICEF, n.d.). However, a large proportion of children eligible to receive vaccines are still not being completely vaccinated.

A high degree of food insecurity across the country in most years has led to a high prevalence of low birth weight and malnutrition, particularly among children. Data from the Demographic and Health Survey (DHS) and Multiple Indicator Cluster Survey (MICS) show that the prevalence of chronic malnutrition in children under five was 48 percent in 2003 and 44 percent in 2008. However, chronic malnutrition rates (CMR) are falling, and in urban areas the CMR has been falling at an average of 0.4 percentage points per year (from 37 percent in 2003 to 35 percent in 2008), while the average annual reduction in rural areas was one percentage point (from 52 percent to 47 percent over 5 years) (Instituto Nacional de Estatística, 2008).

Policy

Mozambique does not have a consolidated health policy. The country has issued several health guidelines and policy statements that together create the framework of the health system. The major documents that have guided recent health policy are the Five Year Government Programme 2005–2009, the Poverty Reduction Strategy Paper (PARPA II), the Social and Economic Plan (SES), and the Health Sector Strategic Plan 2007–2012 (PESS). These guidelines, made with the Millennium Development Goals in mind, primarily advocate for strengthened primary health care, increased equity, higher quality and greater access to care and community involvement in health, including utilization of community health workers. PESS and PARPA II are the two principal health documents: the PESS calls for 1) expansion of hospital and community-based basic health services and 2) a strengthened healthcare workforce, while the PARPA II focuses on strategies to overcome barriers to healthcare access by poor and otherwise vulnerable populations.

Policies Pertaining to Essential Medicines

Mozambique has a law that guides the standard acquisition, distribution and use of medicines—including antibiotics—within the country. In 1978, just a few months before the World Health Organization published the first essential medicines list, Mozambique created its own national list. This list, which included 430 essential medicines, has been updated, though irregularly. The most recent version of the Mozambican national drug formulary is from 2007. Although the national drug formulary contains more drugs than is usual for an essential drug list, the formulary has proven useful in guiding drug acquisition and dispensing within the country.

Organization and Distribution of Services

Mozambique has three main sources of health-care: the public sector, profit-based private providers and not-for-profit providers. Other sources of healthcare include the provision of essential medicines (anti-malarials and antibiotics) by community health workers and the recognition of traditional healers and herbalists.

The National Health System (NHS), a part of the public sector, provides the majority of health services throughout the country. However, it covers primarily urban and peri-urban areas. Private providers are confined to the major cities, while not-for-profit providers, mainly made up of non-governmental organizations (NGOs) and faith-based organizations (FBOs), operate mainly at the district level. The first point of health care access and referral in Mozambique in rural areas, where the majority of population lives, tends to be primary health care centers and traditional healers.

There are three organizational levels within the NHS: national directorates work at the central level in the Ministry of Health (MoH), provincial health directorates work at the provincial level and district health services work at district level. The district level is responsible for delivering most health services to communities.

Table 2: Levels of care in the health referral system

Level	Category of Health Unit	~Number in operation	~Number of beds	Type of care provided
I	Health Posts	700	7200	Primary care
	Health Centers	350		
II	Rural hospitals	30	3,200	First 'reference', with admission and basic surgery services
III	Provincial Hospitals	7	1,800	Surgery, obstetrics, gynecology, pediatrics, internal medicine, orthopedics and stomatology
	General Hospitals	5		
IV	Central Hospitals	3	2,900	Multiple specialties and subspecialties
	Psychiatric Hospitals	2		

Nampula, Beira and Maputo are the major referral level IV centers for Northern, Central and Southern Mozambique, respectively. SOURCE: (World Health Organization Regional Office for Africa, 2009)

Access to Health Care Services and Essential Medicines

Health service provision in Mozambique is based on the framework laid out in the 1978 Alma Ata declaration, with primary care patients referred to specialized services when necessary. Community health services and health centers at the primary level refer patients to rural and district hospitals at the secondary level, which in turn refer patients to provincial and general hospitals at the tertiary level, who in turn refer patients to central or regional hospitals (Table 2).

Health inequalities are evident in Mozambique. Only 50 percent of the entire population, of which 68 percent live in urban areas and 31 percent in rural areas, has access to a primary health care facility. Overall, 36 percent of the population has access to a health care center within a 30-minute radius, while for 4 percent of rural households the nearest health center is 2 or more hours away (World Health Organization Regional Office for Africa, 2009).

Health disparities are also evident across provinces. Only 22 percent of the population in Zambezia Province has access to basic health services compared to 72 percent in Maputo Province (World Health Organization Regional Office for Africa, 2009). A number of districts in rural areas do not have hospitals, and where hospitals do exist they are often less equipped, understaffed and only able to offer basic diagnostic services.

Health centers also often suffer from doctor shortages, particularly in the provinces of Zambezia, Nampula, Cabo Delgado and Tete (World Health Organization Regional Office for Africa, 2009). Mozambique has one of the lowest health worker densities in Africa (0.03 doctors and 0.21 nurses per 1,000 inhabitants), which is an overarching health sector challenge (Ministry of Health, 2012). The central MoH is working to tackle this challenge, seeking to increase the health workforce by 70 percent by 2015 through policies articulated in the National Human Resources for Health Development Plan for 2008–2015.

Mozambique has increased access to medicines from 10 percent of the population in 1975 to 80 percent in 2007, primarily by increasing the number of health units and human resources.

Health Financing

The NHS is financed by both public and external funds and investments. Currently, 28 development partners support Mozambique's health sector, providing over 70 percent of health sector financing (World Health Organization Regional Office for Africa, 2009). In 2007, the Global Fund and PEPFAR provided over 50 percent of health sector funding.

To exercise more control and ownership over external funding sources, the government of Mozambique under the Sector-Wide Approach (SWAp) created a common health funding pool mechanism called ProSaude in 2008 (Ministry of

Health, 2012). Under this common health fund, which operates within an established code of conduct, pooled funds from development partners are allocated according to Mozambique's priorities and plans, and activities are better monitored and evaluated. To date, 15 of the 28 development partners currently working in Mozambique, including the Global Fund, contribute to the ProSaude mechanism (World Health Organization Regional Office for Africa, 2009).

The government of Mozambique's contribution to health financing as a percentage of the total national budget is also increasing yearly, in line with its dedication to increasing resources allocated to health outlined in PARPA II (Ministry of Health, 2012) (Table 3).

The MoH is moving towards providing basic health services for free. Currently, the government subsidizes most care and some medicines, and children under five years of age and pregnant women do not pay any user fees (World Health Organization Regional Office for Africa, 2009). Treatment for malaria, TB, leprosy and HIV is provided free of charge, while patients with chronic illnesses are exempted from paying fees associated with clinical visits and health facility admissions. Although conditions resulting from bacterial infections are important public health threats in Mozambique (Betuel Sigaúque et al., 2009), antibiotics are not included in the list of drugs provided for free.

Table 3: Estimated budget for health expenditure relative to the national budget

Year	2007	2008	2009	2010
National Budget (US\$ million)	317	400	436	474
Percent of the total budget spent on health	11.6	12.6	12.4	12.7

SOURCE: (Ministry of Health, n.d.)

