Global Antibiotic Resistance Partnership

KENYA MEDICAL RESEARCH INSTITUTE
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SITUATION ANALYSIS AND RECOMMENDATIONS

Antibiotic Use and Resistance in Kenya

The GARP-Kenya Working Group

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GARP-Kenya Working Group

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Foreword

Since their discovery in the early 20th century, antibiotics and related medicinal drugs have substantially reduced the threat posed by infectious diseases. Over the years, these antimicrobials have saved the lives and eased the suffering of millions of people, especially in developing countries where infectious diseases remain a big challenge. Even in conditions of abject poverty and poor infrastructure and services, antibiotics have worked wonders. These gains are now seriously jeopardised by the emergence and spread of microbes that are resistant to most commonly available and effective 'first-line' drugs. For most of sub-Saharan Africa, the arsenal of antibiotics is already very limited. Any breach on the list leads to near-total loss of treatment choices for many severe infections.

In Kenya, the bacterial infections that contribute most to human disease are often those in which resistance is most evident. Examples are multidrug-resistant enteric bacterial pathogens such as typhoid, diarrhoeagenic Escherichia coli and invasive non-typhi salmonella, penicillin-resistant Streptococcus pneumoniae, vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus and multidrug-resistant Mycobacterium tuberculosis. Resistance to medicines commonly used to treat malaria is of particular concern, as is the emerging resistance to anti-HIV drugs. Often, more expensive medicines are required to treat these infections, and this becomes a major challenge in resource-poor settings.

Although overuse and misuse of antimicrobials have contributed to the emergence and spread of resistance, paradoxically, underuse through lack of access, inadequate dosing, poor adherence, and substandard antimicrobials may play an equally important role. And of course, complete lack of access can mean death, especially for infants and children. A great hindrance to fixing these problems is the difficulty of implementing policies and guidelines, usually a result of inadequate regulatory authority and insufficient resources for enforcement. Loud whispers of 'capsule! capsule!' at busy and crowded bus stops are common as peddlers hawk drugs on the street. In many chemist shops across Kenya one easily purchases antibiotics (any proportion of actual dosage) over the counter, without prescription.

Even with the best intentions to implement guidelines for improving the use of antibiotics, we cannot. Local data on usage and resistance are inadequate to give a true reflection of the situation in Kenya, and the resources to do the job are not available. Only well-coordinated national surveillance will provide the necessary data for risk analysis and risk assessment. Our central reference laboratory will require personnel and funding support to take up this role. The situation analysis presented here gives a bird's-eye view of the usage and resistance data currently available for Kenya, and the recommendations have been tailored to the situation as we understand it. Using this and information from other parts of Africa and the world, we can plot a course for the short term and beyond by thorough analysis of the policy options open to us. We must make the case that taking steps to control antibiotic resistance is worthwhile and that we can make a difference at reasonable cost. That is our challenge for the next year. We welcome ideas, comments and assistance from all quarters. I invite you to read, reflect and share your ideas with me and other members of the GARP Working Group–Kenya.

Samuel Kariuki
Director of the Centre for Microbiology Research, Kenya Medical Research Institute

Executive Summary

The past decade has been a period of positive change for the public health of Kenya. Looking ahead, the constitution adopted in August 2010 declares health a 'basic human right'. According to results from the 2010 Demographic and Health Survey, poverty and child mortality have decreased, and a larger proportion of the population has access to healthcare—including life-saving antibiotics. Despite these improvements, the infectious disease burden in Kenya remains high. This combination of improved access to medication and demand for antibiotic treatment in fighting infections has brought with it an uninvited but not unexpected guest: antibiotic resistance.

As with other shared resources, antibiotics consumed by an individual—whether the individual benefits from the antibiotic or not—'uses up' a bit of the effectiveness of that drug. As antibiotics become less effective, Kenyan citizens and the government will be forced to either pay more for newer drugs to replace the inexpensive standards or forgo treatment because it is too costly. In some cases, antibiotic resistance rates are already high. The eventual loss of antibiotics that are now effective is inevitable, but it can happen years from now or decades from now, depending upon near-term actions. The growth of resistance rates can be slowed and even reversed as the health of the public is enhanced, by preventing many infections through vaccination; by better targeting antibiotic use for curable bacterial infections rather than viral, fungal, or parasitic illness; and by reducing non-therapeutic uses of antibiotics in livestock and poultry.

The Global Antibiotic Resistance Partnership (GARP), now completing its initial phase, aims to develop policy responses to manage antibiotic effectiveness through the actions and recommendations of multidisciplinary working groups representing both the public and private sectors, which consider the conditions and characteristics that determine what policy changes are feasible and likely to have an effect in the local context. In addition to Kenya, the three other founding GARP countries are India, South Africa and Vietnam. Each has gone through a similar process to assess the current situation and develop a menu of tailored policy options. In the next phase, the Working Groups in each country will finalize detailed recommendations (in a process described below) and new countries will join the Partnership.

Antibiotic Resistance

Around the world, bacterial pathogens are becoming ever more resistant to antibiotics. The 'first generation' of antibiotics is already of little use in many countries. Now some of the more expensive second- and third-generation antibiotics are losing effectiveness against infectious diseases common in low- and middle-income countries. The World Health Organization (WHO) has an ongoing initiative to develop interventions for reclaiming the effectiveness of antibiotics against global and local strains of resistant bacteria.

There can be no doubt that Kenya is already experiencing high levels of antibiotic resistance, and in most cases, it is worsening. Exactly how high the rates are currently or how quickly they are increasing is not known with any certainty, however, because antibiotic resistance surveillance is not systematically conducted in the country. Findings of high rates of resistance—for respiratory infections, for enteric infections and for infections acquired in healthcare facilities—indicate that many antibiotic regimens supplied by the government are unlikely to be effective against infections of wide concern.

Respiratory Infections

Streptococcus pneumoniae. Twenty-five percent of *S. pneumoniae* isolates in Nairobi were resistant to penicillin in the mid-1980s, and by 2003, 43 percent were resistant (Paul, Bates et al. 1996; Kariuki, Muyodi et al. 2003). Half were resistant to cotrimoxazole in 2002, and 7 percent were resistant to two or more first-line treatments (Mwangi, Berkley et al. 2002; Kariuki, Muyodi et al. 2003).

***Haemophilus influenzae* type B.** For children in Kilifi, the combination of amoxicillin plus chloramphenicol was effective against *H. influenzae* type B half the time in 2001 but only 32 percent in 2002 (Scott, Mwarumba et al. 2005). Up to 66 percent of isolates were resistant to cotrimoxazole in 2002 (Mwangi, Berkley et al. 2002; Kariuki, Muyodi et al. 2003).

Severe pneumonia. In 2005, half the children with severe pneumonia were infected with isolates that were resistant to penicillin in the laboratory (Berkley, Maitland et al. 2008).

Diarrheal Infections

Bacterial diarrhoea. In 2001, more than half the pathogens in the Western province were not susceptible to first-line antibiotics, and three-quarters were resistant to three or more agents (Shapiro, Kumar et al. 2001; du Prey, Ford et al. 2004).

Non-typhi *Salmonella* (mainly gastrointestinal infections). In the mid-1990s, more than 45 percent of isolates were resistant to ampicillin, cotrimoxazole or both. By 2005, resistance had risen to 94 percent for ampicillin and 67 percent for cotrimoxazole (Kariuki, Gilks et al. 1996; Kariuki, Revathi et al. 2005; Kariuki 2009). Reports of multi-drug resistant Non-typhi *Salmonella* in hospital and community settings are also cause for concern, rising from 31 percent in 1993 to 42 percent in 2003 (Kariuki, Revathi et al. 2005; Kariuki 2010). Isolates also demonstrate resistance to extended-spectrum cephalosporins and fluoroquinolones.

Dysentery (*Shigella* spp). As early as 2003, *Shigella* isolates were highly resistant to ampicillin (85 percent), cotrimoxazole (94 percent), chloramphenicol (91 percent) and tetracycline (100 percent) (Bartoloni and Gotuzzo 2010). Frequently, isolates are resistant to all of these antibiotics and to coamoxiclav (Kariuki, Gilks et al. 1996).

Typhoid fever (*Salmonella* Typhi). The spread and gradual replacement of drug-sensitive strains of *Salmonella* Typhi with multidrug-resistant strains threatens to reduce clinical options for treating typhoid fever (Kariuki 2010). Surveillance at Kenyatta National Hospital indicates that the prevalence of *S*. Typhi resistant to two or more antibiotics has been rising, from 50 percent in 1998 to 70 to 78 percent in 2004 (Kariuki, Revathi et al. 2004; Okeke and Ojo 2010). From 2000 to 2002 in Nairobi, Embu district and Thika, 82 percent of the strains were resistant to each of the five commonly used drugs—ampicillin, chloramphenicol, tetracycline, streptomycin and cotrimoxazole (Kariuki, Revathi et al. 2004).