Part III. Bacterial Diseases and Antibiotic Resistance

The high disease burden caused by respiratory and enteric infections among all age groups in Mozambique makes these infections critical disease priorities and underscores the importance of ensuring universal access to and appropriate use of antibiotics within the country (Table 1).

The section below summarizes information on the burden of disease, current treatment options and antibiotic resistance for some of the most common bacterial infections in Mozambique. As is the case in the majority of developing countries, the true burden of bacterial infections remains unknown in Mozambique, largely due to the absence of bacterial surveillance systems and diagnostic facilities in community and hospital settings. As a result, the etiologic and resistance data available is hardly sufficient to provide a complete picture of the true national burden.

Data summarized in this situation analysis are drawn from studies conducted in Maputo Province by the Manhiça Health Research Center and by the School of Medicine at Eduardo Mondlane University (Table 4).

Maputo Central Hospital (HCM), a national-level referral facility with a microbiology laboratory for infectious disease diagnosis, did not have any mechanism in place to regularly review and analyze pathogen antibiotic susceptibility trends until 2009. At that time, and in collaboration with the Alliance for the Prudent Use of Antibiotics (APUA), the HCM invited a WHONET expert to install resistance monitoring software and train laboratory staff in its use. Antibiotic resistance data from Maputo Central Hospital were unfortunately not included in this situation analysis, as HCM staff are still in the process of analyzing the data.

Acute Lower Respiratory Tract Infection (Pneumonia) and Invasive Bacterial Disease

Bacterial infections are a leading cause of death in young children in Mozambique. Among neonates, severe infections such as pneumonia, sep-

sis and diarrheal diseases are among the leading causes of death, and pneumonia is the third largest cause of death of children under five (Ministry of Health, 2009). Common invasive bacterial diseases include bacteremia, pneumonia, meningitis and sepsis. Despite the high burden of these infections, not all appropriate vaccines have been introduced and antibiotic treatment only reaches a small portion of the children who need it. This presents a large challenge moving forward, as health workers must balance the need for increased access to antibiotics with increasing evidence of resistance.

Invasive Pneumococcal Disease (IPD)

Streptococcus pneumoniae is among the leading causes of morbidity and mortality among children worldwide, causing more than one-third of the 2 million annual child deaths. Additionally, an estimated 10.6 million children under five present with pneumococcal disease every year, particularly with pneumonia, meningitis and sepsis (WHO, 2009).

One study from a rural Mozambican hospital found that the community-based incidence rate of Invasive Pneumococcal Disease (IPD) in children under five years of age was very high—at 416/100,000 per child-year at risk and higher (A Roca et al., 2006). Children under 2 years of age had the highest IPD incidence and CFR (Betuel Sigaúque et al., 2009). Over a 10-year surveillance period (2001–2010) for invasive bacteria among 34,553 admitted children at Manhiça District Hospital, pneumococcus was the most commonly detected isolate (26 percent) (B., Sigaúque, oral communication, January 2013). Children below the age of two were at the highest risk of IPD, accounting for 62 percent of cases. The most common clinical presentation of IPD was pneumonia (69 percent), followed by other bacteremia (27 percent) and meningitis (4 percent). Hospital mortality due to IPD accounted for 7 percent of overall hospital deaths. IPD had a case fatality rate (CFR) of 11 percent and the majority of IPD deaths (68 percent) occurred within 48 hours after hospitalization.

Table 4: Overview of studies on antibiotic resistance in Mozambique

Authors (year)	Study title	Study location	Age	Sample Size	Percent of isolates resistant to antibiotics										MDR			
Mandomando, I. et al. (2010)	Antimicrobial Drug Resistance Trends of Bacteremia Isolates in a Rural Hospital in Southern Mozambique	Manhiça District Hospital	<15 years	1,592 isolates	Percent of isolates resistant to antibiotics										67			
					Amp	Chlor	SXT	Gen	EES	PCN	74	55	66	16		NA	NA	
					NTS	7	44	NA	2	11	11	7	44	NA		2	11	
					<i>Streptococcus pneumoniae</i>	90	37	31	5	35	90	90	37	31		5	35	
					<i>Staphylococcus aureus</i>	96	78	90	28	NA	NA	92	78	90		28	NA	NA
<i>Escherichia coli</i>	46	50	77	11	NA	NA	50	50	77	11	NA	NA						
<i>Haemophilus influenzae</i>																		
Mandomando, I. et al. (2009)	Invasive non-typhoidal <i>Salmonella</i> in Mozambique can children	Manhiça District Hospital	<2 years or older if severe illness	401 NTS isolates	Percent of isolates resistant to antibiotics										74			
					Amp	Chl	SXT	Gen	Cro	Nal	75	47	65	23		0	2	
					<i>Salmonella T.</i>	77	77	75	2	0	4	77	77	75		2	0	4
					<i>Salmonella E.</i>	63	44	44	6	0	0	63	44	44		6	0	0
Other <i>Salmonella</i>																		
Mandomando, I. et al. (2009)	Antimicrobial susceptibility and mechanisms of resistance in <i>Shigella</i> and <i>Salmonella</i> isolates from children under five years of age with diarrhea in rural Mozambique	Centro de Investigação em Saúde da Manhiça (CISM), Maputo, Mozambique & Manhiça District Hospital	<5 years	149 isolates	Percent of isolates resistant to antibiotics										65			
					Amp	Cro	Chl	Nal	Tet	SXT	56	-	57	-		66	84	
					<i>Shigella</i> (109)	25	-	15	-	15	18	25	-	15		-	15	18
<i>Salmonella</i> (40)																		
Roca, A. et al. (2009)	Surveillance of Acute Bacterial Meningitis among Children Admitted to a District Hospital in Rural Mozambique	Manhiça District Hospital	<15 years	642 samples	Percent of isolates resistant to antibiotics													
					Chlor	PCN	Amp	0/9	1/9*	-	-	5/10	-					
					<i>Pneumococcus</i>	<i>Haemophilus influenzae</i> type b	9/10	-	5/10	-	-	-	-					

*Intermediate resistance rates

Authors (year)	Study title	Study location	Age	Sample Size	Percent of isolates resistant to antibiotics	MDR
Sigaúque, B. et al. (2009)	Community-acquired bacteremia among children admitted to a rural hospital in Mozambique	Manhiça District Hospital	<15 years	1,550 isolates	<p>SXT</p> <p><i>Streptococcus pneumoniae</i> 93</p> <p><i>Haemophilus influenzae</i> 50</p> <p><i>Staphylococcus aureus</i> 63</p> <p><i>Escherichia coli</i> 22</p> <p>NTS 45</p> <p>Group B <i>Streptococcus</i> 71</p> <p><i>Neisseria meningitidis</i> 100</p> <p><i>Klebsiella</i> spp. 45</p> <p>*Susceptibility rates</p>	<p>Chlor 93</p> <p>PCN/Amp 89</p> <p>Gent -</p> <p>56</p> <p>23</p> <p>69</p> <p>10</p> <p>72</p> <p>84</p> <p>0</p> <p>85</p> <p>73</p> <p>30</p>
Roca, A et al (2008)	Invasive <i>Haemophilus influenzae</i> disease in children less than 5 years of age in Manhiça, a rural area of southern Mozambique	Manhiça District Hospital	<5 years	1,351 isolates- blood culture 55 isolates - CSF	<p><i>Haemophilus influenzae</i>*</p> <p>*Non-susceptibility rates</p>	<p>Chlor 39</p> <p>Amp 35</p> <p>SXT 74</p>
Sigaúque, B. et al. (2008)	Acute bacterial meningitis among children, in Manhiça, a rural area in Southern Mozambique	Manhiça District Hospital	<15 years	475 samples, 71 isolates	<p>Pneumococcal meningitis</p> <p><i>H. influenzae</i></p> <p>*Susceptibility rates</p>	<p>OX 81</p> <p>Chlor 93</p> <p>Amp -</p> <p>62</p> <p>54</p>

Authors (year)	Study title	Study location	Age	Sample Size	Percent of isolates resistant to antibiotics	MDR																																																																
Mandomando, I. et al (2007)	Etiology of diarrhea in children younger than 5 years of age admitted in a rural hospital of southern Mozambique	Manhiça District Hospital	<5 years	529 samples, 144 positive for bacteria	<table border="1"> <thead> <tr> <th></th> <th>Amp</th> <th>Chl</th> <th>SXT</th> <th>Tet</th> <th>Nal</th> <th>Cip</th> <th>Amox/Clav</th> </tr> </thead> <tbody> <tr> <td>Salmonella</td> <td>62</td> <td>8</td> <td>38</td> <td>25</td> <td>8</td> <td>-</td> <td>NT</td> </tr> <tr> <td>Campylobacter</td> <td>NT</td> <td>1</td> <td>NT</td> <td>22</td> <td>11</td> <td>11</td> <td>NT</td> </tr> <tr> <td>E. Coli</td> <td>72</td> <td>45</td> <td>58</td> <td>48</td> <td>4</td> <td>1</td> <td>4</td> </tr> <tr> <td>EAEC</td> <td>91</td> <td>61</td> <td>80</td> <td>50</td> <td>7</td> <td>2</td> <td>5</td> </tr> <tr> <td>ETEC</td> <td>46</td> <td>29</td> <td>61</td> <td>36</td> <td>-</td> <td>-</td> <td>8</td> </tr> <tr> <td>EPEC</td> <td>71</td> <td>36</td> <td>57</td> <td>57</td> <td>7</td> <td>7</td> <td>-</td> </tr> <tr> <td>VTEC</td> <td>50</td> <td>17</td> <td>17</td> <td>33</td> <td>-</td> <td>-</td> <td>-</td> </tr> </tbody> </table>		Amp	Chl	SXT	Tet	Nal	Cip	Amox/Clav	Salmonella	62	8	38	25	8	-	NT	Campylobacter	NT	1	NT	22	11	11	NT	E. Coli	72	45	58	48	4	1	4	EAEC	91	61	80	50	7	2	5	ETEC	46	29	61	36	-	-	8	EPEC	71	36	57	57	7	7	-	VTEC	50	17	17	33	-	-	-	
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VTEC	50	17	17	33	-	-	-																																																															
Mandomando, I. et al (2007)	Antimicrobial resistance of <i>Vibrio cholerae</i> O1 serotype Ogawa isolated in Manhiça District Hospital, southern Mozambique	Manhiça District Hospital	All patients with criteria	150 swabs, 91 isolates, 77 tested	<table border="1"> <thead> <tr> <th></th> <th>Amp</th> <th>Chl</th> <th>SXT</th> <th>Tet</th> <th>Nal</th> </tr> </thead> <tbody> <tr> <td><i>V. cholerae</i></td> <td>12</td> <td>58</td> <td>97</td> <td>97</td> <td>4</td> </tr> </tbody> </table>		Amp	Chl	SXT	Tet	Nal	<i>V. cholerae</i>	12	58	97	97	4																																																					
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*Intermediate resistance rates

SOURCE: (Authors)

Antibiotic Resistance

National recommendations for the first-line treatment of IPD are the prescription of penicillin (ampicillin plus gentamicin for under 2 months of age) or chloramphenicol. Ceftriaxone is used for severe cases or if there is resistance to the first-line antibiotic.

Despite global reports of increasing penicillin resistance, studies looking at susceptibility to these drugs in Mozambique found resistance levels to be moderate, with 11 percent of the pneumococcal isolates tested being non-susceptible at a breakpoint of 0.12-1ug/ml, suggesting an intermediate level of resistance (A Roca et al., 2006). This is much lower than the 42 percent non-susceptibility rates recently reported in neighboring South Africa (Bamford et al., 2009). Studies on cotrimoxazole non-susceptibility rates in Mozambique were higher, however, with 37 percent of the isolates testing as non-susceptible (Betuel Sigaúque et al., 2009).

A cross-sectional study among children in the outpatient department in Manhiça looking at the antibiotic susceptibility of *S. pneumoniae* nasopharyngeal isolates reported a much higher rate of non-susceptibility to penicillin and cotrimoxazole (Vallès et al., 2006). In this study, 61 percent of the isolates were non-susceptible to cotrimoxazole, and 52 percent were non-susceptible to penicillin.

However, a more recent study on the colonization of *S. pneumoniae* in HIV-infected children under five in three hospitals in Manhiça, Maputo and Nampula found no resistance to penicillin and 89 percent resistance to cotrimoxazole (Sigaúque et al., 2014 unpublished data).

Several studies (Mwenya et al., 2010) (Hamel et al., 2008) (Feikin et al., 1997) have found that carriage of non-susceptible cotrimoxazole and/or penicillin isolates was associated with receipt of the first-line malaria treatment sulfadoxine-pyrimethamine. Given the high rates of malaria in this region, carriage of these resistant isolates might be a result of the confirmed cross-resistance between the two drugs (Vallès et al., 2006). Additionally, in light of the increased use of cotrimoxazole as a prophylactic drug in HIV/AIDS patients, resistance to cotrimoxazole is likely to increase.

CISM is currently conducting a community- and hospital-based nasopharyngeal study among HIV-infected and uninfected children under five years of age in Manhiça, Maputo and Nampula. Findings from this study should provide a more comprehensive understanding of pneumococcal prevalence and antibiotic resistance.

Meningitis

Acute bacterial meningitis (ABM) is a major cause of mortality among children in Mozambique. ABM was confirmed in 7 percent of cases with suspected meningitis in a rural Mozambican hospital (B. Sigaúque et al., 2008) (A Roca et al., 2009). Infants under one year of age are at the highest risk for ABM, accounting for 67 percent of cases. The most prevalent organisms responsible for ABM were *H. influenzae* type b (Hib) (33 percent), pneumococcus (21 percent) and meningococcus (16 percent) from 2001 to 2009, before the Hib and pneumococcal conjugate vaccines were introduced in Mozambique. Other causes of ABM were *Staphylococcus aureus*, group B and D streptococci, *Pseudomonas* spp., *Escherichia coli* and *Proteus* spp. In Mozambique in 2009, the hospital-based minimum incidence rates of the three most prevalent pathogens—*H. influenzae* type b, pneumococcus and meningococcus—were 27, 19 and 19 per 100,000 person-years at risk, respectively.