Nonpathogenic 'commensal' bacteria. In young children, nonpathogenic *Escherichia coli* isolates are highly resistant to the second-line agent ciprofloxacin and common antibiotics like cotrimoxazole (68 percent), tetracycline (71 percent) and ampicillin (66 percent) (Bii, Taguchi et al. 2005; Kariuki 2009; Kariuki 2010). In Kilifi, *E. coli* exhibited resistance levels as high as 85 percent to cotrimoxazole, 78 percent to amoxicillin and 42 percent to chloramphenicol (Bejon, Mwangi et al. 2005).

Hospital-Acquired Infections

Hospital-acquired infections (HAIs) are a problem worldwide. HAIs increase the likelihood of death, prolong hospital stays, and can be very expensive to treat. And because antibiotics are so heavily used in hospitals, hospitals are perfect breeding grounds for antibiotic resistance. In Kenya, only a few studies have reported HAI rates. These suggest that up to 17 percent of neonatal patients and 40 to 50 percent of intensive-care unit (ICU) patients become infected. As in other countries, surgical site infections, infections of the urinary tract and pneumonias are the most common.

Factors Affecting Antibiotic Resistance Rates

Burden of Infectious Disease

The top five killers in Kenya are infectious diseases, but data documenting the portion caused by bacterial pathogens are not collected systematically. Most of what is known comes from site-specific, hospital-based studies. Yet the majority of illnesses and deaths occur outside the hospitals, where diagnostic facilities are few.

Acute respiratory infections (ARIs) are the second leading cause of death in all ages across the country, with pneumonia as the largest contributor to the burden of disease among children living in 'urban informal settlements' or slums. Diarrhoeal disease in Kenya ranks third as a cause of death, contributing to 16 percent of all mortality in children under five. Specific forms range from watery diarrhoea, treatable with oral rehydration therapy, to regular outbreaks of cholera, typhoid fever, shigella dysentery, and non-typhoidal salmonella. ARIs and diarrhoeal episodes are among the most frequent reason for antibiotic prescription and sales and are often diagnosed empirically. Their high incidence rate and the difficulty of determining their exact etiology remain critical challenges to rationalizing antibiotic use in Kenya.

HIV/AIDS, the country's leading cause of death in all ages, and malnutrition predispose people to invasive bacterial disease and pneumonia. Antibiotics are increasingly used to prevent and treat opportunistic infections in people living with HIV. Many take cotrimoxazole daily as prophylaxis, raising concern over the emergence and spread of resistance to this cheap and well-tolerated drug.

Healthcare Environment and Behaviour

Antibiotics are also misused—their effectiveness wasted—in patients with conditions that cannot be cured by antibiotics. This practice is common not only among people who purchase antibiotics themselves, but also by doctors and other licensed prescribers. Studies from Kenya have uncovered an array of possible reasons for this behaviour that is similar to what has been found in other countries:

- lack of microbiology facilities and diagnostic capacity;
- fear of negative outcomes if antibiotics are withheld, particularly with malaria patients;
- limited access to formal healthcare services and the prevalence of self-medication; and
- insufficient knowledge about appropriate use of antibiotics.

Lack of diagnostics and fear of negative outcomes. Patients who make it to the hospital often arrive with serious infections, but in many places in Kenya, microbiology services are limited to nonexistent. In cases of life-threatening diseases, a culture result often takes longer to obtain than the time necessary to correctly treat the patient at risk of death. Frequently, the expense of laboratory services (often paid directly by the patient), where available, is beyond patients' means, and they decline a culture test. The infecting organism (bacterium or not) cannot be identified in such contexts, nor can its antibiotic resistance profile be determined in the event of bacterial disease. Thus, broad-spectrum antibiotics are applied. Improved use and quality of diagnostics that match pathogens with narrow-spectrum antibiotics could avert some of the resulting loss in effectiveness and would certainly avoid the use of antibiotics for viral and other diseases.

Access and self-medication. Since independence, Kenya's government has given high priority to improving the health status of citizens and has recognised health as a prerequisite to social and economic development. Health spending in Kenya has decreased, however, since reforms in 2002, from 9 percent to less than 6 percent of the government budget at present (Ministry of Health 2007; Ministry of Finance 2009). Of total health expenditures, the government share is low, 30 percent, compared with 75 percent in developed

countries. Households provide the largest share, 53 percent, through user fees (World Health Organization 2006; Wamai 2009). This means that currently, healthcare financing is dependent primarily on household out-of-pocket expenditures. Meanwhile, the 2009 Budget Strategy Report recommends a *decrease* in government health spending.

Inadequate access to formal healthcare and medicines leads to self-medication and fuels irrational use through underdosing and poor adherence. Access is difficult to define but plays an important role in people's healthcare decisions, including those concerning antibiotics. The high costs faced by patients in the formal healthcare system encourage them to bypass providers and purchase medicines without receiving a diagnosis. Around half of ill patients visiting the hospital previously seek care from informal drug sellers in rural, western Kenya and more than one-third of Nairobi residents use retail pharmacies as the first site for outpatient care (Kakai and Wamola 2002; Kwena, Sharma et al. 2008; Thoithi and Okalebo 2009; Bigogo, Audi et al. 2010; Karambu 2011). Legally, a prescription is required, yet consumers can purchase antibiotics over the counter at pharmacies and other shops. An estimated 70 percent of pharmacies dispense antibiotics without a doctor's prescription (Kakai and Wamola 2002; Kwena, Sharma et al. 2008; Thoithi and Okalebo 2009; Karambu 2011).

But while self-medication is very common, it is not very accurate. Staff at retail pharmacies, many of which are unlicensed and poorly managed, may recommend the wrong treatment or provide incorrect dosage levels. Patients with limited incomes may want to purchase only part of a recommended course and can more easily negotiate this practice at a local shop than in a formal healthcare facility. To stem the tide of antibiotic resistance, policymakers look for ways to limit antibiotic use—for example, by enforcing 'prescription only' laws for antibiotic sales. The situation is not simple, however. In Kenya, one is confronted with evidence of both overuse and underuse. The evidence for underuse—a lack of access to antibiotics—comes from the large proportion of deaths from pneumonia during infancy and childhood, which would not occur if those children were properly treated with antibiotics.

Although access is related to socioeconomic status, the reasons may not be directly financial; low education levels, lack of nearby facilities, and inconsistent presence of both medicines and healthcare workers also contribute. Would even more people go untreated and die if nonprescription access were cut off? In Kenya, we do not have the data to answer this question.

Lack of knowledge. Despite national treatment guidelines and other information, knowledge about antibiotic use is poor among healthcare workers. ARI and diarrhoea management often includes antibiotics, whether needed or not. When antibiotics are indicated, the type, dosage and duration of treatment prescribed by health workers are not necessarily consistent with the guidelines. For example, in district hospitals, nearly three-quarters of the antibiotics prescribed for pneumonia were for very severe cases even though only 16 percent of recorded admissions fell into this category (English, Esamai et al. 2004). In a survey of providers' knowledge about watery diarrhoea, 71 percent of clinicians cited antibiotics as among the most effective treatments (Ram 2008). Misinformation among health workers regarding the antiviral properties of common antibiotics was also frequent, with 73 percent of clinicians reporting that antibiotics kill viruses causing diarrhoea.

Antibiotic Use in Animals

Evidence on antibiotic use in farm animals indicates that these medicines are used primarily (90 percent) for therapeutic applications. Further investigation is warranted, however, since a survey of farmers found that the majority conflated treatment with prevention, effectively replacing hygiene and feeding practices as standard disease preventions with disease treatment (Kariuki, Gilks et al. 1997). Growth promotion does not appear to be an important source of antibiotic use in livestock production in Kenya.

More than half of the antibiotics used in livestock production are tetracyclines, popular for their broad-spectrum activity and relative affordability (Mitema, Kikuvi et al. 2001). Sulfonamides follow at around 21 percent, with aminoglycosides, beta-lactams, quinolones and macrolides constituting the rest. Poultry alone accounts for nearly one-fifth of mean consumption per year. The remaining consumption is shared among large animal—cattle, sheep, pigs and goats. Presently, antibiotic use in fisheries is unknown, but may become an important issue as the industry grows.