Despite its relatively low incidence, ABM is much more fatal than most invasive bacterial diseases. Even though it accounted for only 4 percent of IPD isolates, ABM accounted for 56 percent of deaths in one study conducted by Roca and colleagues in 2006. That study also estimated that the mortality rate from Hib meningitis, which had a prevalence of 16 percent, was five times higher than in other invasive Hib cases (Anna Roca et al., 2008). Hib meningitis had a CFR of 24 percent, likely an underestimate of the true rate, as 19 percent of patients left the hospital when their clinical condition worsened. This is an acute disease, with 63 percent of recorded ABM deaths occurring within less than 24 hours of admission (A Roca et al., 2009).

Antibiotic Resistance

Bacterial meningitis can be treated using antibiotics. In Mozambique, national recommendations for first-line treatment are chloramphenicol or penicillin G (ampicillin for infants under 2 months of age) plus gentamicin. However, antibiotic susceptibility tests report high resistance rates to all of these recommended treatments. Thirty-nine percent of all Hib, pneumococcal and meningococcal isolates in the study by Roca and colleagues were non-susceptible to first-line chloramphenicol, and 52 percent were non-susceptible to ampicillin or penicillin.

Haemophilus influenzae Type b

Hib, another important cause of bacterial pneumonia and meningitis, is highly prevalent throughout rural Mozambique. The minimum community-based Hib incidence rate in rural Mozambique from 2001 to 2005 was 125/100,000 child-years-at-risk in the 5th year of life (Anna Roca et al., 2008). The incidence rate was highest at the 2nd year of life (235/100,000 child-years-at-risk) accounting for 58 percent of all Hib episodes. Hib infection resulted in meningitis in 16 percent of all Hib episodes. There was an estimated meningitis incidence of 83 per 100,000 child-years-at-risk at age one, which dropped to 27 per 100,000 child-years-at-risk by age five (Anna Roca et al., 2008).

Mortality among Hib invasive cases was high, with a 21 percent CFR compared with 3 percent for all other causes of hospital admission. The highest rates were observed in children with meningitis, with a rate almost five times higher than the other Hib cases [OR = 4.38; 95 percent CI 1.40, 13.71; P=0.011] (Anna Roca et al., 2008). In 2009, the Hib conjugate vaccine was introduced in Mozambique and since then has been incorporated into the national expanded program on immunization. As a result, the incidence of Hib disease and Hib-related meningitis have significantly decreased, with Hib disease incidence decreasing from 85 to 13/100,000 child-years-at-risk between 2006-2008 and 2010-2011, and Hib-related meningitis decreasing from 38 to 0/100,000 child-years-at-risk over the same period (Betuel Sigaúque et al., 2013). These results underline the impact of vaccine introduction on reducing the burden of dis-

ease, and potentially the level of antibiotic use, which in turn may impact antibiotic resistance levels.

Antibiotic Resistance

As in the treatment of pneumococcal disease, the first-line antibiotic used for treating children with Hib-caused severe pneumonia, suspected meningitis or septicemia is chloramphenicol or penicillin (or ampicillin for infants under 2 months of age) plus gentamicin.

Non-susceptibility of *H. influenzae* isolates to first-line drugs chloramphenicol and ampicillin dramatically increased from 15 percent and 23 percent in 2001 to 63 percent and 42 percent in 2005, respectively (Anna Roca et al., 2008). *H. influenzae* isolates showed high resistance levels, ranging from 65 percent to 89 percent to cotrimoxazole (used to treat non-severe pneumonia outpatient cases) over the same time period. It is important to note that mortality was higher among cases infected with chloramphenicol-resistant strains than those infected with chloramphenicol-susceptible strains (27 percent vs. 7 percent). Data that specifically show the attributable burden of antibiotic resistance on the management of bacterial diseases are important in the development of effective hospital guidelines and policies that target the threat to human health from antibiotic resistance.

Bacteremia

Community-acquired bacteremia is an important contributor to the pediatric health burden in Mozambique, particularly among neonates (Ministry of Health, 2009). In rural parts of the country, the incidence of bacteremia in children under 15 years of age was estimated to be 425 cases per 100,000 child-years between 2001 and 2006, with the highest incidence reported among children under one year of age at an alarming 1,738 per 100,000 child years (Betuel Sigaúque et al., 2009). As much as 44 percent of all bacteremic episodes during this period occurred among children under one year of age.

Sixteen percent of all bacteremia episodes occurred among neonates, and one in five of all hospitalized neonates were bacteremic on admission. Additionally, neonates' risk of bacteremia was

nearly four times that of older children. The most prevalent pathogens isolated were non-typhoidal *Salmonella* spp. (NTS) (26 percent), *S. pneumoniae* (25 percent), *S. aureus* (12 percent), *E. coli* (10 percent) and *H. influenzae* (7 percent) (Betuel Sigaúque et al., 2009).

The most common admission diagnoses of bacteremic children were malaria (20 percent), anemia (19 percent), pneumonia (15 percent), bacterial sepsis (9 percent), malnutrition (8 percent) and acute diarrhea/ gastroenteritis (5 percent). An alarming 21 percent of all hospital deaths were due to bacteremia (CFR=12 percent), with 45 percent of the bacteremic deaths taking place within 48 hours of admission. Pneumococcus, NTS and *H. influenzae* were associated with more than two-thirds of the total bacteremia deaths, accounting for 27 percent, 26 percent and 14 percent of deaths, respectively (Betuel Sigaúque et al., 2009).

Antibiotic Resistance

Antimicrobial susceptibility testing revealed growing resistance to commonly used antibiotics for the most prevalent bacteremia isolates in Mozambique.

Between 2001 and 2006, resistance to first-line drug chloramphenicol steadily increased among the following types of isolates: NTS (26 percent to 63 percent), *S. aureus* (16 percent to 35 percent), *E. coli* (62 percent to 92 percent) and *H. influenzae* (10 percent to 94 percent) (Mandomando, Sigaúque, Morais, Espasa, Vallès, Sacarlal, Macete, Aide, Quintò, Nhampossa, Machevo, Bassat, Menéndez, Ruiz, Roca, & Alonso, 2010). *H. influenzae* resistance rates to ampicillin were also very high, rising from 19 percent in 2001 to 75 percent in 2006.

NTS isolates had high non-susceptibility rates to first-line drugs ampicillin (74 percent) and chloramphenicol (55 percent), but showed hardly any resistance to third-line cephalosporins, ceftriaxone (0 percent); quinolones, nalidixic acid (3 percent); or fluoroquinolones, ciprofloxacin (0 percent) (Mandomando, Sigaúque, Morais, Espasa, Vallès, Sacarlal, Macete, Aide, Quintò, Nhampossa, Machevo, Bassat, Menéndez, Ruiz, Roca, Alonso, et al., 2010). *H. influenzae* also showed high non-susceptibility to ampicillin (46 percent) and to chloramphenicol (50 percent), while the majority

of *S. pneumoniae* isolates were susceptible to these first-line drugs: ampicillin (89 percent), penicillin (89 percent) and chloramphenicol (93 percent). Multi-drug resistance (MDR), defined as complete resistance to two or more unrelated antimicrobial agents, was also observed among some of these pathogens: 92 percent of *E. coli* exhibited MDR, as did 67 percent of NTS, 50 percent of *H. influenzae*, 43 percent of *S. aureus*, and 5 percent of *S. pneumoniae* (Mandomando, Sigaúque, Morais, Espasa, Vallès, Sacarlal, Macete, Aide, Quintò, Nhampossa, Machevo, Bassat, Menéndez, Ruiz, Roca, & Alonso, 2010).

Enteric Infections

Diarrheal infections are the third most common cause of infectious disease-related deaths, killing 1.7 to 2.5 million people globally every year (WHO, 2009). The leading causes of diarrheal infections in children in low-income countries are *E. coli*, Rotavirus, *Shigella* spp., *Salmonella* spp. and *Vibrio cholerae* (WHO, 2009). The diversity of bacterial and viral enteric pathogens makes the etiology of these infections hard to ascertain in the absence of good laboratory facilities, a common problem in Mozambique and in many other low-income countries.

Even though most enteric infections are self-limiting diseases and can be treated with oral rehydration, appropriate antimicrobial therapy is needed for more severe cases. Failure to use antimicrobial therapy in severe cases can lead to dehydration and ultimately death. In rural southern Mozambique, diarrhea-related deaths account for eight percent of all deaths, and are the fourth main contributor to child mortality after malaria (22 percent), pneumonia (10 percent) and HIV/AIDS (8 percent) (Sacarlal et al., 2009). Similarly, in an earlier study in the capital city of Maputo, diarrheal infections were the third greatest cause of pediatric deaths (10 percent) (Dgedge et al., 2001). National guidelines recommend ampicillin (plus gentamicin for children younger than two) and chloramphenicol alone (for children older than two) for treating enteric infections caused by bacteria.

Escherichia coli

In a study looking at the etiology of pediatric community-associated bacteremia infections in

rural Mozambique, *E. coli*, the most common diarrheal bacterial pathogen isolated in low-income countries, was the fourth most prevalent isolate (10 percent) after non-typhoidal *Salmonella*, *Streptococcus pneumoniae* and *Staphylococcus aureus* (WHO, 2009) (Betuel Sigaúque et al., 2009). The incidence rate between 2001 and 2006 was highest in children under one year of age at 225/100,000 child-years, with a 10 percent CFR for all ages.

In a study looking specifically at the etiology of diarrhea in children under 5 years of age, 42 percent of children with diarrhea carried at least one pathogen, and 27 percent of isolates were pathogenic bacteria; 14 percent were parasites and 0.6 percent were viruses (Mandomando et al., 2007). Diarrheagenic *E. coli* (23 percent) was the most common isolate, followed by *Salmonella* spp. (3 percent) and *Campylobacter* spp. (2 percent). Just over 10 percent of patients were co-infected: 71 percent of co-infections were bacteria/parasite and 25 percent were bacteria/bacteria. Only one case was a bacteria/virus co-infection.

Between 2007 and 2012, CISM was part of multicenter study entitled Diarrheal Disease in Infants and Young Children in Developing Countries (Global Enteric Multicenter Study – GEMS) that aimed to quantify the burden of disease, sequelae and microbiological etiology of moderate-to-severe diarrhea (MSD) in Africa and South Asia. Preliminary results showed that rotavirus, *Cryptosporidium*, *E. coli* producing heat-stable toxin (ST_ETEC), *Shigella* spp, and *V. cholerae* were the leading pathogens associated with MSD in different age groups, including 0-11, 12-23 and 24-59 months of age (Nhampossa et al., 2014, manuscript in preparation).

At the Xipamanine Health Center in Maputo, *E. coli* isolates were found in 68 percent of diarrhea cases and in 34 percent of samples from healthy controls (Rappelli et al., 2005). Diarrheagenic *E. coli* was found in 42 percent of the isolates from symptomatic children and 18 percent of asymptomatic children. However, the occurrence of diarrheagenic *E. coli* that was not associated with other pathogens such as rotavirus, protozoa and helminthes was found in only 20 percent and 9 percent of the symptomatic and asymptomatic children, respectively. In this particular study, rotavirus, the leading cause of severe diarrheal disease in chil-

dren under 5 years of age, was isolated from 18 percent of the symptomatic children, and recently rotavirus was also associated with diarrhea in rural Mozambique (Nhampossa, 2014, manuscript in preparation).

Antibiotic Resistance

As with most pathogens in rural Mozambique, *E. coli* showed high levels of resistance to the nationally-recommended and inexpensive first-line antibiotics: 78 percent of isolates were non-susceptible to chloramphenicol and an alarming 96 percent of isolates were resistant to ampicillin/penicillin (Sigaúque et al., 2009). Only 4 percent of the isolates were resistant to nalidixic acid and one percent to ciprofloxacin.

Within the Global Enteric Multi-Center Study (GEMS), among bacterial pathogens, with the exception of third-generation cephalosporins and fluoroquinolones, resistance was as high as 16 percent for diarrheagenic *E. coli* (enteroaggregative and enterotoxigenic *E. coli*) and commensal *E. coli* to chloramphenicol or ampicillin.

Non-typhoidal *Salmonella*

In southern Mozambique, one study showed that non-typhoidal *Salmonella* (NTS) were the most prevalent pathogens isolated from children presenting with community-acquired bacteremia (26 percent) (Betuel Sigaúque et al., 2009). The most prevalent NTS serotypes and serovars isolated were *S. typhimurium* (66 percent) and *S. enteritidis* (25 percent) (Mandomando, Macete, et al., 2009). The incidence rate during the study period (2001 to 2006) was highest in children under one year of age at 388/100,000 child-years, with a 12 percent CFR for all ages. The most common clinical diagnoses for these patients were anemia (56 percent), malaria (55 percent), pneumonia (26 percent), clinical malnutrition (16 percent) and acute gastroenteritis (14 percent).

Antibiotic Resistance

NTS serotypes had high levels of antibiotic resistance to first-line antibiotics: 74 percent of the isolates were non-susceptible to ampicillin/penicillin while 55 percent were non-susceptible to chloramphenicol (Betuel Sigaúque et al., 2009).

The two most prevalent serotypes of NTS, *S. typhimurium* and *S. enteritidis*, also exhibited high levels of multi-drug antibiotic resistance (MDR), with 46 percent and 63 percent of their isolates being non-susceptible to both chloramphenicol and ampicillin (Mandomando, Macete, et al., 2009). Though the chloramphenicol resistance pattern of *S. enteritidis* remained stable over the 5-year period (2001 – 2006), the degree of *S. typhimurium* resistance dramatically increased from 15 percent in 2001 to 65 percent in 2006. MDR in *S. typhimurium* also increased from 64 percent to 74 percent between 2001 and 2006. Resistance to the most expensive antibiotics, however, remained quite low: increasing from 2 percent to 4 percent for nalidixic acid, and remaining at 0 percent throughout the period for ceftriaxone.

Shigella spp.

Antibiotic Resistance

Shigella spp., unlike other enteric infections, usually causes severe infections that require antibiotic therapy. In the absence of a *Shigella* vaccine, antibiotic resistance is a major concern with this particular pathogen.