In Kenya, like most of the African continent, there is no formal system for surveillance of antibiotic resistance in agricultural bacterial isolates. The Department of Veterinary Services does, however, monitor antibiotic residue in agricultural products. A few studies indicate resistance to tetracycline and sulphonamides among chicken and swine bacterial isolates, possibly related to the crowded conditions in which the animals are housed and the greater potential for the spread of disease. An estimated 36 percent of salmonella isolates in pork tissue demonstrated resistance to ampicillin, tetracycline, streptomycin and chloramphenicol. Although ampicillin, tetracycline and streptomycin are easily available to farmers, chloramphenicol is not approved for use in food animals. Resistance, therefore, may indicate illegal use of the drug. Patterns of resistant *Staphylococcus aureus* in cattle imply a significant difference in resistance profiles of large- and small-scale farms, with smaller producers using nearly twice the amount of antibiotics per animal compared with larger producers (Shitandi and Sternesjö 2004). The prevalence of multidrug resistance, at 34 percent on small farms, was likewise almost double the rate found at large farms.

Although laws regulate the use of drugs in animal feed, enforcement and monitoring are inadequate. The Kenya Veterinary Association recently found that 78 percent of veterinary medicine outlets are operated by people not considered legally qualified for the position (Kenya Veterinary Association 2009). As with the human population, lack of access to professional diagnosis spurs self-medication, with farmers purchasing antibiotics from retail pharmacies in an environment of limited veterinary services. Reducing demand through improved sanitation and restricting use to when antibiotics are needed are policy options that deserve greater exploration.

Efforts to Address Antibiotic Resistance

Kenya has an array of policies that, while not directly aimed at containing antibiotic resistance, have proven effective at reducing the demand for and associated irrational use of antibiotics in other countries. They include adoption of the WHO-recommended *Haemophilus influenzae* type b (Hib) and 10-valent pneumococcal conjugate vaccines to prevent frequent causes of pneumonia; the launch of national hospital infection control guidelines; and support of surveillance of bacterial disease and resistance profiles in humans and antibiotic residues in livestock. Other facility-based measures, such as professional education and surgical checklists, are more site- and context-specific. Many of these interventions have yet to be thoroughly evaluated for their effectiveness in Kenya.

Surveillance. National surveillance for antibiotic resistance is a low government priority—lower than microbiology services for patient care. However, efforts exist within Kenya to provide quality surveillance on the resistance trends in clinically significant pathogens. These include facility-level reports on resistance patterns in HAIs (U.S. Centers for Disease Control and Prevention offices in Kenya [CDC-Kenya]), the number of episodes and drug susceptibility profiles of pneumonia (KEMRI - Wellcome Trust Research Programme), and tracking drug resistance, use and MRSA infections at Aga Kahn University Hospital in Nairobi. The Department of Veterinary Services monitors antibiotic residue in agricultural products for purposes of food safety, and the Kenya Medical Research Institute started a country-wide surveillance study on antibiotic resistance rates in poultry.

GARP–Kenya Research

One of the aims of GARP–Kenya is to fill information gaps by identifying the groups working on resistance issues nationally and supporting their research. Projects during the first phase of GARP included two areas not well studied in Kenya:

- **Survey on perceptions of antibiotic resistance and use in district hospitals**
  Ecumenical Pharmaceutical Network, Donna Kusemererwa (PI)

  Data on antibiotic prices, profitability to the supplier, and affordability to the patient or consumer were gathered, along with information on the volumes of antibiotics stocked at various district hospitals. Researchers also surveyed the knowledge and perceptions of health workers in hospitals to inform interventions focused on raising awareness and conducting education campaigns. The results from this study are found in Part IV (Antibiotic Use and Supply Chain).
- **Antibiotic resistance in livestock and associated follow-back survey on antibiotic use in livestock producers**
  Kenya Medical Research Institute, Centre for Microbiology Research, Samuel Kariuki (PI), and University of Nairobi, Patrick Irungu (PI)

  This pilot study lays the groundwork for ongoing surveillance of antimicrobial resistance and use in farm animals. It first determined patterns of resistance in *Salmonella* spp, *Campylobacter* spp, *Escherichia coli*, and *Enterococcus* spp isolates collected from healthy livestock and animal products found at retail meat outlets. Second, it assessed whether low or high resistance patterns were correlated with demographic and behavioural factors of animal husbandry, including the volumes and applications of antibiotics used in livestock production. Specific findings can be found in Parts III (Burden of Disease and Antibiotic Resistance) and IV (Antibiotic Use and Supply Chain).

Vaccines and prevention. Vaccines are among the best ways to prevent bacterial disease. In 2001, Kenya was among the first nine countries to introduce the Hib vaccine into routine immunisation services, dramatically cutting the annual incidence of Hib meningitis from 71 to 8 and Hib pneumonia from 296 to 34 per 100,000 children under five years (Sinha, Levine et al. 2007). Following the success of the Hib vaccine, the government introduced the 10-valent pneumococcal conjugate vaccine in February 2011. As coverage expands for these vaccines, mortality is expected to be cut by half in young children (English and Scott 2008).

Insurance and access. Who pays for healthcare—for antibiotics, for vaccines and for services in general—is important. Kenya's current heavy reliance on out-of-pocket expenditure affects decisions about whether to seek formal healthcare, purchase a drug directly, or visit an informal provider. To improve the situation, Kenya is attempting to expand health insurance through the National Hospital Insurance Fund (NHIF). The NHIF board has proposed a progressive increase in statutory contributions, to enable the fund eventually to provide universal healthcare, including medicines. An estimated seven percent of the population is currently enrolled in health insurance through NHIF.

The drive for greater insurance coverage is not without controversy, however. NHIF's chequered past includes fraud and mismanagement, causing concern that an increase in fees will not bring added benefits or expanded membership.

Infection control. The Ministries of Health launched national and site-specific policies and guidelines on infection control in December 2010. The policy calls prevention and control of infections 'essential cornerstones' in addressing the emergence of antibiotic resistant bacteria and notes resistance as a 'major problem for patient safety'. It also states that the increase in antibiotic-resistant organisms 'undermines progress made in the fight against infectious disease and poses a serious challenge to healthcare systems'.

As part of its vision, the policy intends to respond to resistance by providing guidance to healthcare workers on ensuring the safe management of infectious conditions. Although these guidelines are an important step towards national recognition of the issue, their ability to lower rates of hospital-acquired infections and reduce the development of antibiotic resistance is unknown.

Recommendations: Interventions against the Development and Spread of Resistance

Ideally, new policies would be designed to improve access to antibiotics where it is lacking and where the drugs might save lives, at the same time curtailing use where these drugs are unnecessary. Unfortunately, the evidence supporting interventions invariably comes primarily or exclusively from outside Kenya, and only a small amount from other low- and middle-income countries. As a result, the approaches that are emphasised generally do not concern improving access. With awareness of potential adverse effects on access, however, modifications could be made to avoid them.

- Three main approaches are applicable in Kenya:
- increased use of vaccines that reduce disease and, therefore, the demand for antibiotics;
- improved infection control, including procedures (e.g., hand hygiene, checklists) and information (e.g., guidelines, feedback), particularly in hospitals; and
- education and public awareness campaigns for providers and consumers.

The success of all approaches is dependent on better information from microbiology laboratories, in the form of surveillance. The specifics of developing an appropriate nationwide surveillance system and standardizing methods must be determined, but without knowing where we are with antibiotic use and resistance and a way to monitor changes over time and different between places, we will never know what is and is not working.

Three additional approaches deserve mention though they are not immediately implementable. They are:

- Increased use of (and improved) diagnostics, to better target antibiotic use,
- Fixing supply chain constraints and failures and
- Developing economic incentives (which may involve subsidies) to encourage better use of antibiotics

In March 2011, the Global Antibiotic Resistance Partnership (GARP)–Kenya Working Group, in collaboration with the Center for Disease Dynamics, Economics & Policy (CDDEP), convened a policy development workshop to identify ways stakeholders across diverse sectors and specialties could respond to the emergence of antibiotic resistance. The summary table (Table 1) outlines the policy actions discussed, their benefits and feasibility. Ongoing collaboration and discussion will be vital to determining implementation strategies for each recommendation. Facilitating consultations with stakeholders and updating recommendations as necessary will be an important aspect of the next phase of the GARP–Kenya agenda.

Focus Areas

In addition to producing necessary information on which to proceed, the recommendations are aimed at *reducing the need* for antibiotics and better *targeting* of antibiotics. Both approaches should lower overall demand. Five critical areas of disease management and access to effective treatment are targeted:

- surveillance and monitoring,
- training and education,
- vaccination,
- quality control and supply chain improvements and
- veterinary use of antibiotics.

Surveillance and Performance Monitoring. Although antibiotic resistance surveillance and performance monitoring do not themselves produce change, without knowing the levels or trends of antibiotic resistance or how key actors are performing, it is impossible to make rational recommendations or monitor the effectiveness of interventions. The prevalence of resistance, influenced by a host of local factors, varies within the country and between pathogens. This is particularly worrying in countries like Kenya, where the majority of infectious diseases are empirically diagnosed and patient management often depends on early, appropriate antibiotic administration.