In a rural Mozambican study looking at resistance rates among *Shigella* isolates collected between 2001 and 2003 from children under five years of age, 56 percent of the 109 isolates were resistant to first-line ampicillin and 52 percent to chloramphenicol (Mandomando, Jaintilal, et al., 2009). An alarming 65 percent of the isolates were MDR, with 42 percent of isolates resistant to ampicillin, chloramphenicol, tetracycline and cotrimoxazole. None of the isolates were resistant to nalidixic acid or to ceftriaxone. Similarly, within GEMS, resistance among *Shigella* spp. was higher than 17 percent to almost all antibiotics, with the exception of fluoroquinolones and third-generation cephalosporins (Mandomando et. al, 2014, manuscript in preparation).

Vibrio cholerae

Although *V. cholerae* infections do not usually require antimicrobial treatment, in populations with high HIV prevalence, such as in the Manhiça region, antibiotics can be useful. However, the choice of antibiotics available to manage cholera may be limited due to the high prevalence of resistance, especially to those antibiotics used for empirical treatment, such as chloramphenicol (58 percent), cotrimoxazole (97 percent) and tetracycline (97 percent) in cholera isolates recovered from 2002 to 2004 (Mandomando et al., 2007).

During a cholera outbreak in Maputo, the microbiology department at the School of Medicine at Eduardo Mondlane University conducted a survey from 2007 to 2011 to determine the etiology and antibiotic resistance of cases with acute diarrhea. From 459 stool samples examined, *V. cholerae* was identified in 44 percent, all of which were serotype Ogawa.

In this study, sensitivity testing was conducted for six antibiotics, but testing was inconsistent and depended on the availability of testing materials. For ciprofloxacin, 200 isolates were tested and 11 (6 percent) were intermediate (I) or fully resistant (R) (range: 0 to 21 percent by year). For gentamicin, 132 of 193 isolates (68 percent) were I/R (range: 42 percent to 93 percent). For erythromycin, 93 of 183 (51 percent) were I/R (range: 24 percent to 93 percent). For nalidixic acid, 167 of 193 (87 percent) were I/R (range: 76 percent to 86 percent). For tetracycline, 112 of 175 (64 percent) were I/R (range: 42 percent to 93 percent). For cotrimoxazole, 165 of 174 (95 percent) were I/R (range: 61 percent to 100 percent). For chloramphenicol, 106 of 146 (73 percent) were I/R (range: 51 percent to 82 percent).

Part IV. The Supply Chain and Implications for Antibiotic Access

Pharmaceutical Licensing, Registration, and Inspection

The Pharmaceutical Department of the Ministry of Health is the main regulatory body for drugs in Mozambique. The Department oversees the registration of medicines and health professionals as well as licensing and inspection of drug manufacturers, importers, wholesalers and retailers in the country (Russo & McPake, 2010). The Department has four sections: registration, inspection, quality control and pharmacovigilance, and is also responsible for rational drug use policies and the regulation of clinical trials and drug quality. The legal frameworks governing the public and private pharmaceutical sectors in Mozambique are the Law No. 4/98 and the regulations Exercise of the Profession and Pharmaceutical Drug Registration.

Importation and Local Production of Medicines

Fifty-three companies currently import medicines into Mozambique, including antibiotics. One of the major importers was previously Medimoc SA, a semi-private nationwide company based in Maputo, with offices in Nampula and Beira. The Mozambican government owns 65 percent of Medimoc SA's shares and the technical managers and workers own the remaining 35 percent. However, the Center for Medicines and Medical Supplies (CMAM) is now the major importer for the public sector.

Currently, there is no private factory production of medicines, including antibiotics, in Mozambique. However, a "State Society of Medicines" factory is currently under development as a public-private partnership with the Government of Brazil. For now, this factory exclusively produces serum, but it will soon manufacture antiretroviral drugs and 20 essential medicines, though no antibiotics will be produced. In addition, the MoH plans to establish a Nampula-based factory for the production of essential medicines in the near future.

Formal Drug Sellers

Private pharmacies are primarily located in urban areas. There are 293 pharmacies in the country, 60 percent of which are located in Maputo. Eleven companies manage more than one pharmacy. The number of pharmacies has increased significantly in urban areas over the past 10 years, but national coverage has not increased at the same pace. Although recent public policies have encouraged the decentralization of pharmacies to increase coverage outside Maputo, there is still a high concentration of pharmacies in the capital and requests to establish pharmacies are primarily made in Maputo. For instance, of the 25 current applications for permits to open a new pharmacy, over 90 percent are for Maputo.

There is also a network of 41 state-owned self-financing public pharmacy outlets, called FARMAC. The FARMAC chain imports and retails the majority of all medicines in Mozambique. Payments for medicines at both private pharmacies and within the FARMAC chain are largely out-of-pocket.

According to the Mozambican medicines law 4/98, it is illegal to sell antibiotics without a prescription. Nonetheless, this policy is rarely enforced and antibiotics continue to be sold without a prescription, especially within private pharmacies in urban areas. A recent study on self-medication practices conducted in the city of Maputo found that antibiotics were the second most-used drug for self-medication (18 percent), after analgesic/anti-inflammatory drugs (46 percent) (Mahomed et al., 2014, manuscript in preparation).

Informal Drug Sellers

There is little published literature on the informal retail of antibiotics in Mozambique. However, the few studies that exist suggest that this may be a considerable problem.

Researchers found that drugs were sold in 36 commercial sites in Maputo city, including 8 supermarkets, 20 grocery stores and 8 markets, and antibiotics represented five percent of all medicines sold (Libombo, 2009, unpublished data).

Moving beyond urban Maputo and into the provinces, researchers found that antibiotics are the primary type of medicine sold in markets. Medicines ranging from oral and injectable penicillin to anti-tuberculosis and antiretroviral drugs can be found at these markets at lower than formal sector retail prices. Nothing is known about the quality of these products (Williams, oral communication, 2013).

A study by Ferrinho and colleagues in 2004 confirmed that the misuse of privileged access to medicines by health professionals is a common practice. Most of this misuse pertains to antibiotics, and it impacts public health facilities and medical stores at all levels. The study found that some medicines were found in health professionals' homes, where they treat patients for a fee (Ferrinho et al., 2004). The fact that antibiotics are not dispensed free of charge within the public health system like other drugs, such as antimalarial, anti-retroviral and anti-tuberculosis drugs, contributes to the misappropriation of antibiotics from the national system.

Procurement and Distribution

The public health logistics system for medicines is managed centrally by two institutions: the CMAM and the Supply Center (CA). CMAM is responsible for procurement and distribution within the public health system. Public sector drug expenditure accounts for 60-70 percent of the total national pharmaceutical expenditure. At the provincial and district levels these two structures replicate themselves in the form of provincial or district medicine and medical supply stores. CMAM reports to the National Directorate of Medical Care (DNAM) and is responsible for planning, forecasting, importing, storing and distributing medicines and supplies. The CA reports to the Department of Administration and Finances (DAF) and is responsible for the storage and distribution of centrally-supplied consumables, medical equipment, hospital furniture and vehicles. The CA is also responsible for managing health care products and medical supplies that are not in regular use. Forecasting of product requirements is done by DNAM or by the health programs themselves, while purchasing is carried out by CMAM, the executor of the acquisitions man-

ing unit within the MoH (UGEA, a part of DAF), or directly by cooperating partners.