Surveillance of antibiotic use (including indications) and of antibiotic resistance is recommended. Models that could be adapted for Kenya are available and should be considered.

Training and Education. Training and education can target healthcare staff at hospitals and dispensaries, clinicians and other prescribing health workers, and chemists and workers in private pharmacies, all of who can be sources of health advice and treatment. These groups receive varying amounts of information on antibiotic use and resistance.

Further, even though the development of standard treatment guidelines (STGs) and essential medicines lists (EMLs) in Kenya is cited as a model example, up-to-date guideline revisions are poorly communicated and the documents are hard to access within facilities. When coupled with educational interventions, however, guidelines can improve prescribing.

Vaccination. Every year, millions of children in Africa die before reaching their fifth birthday from treatable illnesses such as pneumonia and diarrhoea. The primary causes of most cases of these diseases—pneumococcus, *Haemophilus influenzae* type B (Hib) and rotavirus—are now preventable through vaccination. The health gains from these vaccines are unmatched by any other interventions. As a secondary benefit, vaccination can also decrease the use of antibiotics by reducing the need for them. In some cases, such as acute diarrhoea, vaccines may reduce unnecessary and inappropriate antibiotic use. A major constraint to introducing new vaccines or increasing coverage is financing, which will not be resolved in relation to antibiotic use or resistance.

Continued emphasis on adding vaccines and improving coverage are recommended. Strategies for this are well established, as are the challenges.

Quality Control and Supply Chain Improvements. The problem of antibiotic resistance cannot be addressed through interventions aimed solely at reducing antibiotic use. In countries where the burden of infectious diseases remains high and barriers to treatment are common, ensuring greater access to effective antibiotics is important. Most people who lack access to antibiotics are struggling with extreme poverty or living in remote areas and may face the highest burden of infectious disease.

The prevalence of substandard antibiotics in Kenya is unknown, yet the issue of poor-quality medicines is widely discussed in the media and inside government ministries. Poor-quality manufacturing, packaging,

transportation and storage conditions, as well as counterfeiting can place substandard drugs in patients' hands.

Access to effective treatment also encompasses adequate financing and supply of essential antibiotics. Even if patients can afford medicines and reach a facility, a large number of 'vital' antibiotics listed on the Kenya essential drugs list are absent or in short supply in dispensaries and hospitals.

Each of these problems has been addressed successfully in other low-resource settings, and beginning this process is recommended for Kenya.

Reducing Veterinary Use of Antibiotics. Animals require antibiotics for treatment of infections, but antibiotics are widely used in low doses as growth promoters and for disease prophylaxis. In Europe, it has been demonstrated that much of this use can be avoided without harming animal or human health. The particular actions have been to outlaw the use of antibiotics for growth promotion, to prohibit the use in animals of antibiotics of particular importance to human health and to limit antibiotic residues permitted in food. Since 2010, the Kenyan government has prohibited the use of chloramphenicol and nitrofurans in food-producing animals, including for use in growth promotion but little is known about how effective this ban has been.

As with human, increased adoption and coverage with appropriate animal vaccines is also important and a strategy welcomed by Kenyan farmers.

Finally, education and training about the use of antibiotics and ways to reduce that use for the range of stakeholders may also be of benefit.

Additional Strategies. Three additional strategies would support the four critical areas described above—monitoring and surveillance, training and education, vaccination, and quality control and supply chain improvements—but require further development and detail before being recommended. All may be addressed in the next phase of GARP.

- improved microbiology services and rapid diagnostic testing;
- chemist accreditation; and
- stronger medicine and therapeutic committees in hospitals.

Summary Table of Policy Options

Addressing antibiotic resistance requires action by hospitals, the community, livestock producers, health workers and the government. The table below presents the major action items recommended by the GARP–Kenya Working Group and additional stakeholders. These will be taken up in the next phase of GARP, when 'critical paths' will be developed for those policies with the highest likely impact and feasibility.

Action area	Intervention, policy	Notes	Feasibility
Hospital Infection Control			
Surveillance and monitoring	Conduct HAI surveillance, with public reporting. Document rates of HAIs and, where possible, consequences (mortality, extended hospital stay, attributable cost, resistance).	Useful where HAI rates are mistakenly perceived as low and ICP is presumed good. Studies in other countries show improved infection control practices following outcome surveillance. Could discourage patient transfers and referrals.	Hospitals lack ability to determine HAIs. Referral system makes it difficult to determine origin of infections.
Education and training	Incorporate ICP into all curricula. Base curricula on national ICP guidelines and include activities and projects in hospitals to increase learning. Rely on professional associations to provide schools and trainings. Support IPC curricular development and coordinate across schools and training opportunities through MoH.	Doctors and other clinical staff may not consider themselves part of hospital ICP system. Inadequately trained members of ICCs may lack knowledge or motivation. No studies show long-term improvement in practice from education interventions alone.	Not expensive, but difficult to maintain over time. Members of ICCs and professional associations generally express interest in ongoing education. Requires administrative support to develop curriculum and ensure use in educational settings.
Hospital Antibiotic Use			
Surveillance and monitoring	Conduct resistance and antibiotic use surveillance, with public reporting and STGs based on regional susceptibility data. Document and report resistance rates and, where possible, the consequences (mortality, extended hospital stay, attributable cost). Include antibiotic use rates by department.	Useful where HAI rates are mistakenly perceived as low or without consequence. Potential to address appropriate medicine use, as well as capture emergence and spread of resistance.	Hospitals lack human resource capacity, infrastructure and financial means to perform resistance surveillance. Labs are underutilized.
Education and training	Educate and train all providers on STGs and antibiotic use. For prescribers, focus on new (2010) STGs and antibiotic use and resistance. Conduct audits on prescribing patterns to monitor intervention effect. Include feedback from handouts, group discussions and peer review, or from refresher courses.	Helpful where STGs exist and standards are known but not followed. Studies show that training on STGs plus audits, feedback and peer review reduce antibiotic use. Training alone has little effect; audits and feedback are critical.	At hospital level, not expensive to implement. May be difficult to implement monitoring and feedback at regional or national scale. Hospital administrators must be motivated to adopt practice. Collecting prescribing data is challenging in district-level hospitals.

Community Use			
Vaccination	Improve long-term financing for vaccines against bacterial pneumonia (Hib and PCV-10). Build capacity of local manufacturers to produce vaccines for domestic market at reduced prices through technology transfers and private-public partnership.	Can decrease antibiotic use by reducing the need to treat bacterial disease. Long-term financing concerns for national immunization program could be eased by producing vaccines locally at lower cost.	Strategy is relatively untested. Good strategy and implementation models do not exist.
Education and training	Train staff at private pharmacies and provide certification for training. Use one-on-one sessions to train chemist shop owners in antibiotic use, resistance and STGs and laws on prescribing. Follow with small-group training for counter attendants. If possible, collect feedback or conduct sales audits for private pharmacies and chemists.	Study found that one-on-one meetings with pharmacists, followed by small-group training sessions with attendants, improved use of oral rehydration therapy and antibiotics in short term. Long-term effects and generalizability to other health conditions (e.g., acute respiratory infections) are uncertain. No studies show long-term improvement in practice after workshops.	Not expensive to implement. Organizations capable of providing training are available. Unlicensed chemist shops concerned about being discovered and shut down may be reluctant to participate. Turnover of trained staff would undermine effectiveness.
Education and training	Conduct broad public awareness campaign about antibiotic use, coupled with small-group training for mothers about medicines; involve community advocacy groups. Use popular media (radio, TV, newspapers) and gatherings (village market days, mamas groups, community leader meetings) to disseminate messages about antibiotic use, antibiotic substitutes (e.g., oral rehydration therapy), and dangers of self-medication. Consider use of package inserts in literate communities.	Broad media campaign launched with package inserts was effective in Indonesia with small groups of mothers taught to review inserts.	Not difficult to plan or implement. Can replicate models used for other public health campaigns in region.

Insurance	Review expansion of NHIF by committee within PPB or MOMS pharmaceutical division. Consider how NHIF expansion can help or hinder community access to clinical diagnosis and full courses of appropriate antibiotics.	High out-of-pocket costs drive OTC sales of small doses of antibiotics and sharing and hording of drugs; insurance may offset this.	NHIF expansion must reach those most in need. Unclear whether mandate will cover those who now buy small doses of antibiotics OTC.
Livestock Use			
Surveillance	Establish national surveillance system for antibiotic resistance and use in livestock production.		
Education and training	Train farmers in alternative methods of disease prevention (e.g., herd and flock hygiene). Consider demonstration booths or lecture sessions on market days, village demonstrations on agricultural hygiene and sanitation, and small-group training sessions with agricultural cooperatives at district or village level.	Education interventions have not had sustainable effect on practice in human medicine. Effect on animal husbandry is unknown.	Unclear who should conduct training for farmers. Cost is unknown: inputs are not expensive, but reaching farmers in rural areas may be costly. Farmers may require demonstration of economic benefit.
Supply chain and vaccines	Review current recommendations for vaccines and rates of vaccination for poultry, cattle and hogs. If necessary, update recommendations to include vaccines that prevent diseases commonly treated with antibiotics. Review and improve coverage of vaccines.	Animal vaccination may reduce therapeutic use of antibiotics by reducing incidence of disease.	DVS policy on vaccinations is unclear. Farmers' access to vaccines is unknown, as is cost of vaccination compared with antibiotic prophylaxis and treatment. Field assessments show that demand for vaccines is high and farmers want to learn more.

Government Regulation and National Health System			
Quality control	Enhance anticounterfeit and medicine quality control efforts. Consider education for judiciary, improved reporting channels, public information campaigns, routine surveys of medicine quality, blister packaging, and mPedigree platform.	Options listed have shown some effectiveness in case studies. Legal measures have not proven significant.	Enforcing regulations would be difficult. Such interventions lack funding support from donors and international agencies.
Education	Create national antibiotic guidelines ('guideline of guidelines for antibiotics') listing clinical situations in which antibiotics can be used and describing economic and health costs of resistance. Provide training for health workers on using guidelines.	Can be used as advocacy tool with government and as assessment tool at facility level. Guidelines have shown little effectiveness without training and education.	Feasible and relatively simple to produce but will take time to develop.
Supply chain improvement	Place price or mark-up controls on antibiotics to increase access. Legislate a maximum retail price on essential antibiotics, based on constitutional right to have access to essential medicines. Institute measures to improve prescribing and dispensing of antibiotics in formal and informal health sectors.	Could be effective, but examples and case studies are few. Experiences from other countries should be assessed as models to follow or mistakes to avoid.	Possible EAC implications and backlash from retailers and hospital administrations.

Abbreviations: DVS = Department of Veterinary Services; EAC = East African Community; HAI = Hospital-Acquired Infection; ICC = Infection Control Committee; ICP = Infection Control Practice; MoH = Ministry of Health; MOMS = Ministry of Medical Services; NHIF = National Health Insurance Fund; OTC = over-the-counter; PPB = Poisons and Pharmacy Board; STG = standard treatment guideline

Part I. The Global Antibiotic Resistance Partnership (GARP)

The global problem of antimicrobial resistance is particularly pressing in developing countries, where the infectious disease burden is high and cost constrains the replacement of older antibiotics with newer, more expensive ones, even when the older ones are no longer effective. Gastrointestinal, respiratory, sexually transmitted, and hospital-acquired infections are leading causes of disease and death in the developing world. Management of all these conditions has been compromised to some extent by the appearance and spread of resistance, but the most severe effects are yet to come. Actions taken now can slow the spread of resistance without impairing access to antibiotics when they are appropriate. These, as well as extending access where it currently is inadequate, are the aims of the Global Antibiotic Resistance Partnership.

Drug resistance is usually viewed as a medical problem, but the causes of resistance—at least the pace of escalation—are also cultural and economic. In hospitals and clinics, large pharmacies and small shops that sell drugs, healthcare providers and their patients are motivated (financially or otherwise) to do what is best for their health and their bottom lines. Because antibiotics are considered generally safe (despite some adverse reactions), this means using them 'just in case'. No seller or user has an incentive to weigh the long-term societal impact of using antibiotics, particularly when alternative treatments are few or nonexistent and the consequences are likely to occur sometime in the future to people unknown. Standard government responses, such as increasing surveillance and launching public information campaigns on the hazards of resistance, while a necessary part of an overall policy response, are unlikely to work on their own. To be effective, policy solutions must alter incentives for patients, physicians and others in the healthcare system to act in society's best interests. Evaluating policy solutions involves understanding the epidemiology of infectious diseases in populations and making sure that changes are beneficial—or at least not detrimental—immediately *and* in the longer term. Research evaluating focused, context-specific policy solutions is a first step. Translating these policy solutions to policy action is the second.

Antibiotic resistance does not top any list of national problems, nor should the strategies proposed drain resources from more pressing concerns. At its best, controlling antibiotic resistance should not result in extra costs. In the long run—and maybe even in the shorter term—it will likely save money and save lives.

Country-Specific Goals

GARP, funded through a grant from the Bill & Melinda Gates Foundation, aims to address the challenge of antibiotic resistance by defining policy solutions and opportunities. Four countries began phase one in 2009-2010—India, South Africa, Kenya and Vietnam—following similar, but not identical, pathways. In Kenya, after assembling and reviewing as much related information as could be found (including the results from GARP-funded studies), the Kenya Working Group has developed the short list of possible policy strategies found at the end of this report. They have consulted with additional stakeholders, international advisors, and the Center for Disease Dynamics, Economics & Policy (CDDEP) in Washington, D.C. during this process. The proposals address weaknesses in how antibiotics are regulated and managed, how countries track antibiotic use and resistance, and alternative means to reduce demand for antibiotics. A 'critical path' of implementation will be linked to each recommendation over the next year, followed by supportive activities and research in the second phase of the initiative.

Global Efforts

One of the visions for GARP is the creation of a global network of low- and middle-income country professionals interested in pursuing solutions to antibiotic resistance and access problems. Encouragingly, even during the initial phase, a signifi-

cant amount of information sharing and reviewing has taken place across the four founding countries, and the GARP-Kenya Working Group has been an important part of this. As the partnership grows—both in added countries and deepening expertise and experience—the sharing aspect will be fostered and is bound to become more important.

A second major thrust of GARP is developing tools that can be used in countries all over the world. The first tool is 'PneuMOD', a pneumococcal disease-modeling framework to explore the costs and benefits of vaccination and strain replacement, improved access to drugs and interventions to reduce resistance.

The second tool is the 'Drug Resistance Index' (DRI), actually a family of indexes that can be used to assist countries in gauging their efforts against drug resistance over time and in comparison to other countries. DRIs can be calculated for units as small as single hospitals or as large as countries or regions. On a practical level, DRI data are also critical to informing evidence-based development of national treatment guidelines, essential drug lists, and hospital formularies.

Part II. Health and Economic Context

This section provides an overview of Kenya's demographic profile, economic development and health system as a context in which to view the situation of antibiotic resistance. It presents information on national health policies, infrastructure and human resources, and financing mechanisms. Their presence and utilisation within the system are discussed in relation to access to essential medicines and hospital infection control, with a particular focus on antibiotics.

Demographics and Economy

Demographic Context

Kenya has an estimated population of 39 million, 68 percent of whom live in rural areas (Kenya National Bureau of Statistics (KNBS) and ICF Macro 2010). The majority of the country's residents rely on agriculture for their livelihoods, yet only about 17 percent of the total land area has agricultural potential. The bimodal climate, disparity in rainfall distribution and recurrent drought affect the national health and economic activity, which is heavily dependent on agricultural productivity (Government of Kenya 2008).

With about half the population below the age of 15, Kenya has a high dependency burden, defined as the ratio of dependent youth (ages 14 years and below) and seniors (ages 66 years and above) to the population of working age (ages 15 to 65) (Ministry of Health 2004). The youth-heavy age structure is typical of populations experiencing high fertility and high mortality. Dependency differs around the country, with the worst ratios in areas with the largest proportions of households living below the poverty line (Government of Kenya 2008). The Northeastern province, with the highest poverty incidence and the highest mean household size, has the highest dependency ratio, at 132, compared with the wealthiest province, Nairobi, at 53. This results in high demand for social services such as health and sanitation.

Household levels of education and living conditions have demonstrated impacts on health outcomes—from health seeking behaviour to indoor use of kerosene for cooking and consumption of clean water. Most Kenyans have received some education. However, 13 percent of women and 6 percent of men aged 15 to 49 have had no education at all with levels varying around the country (Ministry of Health 2004). Housing conditions vary as well. Half of urban households have electricity, compared with only 5 percent of homes in rural areas (World Health Organization 2006). About half of Kenyans live within 15 minutes of their drinking water supply; fully half live farther from their water source. In urban areas, 22 percent of households collect water from public taps; rural households rely primarily on springs, rivers and streams for their drinking water.