CMAM has two national warehouses, in Maputo and Matola, and one regional warehouse in Beira. The national warehouses supply medicines, including antibiotics, to the southern provinces (Maputo, Gaza and Inhambane) and northern provinces (Nampula, Niassa and Cabo Delgado), while the regional warehouse supplies medicines to the central region of Mozambique (Beira, Manica, Tete and Zambezia). About 60 percent of all medicines and medical supplies imported by CMAM are stored in the national warehouses while 40 percent are allocated to the regional warehouse. By law, Mozambique uses competitive bidding to procure medicines.

Following national-level procurement, all medicines and supplies, with the exception of anti-retroviral therapies, are distributed through the drug kit system or the Via Classic system. Under the drug kit system, CMAM distributes pre-packaged kits with a fixed quantity and range of essential medicines for primary health care directly to provincial stores. The provincial stores are then responsible for distributing the kits to their respective health care units. The quantity and composition of medicines within the kit is determined based on the average consumption of medicines that some provinces, districts and localities send to CMAM on a monthly basis. Forecasting based on previous average consumption, rather than estimated need, is thought to be the best way to overcome the challenges of poor quality storage conditions, lack of storage space and unskilled personnel.

Under the Via Classic system, CMAM delivers requested medicines and supplies to central hospitals, general hospitals and provincial warehouses based on the quarterly combined estimated need of the health facilities in that area. Supplies are then distributed to each health system level by the level directly above it, according to the supply requests of the former and the amount contained in the latter's stock. In the Via Classic system, drug requests are made using a requisition book from the national drug formulary. Since 2010, an electronic program has been used to manage drugs and drug requisition, and this system will facilitate and

expedite the process compared to the manual processes used in past.

The allocation of funds from the government for drug procurement is based on estimated need, which may not be accurately calculated due to a lack of available data. In addition, the allocation of funds is often insufficient to cover the estimated drug costs.

CMAM's biggest procurement constraint is a lack of funding. Insufficient funds for the import and distribution of medicines has resulted in frequent emergency procurements. Given the high rate of antibiotic consumption compared with other drugs, antibiotics are the most affected by periodic stock outs.

Another main challenge of the distribution system is the inefficient delivery system, which also affects drug quality. A cumbersome delivery schedule that takes place only every three months increases the risk of long-term drug storage in less than adequate conditions or past expiration. This results in reduced drug efficacy and the waste of supplies. Additionally, the packaging of some drugs does not appropriately protect and preserve the medicines. Hospitals require a large amount of supplies and drugs, and the regular occurrence of essential medicine stock outs raises concerns about inappropriate or compromised medical treatment.

Rational Use of Drugs

While there is little data available this topic, it is believed that self-medication with antibiotics is a common practice in Mozambique. For example,

one study looking at university students in Maputo revealed that 14 percent of respondents had used un-prescribed anti-infectives (which included antibiotics) during the previous month (Lucas et al., 2007).

Mozambican pharmaceutical law dictates that medicines be prescribed by their generic name and that prescriptions include the associated reference number from the national drug formulary. Different medicines can be prescribed by health professionals depending on their level, which is dictated by the formulary. Until recently, level 0 health professionals (community health workers) were not allowed to prescribe antibiotics. Since 2010, some oral antibiotics, such as amoxicillin, have been included in community health worker kits. This change should drive increased appropriate antibiotic access within the community, but may also drive inappropriate overconsumption.

The national drug formulary also provides guidance to health professionals on how to prescribe antibiotics. While for malaria, TB and HIV there are specific treatment guidelines, no guidance is available for other bacterial infectious diseases.

The Drug Information Center (CIMed) within the Faculty of Medicine, Eduardo Mondlane University, organizes an annual course on rational drug use aimed at doctors and pharmacists who have recently graduated in order to encourage the rational use of medicines, including antibiotics, and to increase knowledge about ways to slow antibiotic resistance.

Part V. Veterinary Antibiotic Use Policies

Antibiotic Use and Resistance in Production and Companion Animals

Antibiotics used in animals can affect both human and animal health in numerous ways. Non-judicious use of antibiotics in production animals may result in the accumulation of drugs in food products for human consumption. In addition, antibiotics used in animals select for bacteria resistant to antibiotics used in humans, which might spread resistance through the food chain (Phillips et al., 2004). While emphasis is often placed on the role of production animals and the food chain in increasing resistance rates, there is a smaller but important risk caused by other interactions between animals and humans that should also be addressed (Surgeons, House, Road, & Sw, 2004).

In Mozambique, there is little data available to quantify the situation of antibiotic use and resistance in animals. However, it is known that antibiotics are commonly used in the veterinary field for growth promotion purposes (mainly in chickens). Antibiotic use in other animals, particularly in food-producing animals such as cattle and pigs and in companion animals, is primarily to prevent and treat infections, rather than for growth promotion. Veterinary antibiotic use is a key component of the

national antibiotic resistance picture, and studies documenting antibiotic use and resistant strains in animals are urgently needed for the development of evidence-based policies in Mozambique (Fafetine, oral communication, 2013). The risk of zoonotic transmission—from animals to humans and vice versa—of infections is unknown in Mozambique but several studies reviewed elsewhere (Guardabassi, Schwarz, & Lloyd, 2004) (Harrison et al., 2014) have demonstrated that companion animals and humans do exchange pathogenic and commensal organisms, highlighting the “one health” view of infectious diseases that the pathogen pool of human and animal populations are intrinsically linked.

Given the low coverage of National Veterinary Services and the absence of a Mozambican Veterinary Council (which will soon be established) responsible for regulating the Vet Act, misuse of antibiotics by technicians and farmers is probably common.

Many private companies sell antibiotics for animal use (Table 5) and anyone can purchase these antibiotics without a prescription. More than half of the available antibiotics are commercialized in various combinations including with other biologically active substances.

Table 5: Typical antibiotics currently available for use in animals in Mozambique

Item	Commercial name	Active ingredient
1	Aliseryl	erythromycin + oxytetracycline + streptomycin + sulfate colistin + vitamins
2	Doxin-200WS	doxycycline + tylosin
3	Intertrim-480 WS	sulfadiazine + trimethoprim
4	Limoxin-400 WS	oxytetracycline
5	Limovit WS	oxytetracycline + vitamins
6	Sulfacox WS	sulfadiazine + sulphaquinoxaline + pyrimethamine + furaltadone + Vitamins
7	Nemovit WS	oxytetracycline + neomycin + vitamins
8	Limoxin-200 LA	oxytetracycline 20 percent
9	Biocilin-150 LA	amoxicillin
10	Procaben LA	procaine penicillin + benzathine penicillin
11	Penstrep-400 LA	procaine penicillin + benzathine penicillin + streptomycin
12	Sulfa-333	sulfadimidine
13	Limoxin-100	oxytetracycline 10 percent

Item	Commercial name	Active ingredient
14	Intertrim LA	sulfadoxine + trimethoprim
15	Cosumix	sulfadoropyradizine + trimethoprim
16	ESB3	sulfadoropyradizine
17	Hipralona	enrofloxacin
18	Hipradox-s	doxycycline
19	Clortadona	erythromycin + oxytetracycline + streptomycin + sulfate colistin + vitamins

SOURCE: (Ministério da Agricultura, n.d.)

Antibiotic Policies

There is an urgent need to develop an antibiotic-resistance management program focused on the use of antibiotics in animals. This program would include the regular assessment of levels and patterns of antibiotic resistance (which pathogens to which drugs in which animals); the development of guidelines and clinical practices; the assessment of current knowledge and practices of farmers and associated antibiotic use and resistance; and the development of a farmers' education program.

The Pharmaceutical Department of the MoH registers all drugs approved for human use. To date, no equivalent procedure exists for veterinary drug use. However, the DNSV recently produced a draft document outlining a process for the regulation and registration of veterinary medicinal products. This document has recently been submitted to the Pharmaceutical Department of the MoH and other stakeholders for revision (Álvaro, personal communication, 2013).

Several laws and regulations govern the use of drugs in animals in Mozambique. These include the 1986 national veterinary medicine formulary, the 1975 animal health regulation, the 2002 regulation on pesticides and the 1973 regulation on meat inspection, among others. The DNSV, which is within the Ministry of Agriculture, is the governmental body responsible for the import of veterinary drugs and medicinal products on the national veterinary medicine formulary in Mozambique. Several attempts to revise the formulary have been made by different entities, including by researchers at the Veterinary Faculty of Eduardo Mondlane University. However, the document has never been successfully modified and is currently non-functional. The DNSV is also responsible for issuing licenses to import drugs and products for veterinary use. There are many companies in Mozambique that import and commercialize veterinary drugs, including antibiotics (Table 6). No pharmacovigilance of veterinary products, including antibiotics, is currently in place in the country and there is a clear need for

Table 6: Main companies that import veterinary drugs, including antibiotics, to Mozambique

Import for sale	Import for consumption	Import for veterinary clinics
Medimoc	Higest	Iba-vet
Tecap	Irvines	Val
Intermed	Companhia industrial da matola	Vet farm
Agro global		HEV – Veterinary School Hospital
Bedson		PETS – Veterinary Clinic
Biochem		
Imunovet		
Avemed		
Mais saúde		
Sogrep		
Merec		

Import for sale	Import for consumption	Import for veterinary clinics
Vetagro		
Okanga representações lda		
Jamon lda		
Agrifocus		
Tijos		
Aca lda		
Delta lab		
Agrobusines		
Crc		

los & oceanic services and trading

SOURCE: (Ministério da Agricultura, n.d.)

monitoring antibiotic use both in animal production and in clinical practice for companion animals.

The use of veterinary drugs in aquaculture is regulated by the Ministry of Fisheries, in accordance with Decree 35/2001. The National Plan for the Control of Veterinary Antibiotic Residues and Environmental Contaminants, managed by the National Institute of Fisheries Inspection, includes an inspection system to ensure that aqua-

culture and fish are safe for human consumption. However, though no formal documentation exists, it is known that during the outbreak of the “White Spot Virus”, Oxytetracycline was used by many of aquaculture businesses affected by the outbreak without much of an impact, in spite of the prompt response (Ministry of Fisheries, n.d.). It is imperative that appropriate legislation for the regulation of antibiotic use in aquaculture is developed.

Part VI. Conclusion

To summarize, in Mozambique the epidemiology, virulence and resistance patterns of bacterial infections both in the community and in hospitals remain unknown in the majority of cases. Very few studies have been conducted outside the Manhiça district, so the summary provides just a fraction of the entire picture. Increased data collection and knowledge about antibiotic use and resistance patterns is important to guide local hospital administrators and clinicians in the reassessment of empiric antibiotic therapy guidelines. Even more importantly, antibiotic resistance levels and patterns need to be regularly monitored through a more systematic national surveillance structure in order to take measures to appropriately address increasing resistance rates.

There is a high burden of bacterial infections in hospitalized children in Manhiça, with the highest

risk occurring among children who are less than one year of age. These infections have an elevated CFR and account for a large proportion of the mortality and morbidity rates within the hospital. Most of these deaths result from acute infections, occurring within 48 hours of hospital admission. Additionally, antimicrobial resistance rates are particularly high to the national recommended first-line antibiotics G penicillin, ampicillin and chloramphenicol. However, quinolones (nalidixic acid and ciprofloxacin) and third generation cephalosporins (ceftriaxone) are still effective against these pathogens. Unfortunately, the majority of the effective classes of antibiotics are expensive and in limited supply, which will constrain their use among the poor even when the recommended antibiotic therapy is ineffective.

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GARP-Mozambique leaders and CDDEP collaborators at the working group launch. (L to R: Antonio Assane, Esperança Sevene, Hellen Gelband, Alix Beith, Betuel Sigaúque.) Photo courtesy of Betuel Sigaúque.



GARP-Mozambique leaders, African GARP collaborators and CDDEP colleagues at the working group launch. Photo courtesy of Betuel Sigaúque.

ABOUT CDDEP

The Center for Disease Dynamics, Economics & Policy (CDDEP) was founded with the objective of using research to support better decision-making in health policy. The CDDEP team employs a range of expertise—including economics, epidemiology, disease modeling, risk analysis, and statistics—to produce actionable, policy-oriented studies on malaria, antibiotic resistance, disease control priorities, environmental health, alcohol and tobacco, and various other diseases.

Many CDDEP projects are global in scope, spanning Africa, Asia, and North America. The strength of CDDEP derives from its researchers' experience in addressing country and region-specific health problems, as well as truly global challenges, while recognizing the circumstances in which the answers must fit. The outcomes of individual projects go beyond the usual models to inspire new strategies for analysis, and innovative approaches are shared through publications and presentations focusing specifically on methodology.

Founded in 2009 as a center of Resources for the Future, CDDEP is an independent non-profit organization. With headquarters in Washington D.C. and New Delhi, CDDEP currently employs full-time staff members in India and the United States, and relies on a distinguished team of academics and policy analysts around the world.

ABOUT CISM

The Manhiça Health Research Centre (Centro de Investigação em Saúde de Manhiça, CISM) was established in 1996 to foster and conduct biomedical research in priority health areas. Begun as a collaboration between the governments of Mozambique and Spain, since 2008 CISM has been managed by the non-profit Manhiça Foundation, created by Mozambique and Spain, the Mozambican National Health Institute (INS) and the Fundació Clínic per la Reserca Biomèdica (Spain). Core funding for CISM is provided by the Spanish Agency for International Cooperation & Development (AECID). Dr. Pascoal M. Mocumbi, a former Prime Minister and medical doctor, is the honorary founder. Representatives of the Universidade Eduardo Mondlane (UEM), the Fundação para o Desenvolvimento da Comunidade (FDC) and ISGLOBAL serve on the Board of Trustees.

CISM studies priority health problems, including malaria, HIV/AIDS, tuberculosis, diarrheal diseases, acute respiratory infections and invasive bacterial diseases, including antimicrobial-resistant infections. CISM generates scientific evidence relevant to health policies in Mozambique and the world at large. It has become a leading biomedical research organisation on the African continent, and one of the few rural African research centres. CISM's Training Fellowship Program has contributed to Mozambican scientists completing 15 PhDs and 18 Masters degrees.

CISM participates in a host of international and regional research networks, collaborating with nine national institutions and 40 international organizations in 19 different countries in Africa, Europe, America, Asia and Oceania.

**The full report and executive summary are available at
www.cddep.org/GARP**

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