Economic Context

Poverty levels are very high, with 47 percent of the population living on less than US$1 a day and 58 percent on less than US$2 a day (Ministry of Health 2004; Ministry of Health 2007). The gross national income per capita is US$680 (The World Bank 2008). As in other sub-Saharan countries, poverty remains a major challenge. Advances made in the 1970s deteriorated from the mid-1980s with a growing population and a worsening political environment; the setback ultimately triggered a severe social development crisis in the 1990s (Wamai 2009). Economic growth steadily declined after Kenya embraced the Structural Adjustment Program recommended by the World Bank and the International Monetary Fund in 1992 (Ministry of Health 2003). The economic growth rate fell to –0.3 percent in 2000 (Wamai 2009).

Today the economy in Kenya and the East Africa region is at one of its lowest points in history. In Kenya, following the postelection violence in 2007, real GDP growth slowed to less than 2 percent in 2008 from 7 percent in 2006-07 (Ministry of Finance 2009). The negative effects of drought and the global financial crisis are expected to have further hampered economic growth in 2009.

Kenya Vision 2030: Driving Change in National Development across Kenya, or V-2030, is the policy document used by the government and Ministry of Finance for long-term economic and social development planning (Ministry of Health 2005; Ministry of Finance 2009). It is implemented through five-year medium-term plans, with the first covering 2008 to 2012, and identifies three main 'pillars' (economic, social, and political) through which it aims to transform Kenya into a rapidly industrializing, middle-income nation by 2030. It targets a rise in real GDP growth, achievement of the Millennium Development Goals and a more equitable society. Notwithstanding the global recession and local political unrest, the government says it is committed to attaining the V-2030 targets and will continue to focus on allocating a significant share of budgetary resources to the social pillar: health, education and training, water and sanitation, environment, urbanisation, gender and youth.

The document's implications for policies targeting antibiotic resistance are several. First, V-2030 plans to shift the focus from curative to preventive care and expand immunisation coverage. Second, it mandates an expansion of medical insurance to reduce out-of-pocket expenditure on healthcare. The document itself, however, does not propose increased funding for health and asserts that 'the sector is already receiving adequate budgetary resources'. When compared to the government's commitment to meet the Abuja Declaration target for national spending on health (15 percent), public resources allocated to health are inadequate (less than 6 percent).

Health System

Health Indicators

Life expectancy in Kenya has declined in the past decade, with current estimates at 51 years for males and 50 years for females, compared with 55 years on average in 2002 (The World Bank 2008; Kenya National Bureau of Statistics (KNBS) and ICF Macro 2010). Morbidity and premature mortality rates have improved over the past decade, but remain high (Ministry of Health 2004; Ministry of Health 2004; Kenya National Bureau of Statistics (KNBS) and ICF Macro 2010). The infant mortality rate (IMR) decreased from 62 to 52 per 1,000 live births from 1993 to 2009 (The World Bank 2008; Kenya National Bureau of Statistics (KNBS) and ICF Macro 2010). The under-five mortality rate (child mortality rate, CMR) also decreased from 120 deaths to 74 per 1,000 live births from 2004 to 2009 (World Health Organization 2006; Kenya National Bureau of Statistics (KNBS) and ICF Macro 2010).

Mortality rates for infants and children are higher in rural than in urban areas and vary considerably by province, with the IMR ranging from 44 in the Central province to 133 in Nyanza, and the CMR ranging from 54 in the Central province to 206 in Nyanza (Ministry of Health 2004; Ministry of Health 2004). Children born to women with some secondary education have a reduced IMR of 44 per 1,000 live births, compared with 97 for those whose mothers did not complete primary school.

In 2000, maternal mortality—which signals a lack of access to healthcare—was estimated at 1,000 per 100,000 live births (World Health Organization 2006). By 2009, this figure had declined to 488 per 100,000 live births (Kenya National Bureau of Statistics (KNBS) and ICF Macro 2010). Maternal deaths account for 15 percent of all deaths of women aged 15 to 49.

Other major indicators of child health include vaccination coverage and the prevalence of malnutrition. In 2009, 77 percent of Kenyan children aged 12 to 23 months had received all recommended vaccinations, including one dose of BCG, three doses each of DPT/hep B/influenza and polio, and one dose of measles. There are no significant differences in vaccination coverage between urban and rural areas. There are, however, large variations by province (Ministry of Health 2004; Ministry of Health 2004). In the Central province, 79 percent of children are fully vaccinated, and only 2 percent have received no vaccinations. By contrast, in the Northeastern province, only 9 percent of children have been fully vaccinated, and 46 percent have not received a single vaccination.

Finally, poor nutritional status is one of the most important health and welfare problems fac-

Table 1. Economic Development and Health Indicators

Population (2010)	39 million
Population growth rate (2001–2007)	3%
Life expectancy (2004)	51 years (male), 50 years (female)
Gross national income per capita (2007)	US$680
Child (under 5 years) mortality rate (2009)	74 per 1,000
Maternal (15–49 years) mortality rate (2009)	488 per 100,000
Population living in poverty (<US$1 per day) (2006)	47%
Population with access to clean water (2003)	45%
Adult literacy rate (2000)	74%

Sources: Kenya Demographic and Health Survey 2003 (Ministry of Health 2004), Kenya Demographic and Health Survey 2008-2009 (Kenya National Bureau of Statistics and ICF Macro 2010), World Summit for Children Indicators – Kenya 2003 (World Summit for Children 2003), Kenya at a Glance (The World Bank 2008), Country Health System Fact Sheet Kenya (World Health Organization 2006), Kenya 2009 Population and Housing Census Highlights (Kenya National Bureau of Statistics and ICF Macro 2010).

ing Kenya. According to the 2010 Demographic and Health Survey, nearly one in five children is underweight (Kenya National Bureau of Statistics and ICF Macro 2010). Stunting, an indication of chronic malnutrition, afflicts 35 percent of children under five, of whom 14 percent are severely stunted, and 7 percent are suffering from acute malnutrition (wasting). Wasting is extremely high in the Northeastern province, where 20 percent of children are underweight for their height.

Table 1 presents a snapshot of the state of the country.

Current Health Policies

Kenyan Health Policy Framework. Since independence, Kenya's government has given high priority to improving the health status of citizens, and health policy has been based on the country's landmark nation-building and development blueprint, the 1965 Sessional Paper No. 10, on African socialism and its application to Kenya (Ngigi and Macharia 2006; Wamai 2009). This paper recognised health as a prerequisite to social and economic development, emphasizing the elimination of disease, poverty and illiteracy as interconnected challenges. Since 1994, the Kenya Health Policy Framework Paper has guided the health sector agenda. It delineates the long-term strategic imperatives of the government and explicitly sets forth that the provision of health services should be 'acceptable, affordable, and accessible to all.' It stresses preventive services, while noting the importance of curative care.

In the past decade, the government identified decentralisation as a primary health management strategy and developed a series of two five-year documents called the National Health Sector Strategic Plan (see below) to oversee the implementation process (Ministry of Health 2005). Health sector planning is also informed by economic and structural strategies adopted by the government. The most important reforms include the 2005 medium-term Poverty Reduction Strategy Paper, stipulated as part of the lending criteria of the World Bank and the International Monetary Fund, and the previously mentioned long-term economic development policy, V-2030 (Government of Kenya 2000; Government of Kenya 2005). The Poverty Reduction Strategy Paper states that the healthcare system in its current form operates inefficiently; it targets improvements in medicine supply, personnel development, and facility utilisation. Medicines were deemed the most promising area for improvement, particularly in their selection and quantification.

National Health Sector Strategic Plan (NHSSP). The first NHSSP, for 1999–2004, was developed to implement the Ministry of Health's policy agenda as articulated in the Kenya Health Policy

Framework Paper (Ministry of Health 2005). Specific tasks included strategies to reduce the burden of disease, define a cost-effective essential healthcare package, and decentralise healthcare delivery through redistribution of health services to rural areas. It was evaluated in 2004 by an external team of consultants, who found that 'the overall implementation of NHSSP-I did not manage to make a breakthrough in terms of meeting the most significant targets and indicators of health as expected by the plan'.

In other words, the NHSSP-I was not regarded as having contributed to improving the health status of Kenyans. Indeed, health indicators during the implementation of the first NHSSP showed a downward trend, with increased child and infant mortality and a stagnation of the public sector's contribution to healthcare, going from US$12 per person in 1990 to US$6 in 2002.

To improve the delivery of health services, the Ministry of Health reviewed problems within NHSSP-I and recommended changes, spelled out in the second version of the policy. NHSSP-II emphasises better coordination of health services across the country and adopts a sector-wide approach, called SWAp, to bring together government, donor, and private sector (for-profit and nonprofit) stakeholders to support health priorities. In 2006, the Joint Program of Work and Funding convened to implement SWAp, and 17 leading donors developed the Joint Assistance Strategy (2007–2012) in 2007 (Wamai 2009).

Millennium Development Goals (MDGs). Kenya adopted the Millennium Declaration in September 2000, agreeing that the Millennium Development Goals be attained by 2015 (Government of Kenya 2008). In 2004, the country launched its official MDG planning process to demonstrate the government's commitment to the declaration. There followed a shift in resources for social and economic sectors linked to the MDGs, from 56 percent of the budget in 2004–2005 to 64 percent in 2007–08. The MDG Needs Assessment Study, conducted in 2005, aimed to determine how the country could achieve the goals and remains influential in the budgeting and planning process. A cabinet directive issued in 2005 requires all government ministries to mainstream MDGs into their specific policies and budgets. In a prime example of this effort, the 2009–2012 Medium-Term Plan, which represents the first phase of V-2030 implementation, explicitly recognises the MDGs as priorities within the three development pillars (Ministry of Finance 2009).

As a result, the MDGs have become central to allocating resources and forming national development plans. Although it is unlikely that the goals will be fully met by 2015, they provide impetus for investment in the health of Kenyans (Government of Kenya 2008). Three of the MDGs prioritised by the government—reduction of child mortality, improvement of maternal health, and combating HIV/AIDS and other diseases—are dependent in part on the availability of effective antibiotics and thus involve the problem of antibiotic resistance (Bennish and Khan 2010). Additionally, reduction in disease and mortality associated with child and maternal health has the ancillary benefit of reducing the need for antibiotics.

Organisation and Distribution of Services

There are three main sources of healthcare in Kenya: (1) the public sector, headed by the Ministry of Public Health and Sanitation and the Ministry of Medical Services*; (2) profit-based private providers; and (3) mission or faith-based not-for-profit providers. According to the most recently available Health Management Information System data, Kenya has more than 5,000 health facilities, 41 percent of which are run by the government, 15 percent by nongovernmental organisations (NGOs) and 43 percent by private or mission providers (Wamai 2009). The public sector controls about 79 percent of health centres, 92 percent of subhealth centres and 60 percent of dispensaries (Ngigi and Macharia 2006). NGOs and mission organisations are dominant in health clinics and specialty medical facilities (94 percent). The public and private sectors have about equal shares of hospital control.

* In 2008 the Ministry of Health split into two ministries. 'Ministry of Health' refers to the single pre-2008 ministry and 'Ministries of Health' refers to the two ministries post-2008. In places, the document refers to both ministries by their full names.

Figure 1. Levels of Care in the Health Referral System

Public healthcare is implemented through a pyramidal network with five levels, starting with village dispensaries and health centres, up to subdistrict hospitals, district hospitals, provincial hospitals and finally the national referral hospitals, Kenyatta National Hospital and Moi Teaching Hospital (Figure 1).

The private sector, for-profit and nonprofit combined, accounts for more than 58 percent of health services in the country, providing mainly curative health services. No estimate exists of the population covered by these services. The government supervises and coordinates NGO work in collaboration with local authorities.

At the national level, the mandate for supervision and coordination, development of policies and mobilisation of resources rests with the Ministries of Health. The original ministry was split into two sections, the Ministry of Public Health and Sanitation and the Ministry of Medical Services, following the formation of a coalition government in 2008. The rationale behind the divide was power sharing, causing the government to double its ministerial portfolios (Wamai 2009). This has resulted in politicisation of service provision, competition for resources and lowered morale among senior planners and district managers torn between allegiances as the departments were reorganised into parallel management structures. They also share a common budget that has not increased in correspondence to the expansion. At present, there are no published organisational diagrams reflecting this split, and it is not clear how aspects related to the Child Health Programme, National AIDS/STI Control Programme, medical research, the pharmaceutical supply chain, and other areas of health services related to essential medicines and infectious diseases are managed between the two new ministries.

Kenya has eight provinces divided into lower levels of administration called districts, which, under the decentralisation programme, are responsible for delivering health services and implementing health programmes. The provincial tier acts as an intermediary between the health ministries and the districts, overseeing the implementation of health policy at the district level and assuming responsibility for maintaining quality standards (Ngigi and Macharia 2006). Districts, the backbone of the public health system, concentrate on the delivery of services and generate their own expenditure plans and budget requirements based on guidelines provided by the health ministries through the provinces. Management of healthcare at the district level—including subdistrict hospitals, health centres and dispensaries—is headed by the Office of the District Medical Officer and supported by the District Health Management Board (Ministry of Health 2007). A management team prepares technical advisories and writes the district health plan in consultation with local health leaders. NGOs and mission organisations report to the management boards, which report to the health ministries through the provincial authorities. Dispensaries and health centres handle the Kenya Essential Package for Health activities related to health promotion and preventive care, as well as some curative services. As recommended in the NHSSP-II, village health committees are organised at the community level in the hopes that they will allow individuals and households greater participation in their own health (Ministry of Health 2005).

Concerning issues related to antibiotic management, the Office of the District Medical Officer provides support to service delivery functions provided by health facilities, including the monthly supervision of medicine supplies (stock cards), in-service training for critical skills gaps (including prescribing and treatment with antibiotics) and provision of containers and media for laboratory

Table 2. Services provided by Kenya Essential Package for Health

Life cycle cohort	Examples of services needed
Pregnancy and newborn (expectant mothers and infants up to 2 weeks of age)	Antenatal and nutritional care, skilled birth attendants, clean delivery, breast feeding support, supplementary feeding
Early childhood (2 weeks–5 years)	Community and clinical Integrated Management of Childhood Illness (IMCI), appropriate nutrition and extended breast feeding, growth monitoring, provision of micronutrients, oral rehydration therapy, antibiotics and antimalarial drugs, antiretroviral treatment (ART, for HIV/AIDS)
Late childhood (6–12 years)	Essential school health programme, overall treatment and care, timely treatment of infectious and parasitic diseases
Youth and adolescence (13–24 years)	HIV/AIDS and sexually transmitted infection (STI) counselling, accident prevention, substance abuse counselling, adequate nutritional care, reproductive health services, overall treatment of care, especially for tuberculosis directly-observed therapy, short course (DOTS), STIs and opportunistic infections
Adulthood (25–59 years)	Annual screening and medical examinations, accident prevention, reproductive health services, ART, DOTS, palliative care
Elderly (60+ years)	Annual screening and medical examinations, exercise, access to drugs for degenerative illnesses

Source: NHSSP-II pages 16-17 (Ministry of Health 2005).

specimen transportation. Under the current organisational structure, the Office of the Provincial Medical Officer is expected to coordinate systems support for crosscutting functions needed by districts to ensure timely and quality service delivery. Although NHSSP-II plans for this level of care to include service baselines and targets, provincial support to the districts does not incorporate any activities related to the treatment or prevention of bacterial diseases, access to effective drugs or a clear delineation of responsibility for hospital infection control. There is a brief mention of 'reliable and consistent supply of drugs and medical supplies to all health facilities' under provincial planning, with a pharmacist named as the person in charge. Finally, HIV activities listed under current policies for 'crosscutting' issues in which provincial management should support districts do not include treatment of opportunistic infections or pneumonia (Ministry of Health 2007).

The NHSSP-II adopted a broad approach to the country's health service delivery system, moving away from emphasis on disease burden to promotion of individual health (Ministry of Health 2005). In this approach, the Kenya Essential Package for Health integrates all health programmes into a single package that aims to improve health at different phases of human development. The phases represent various age groups or cohorts, each with unique needs (Table 2). The package also defines where health services will be delivered throughout the five levels of care described above.

Financing. The 1994 Kenya Health Policy Framework identified taxation, user fees, donor funds and health insurance as the major sources of healthcare financing. The government (central and local) funds 30 percent of the budget, households provide 53 percent, and donors (international and domestic) contribute 16 percent (World Health Organization 2006; Wamai 2009). Most donor

support is earmarked for specific interventions according to agreements made between the government and the donor. Funds donated through major programmes, such as the Global Fund and PEPFAR, are off-budget support and go directly to the implementing agencies, whether public or private.

In terms of actual dollars spent, the health budget has grown from US$197 million (2008 exchange rate) in 2002 to US$447 million in 2009 (Ministry of Health 2007; Ministry of Finance 2009). However, as a share of the entire government budget, public spending on health has declined, from 9 percent in 2002 to less than 6 percent at present. This is significantly less than is required by the government's commitment of 15 percent to meet the Abuja Declaration target for total public spending allocated to health. According to the most recent WHO figures (2003), Kenya spends a little over 4 percent of its GDP on health (World Health Organization 2006). Total per capita health spending stands at about US$6.20, far below the WHO-recommended level of US$34 per capita. Malaria and reproductive health receive the largest proportion of the government health budget (Ministry of Health 2007). About half of the public contribution goes to fund health personnel, and 30 percent goes for essential drugs and pharmaceuticals. Finally, the health budget is skewed towards tertiary- and secondary-care facilities, which absorb 70 percent of health expenditures. Yet primary-care units remain the first line of contact with the population and provide the bulk of health services for prevalent conditions.

Including all donor resources, the total resource gap between the healthcare budget and funds available for 2009 stands at 19 percent. Budget policy documents assert that the health sector is 'already receiving a significant share of resources in the budget' (Ministry of Health 2005; Ministry of Finance 2009). According to the 2009 budget strategy report, the government must 'more efficiently generate fiscal space to accommodate strategic interventions', including those affecting staff training and access to affordable medicine. It is worth noting, however, that when the V-2030 and other documents refer to the sufficient allocation of resources for healthcare, they merge expenditures for all priority social sectors. When health is combined with education, social sector funding stabilises at about 30 percent of total budget expenditure, well above the government target for health spending. Separating health and education, however, reveals that education accounts for over 20 percent but health remains below 6 percent. Having taken the position that the 30 percent figure accurately represents the budget priority given to health, the 2009 Budget Strategy Report recommends a decrease in health spending.

Fee collection in health facilities was abolished in 1965 but reintroduced in 1989. A few years ago, the government instituted the '10/20 policy', in which village-level dispensaries and health centres can charge user fees for curative care of only Ksh10 or Ksh20 (about US$0.13 to US$0.27). There are no reports on how well this is followed in practice or the exact fees charged at higher-level facilities. Nearly three-fourths of the revenue collected through fees is used at the collecting facility and one-fourth set aside for the district management of primary healthcare (Ngigi and Macharia 2006). However, 'leakage' due to corruption reportedly amounts to 22 percent of the user fee revenue collected (Ministry of Health 2004). Primary public health facilities continue to provide free medical services for children under five years of age and for services related to treating tuberculosis, providing contraceptives, and delivering immunisations. Mission organisations and NGOs provide care at subsidised rates, and private sector facilities require fees to be paid either through private health insurance or by the patient. Importantly, cost-sharing revenue is also used to supplement tax-financed government expenditures on medicines. In some hospitals, donor organisations provide additional funds for purchasing medicine. There are no pricing policies on essential medicines that cover both public and private sector.

Insurance coverage is primarily through the National Hospital Insurance Fund, covering about 2.5 million people or 7 percent of the population. Membership is primarily drawn from government, NGO and corporate employees who are required to pay into the fund (Wamai 2009). A social health insurance scheme was outlined in the Sessional Paper No. 2, in 2004, but failed to materialise. Following the adoption of the new constitution in August 2010, in which health is declared a right for which the government must act, the National Hospital Insurance Management Board proposed a series

of reforms based on higher contributions. With the increased revenue, the Board plans to expand services to include general consultations with doctors, laboratory testing and provision of medicines. It is also hoped that reforms will help create a path to universal healthcare, although at present the scheme would still collect Ksh 150 from Kenyans earning below Ksh 6,000 annually. The change is not without controversy and the Industrial court has been involved in resolving disputes. While health advocates push for the government to meet the NHSSP-II and V-2030 goal of 'ensuring provision of basic health package to all Kenyans and increasing coverage of quality healthcare for the poor', there remain concerns about NHIF's ability to manage the additional funds to the benefit of members (Ministry of Health 2005). In addition to insurance schemes, an estimated 10 health management organisations support about 200,000 persons (Export Processing Zones Authority 2005).

Access to Essential Medicines and Healthcare Services

The 2003 reforms attempted to make it easier for households to obtain primary health services. At the time, a survey conducted by WHO, Health Action International and the Ministry of Health found that accessibility was poor, especially in rural areas, where many families were located more than 10 kilometres from a health facility (Ministry of Health 2003). The urban-rural divide was still evident in 2005, when another report found that although 70 percent of the urban population had access to health facilities within 4 kilometres, only 30 percent of the rural population enjoyed the same proximity to healthcare (Export Processing Zones Authority 2005). Comparing public and private facilities, half the population was within one hour's walk to a public health facility, and 70 percent were within an hour's walk of a more expensive private health facility.

Utilisation of healthcare facilities and related goods, an important indicator of the cost and quality of services, is low. Only 42 percent of women have births attended by skilled health personnel, and 95 percent of young children are not sleeping under insecticide-treated bed nets (World Health Organization 2006). Although virtually all mothers know the specific signs of illness that would indicate a child should be taken to a health provider, only one-third of children under five receive appropriate rehydration treatment for diarrhoea, and only half of caregivers of children experiencing ARI symptoms seek healthcare (World Summit for Children 2003; World Health Organization 2006; Burton, Flannery et al. 2011). On average, 43 percent of young children with diarrhoea, fever, and/or ARI symptoms are taken to a health provider. In rural areas the situation is even worse, where utilization of clinics for diarrhoea, fever, and ARI symptoms were several-fold lower than in urban sites (Burton, Flannery et al. 2011; Feikin, Olack et al. 2011).

Only about 30 percent of Kenyans have regular access to essential medicines (Ministry of Health 2004; Ngigi and Macharia 2006). In dispensaries and health centres—the first point of formal healthcare for most of the population—essential medicines are available at half the sites and in about 65 percent of hospitals (Oxfam 2011). Most stock-outs last about a month and 10 percent of stock-outs last more than three months (Ministry of Health 2004). Antibiotics on the Kenyan Essential Drugs List range in availability, from below 20 percent for ciprofloxacin and ceftriaxone in the public sector to more than 90 percent for doxycycline and amoxicillin in all sectors (Ministry of Health 2004). The low level of availability of ciprofloxacin in the public sector may result from restrictions limiting its use to high-level facilities—that is, district hospitals and above.

With more than half of Kenya's population living on less than US$2 a day, medicines and the cost of healthcare represent a significant and frequently prohibitive expenditure for most households (Ministry of Health 2004). Of those who reported being ill but were not seeking treatment, 44 percent cited direct healthcare costs and 18 percent named distance and transportation costs as the main barriers to utilisation. WHO, Health Action International, and other health advocates in Kenya assert that the price of medicines contributes to lack of access. The Kenya Household Expenditure and Utilisation Survey in 2003 found that medicines constitute 69 percent of total out-of-pocket outpatient expendi-

tures on health. Although the government bars direct taxes or tariffs on essential medicines, it does permit substantial markups along the distribution chain, and prices vary greatly across sectors, regions and treatments. In 2004, the cost of treatment of the most common diseases demonstrated considerable variation, ranging from an equivalent of more than a day and a half's wages for the treatment of adult pneumonia in a private facility to about a quarter of a day's lowest government salary for the treatment of child malaria in a public health facility. Important costs related to accessing healthcare, such as consultant fees, transportation and lost wages due to travel or waiting, have not been analysed.

Hospital Infection Control

Infection control measures are easily compromised in developing countries (Okeke, Aboderin et al. 2007). Although data on hospital acquired infections (HAIs) have rarely been collected in Africa, WHO suggests that the infection rate in developing countries is 15.5 per 100 patients, three times higher than in the United States. Intensive care units face infection rates of 48 per 1,000 patient-days, compared to 14 in the United States (Allegranzi, Bagheri Nejad et al. 2011). Standard barriers between the hospital and the community rarely exist, especially when in contexts of overstretched health systems friends and relatives are called upon to assist in patient care. The potential for infectious organisms to be transmitted into, within, and beyond the hospital is thus elevated. In Kenya, the number of patients with serious infectious diseases like HIV/AIDS, tuberculosis, cholera and hepatitis B is high, and failure to follow proper infection prevention places healthcare workers and patients at risk (Ndegwa, Ellingson et al. unpublished data). Historically, the country has lacked dedicated resources and administrative support for infection control activities in hospitals, and many older facilities face infrastructural deficiencies, such as lack of running water and inaccessible sinks.

Such challenges continue to hinder HAI prevention. A 2001 report found that staff practiced minimal infection prevention and that the necessary supplies were inconsistently available at Coast Provincial General Hospital (Edgeworth 2001). A 2009 rapid assessment of hospital infection control practices nationwide revealed significant differences across facility levels and regions (Ministry of Health 2010). In hospitals where the administration recognised the importance of preventing HAIs, infection control committees were visible and active. Infection control practice was of good quality and factored into the annual budgetary process, thereby ensuring consistent availability of supplies and equipment. As would be expected, facilities without active infection control committees performed poorly on both institutional and individual provider levels. Hand hygiene, the most basic infection prevention measure, was infrequently practiced in a large proportion of the assessed facilities. And even though not all facilities had piped water, all were able to obtain and store water for hand washing. Adherence to standard precautions and waste management systems mirrored patterns observed in hand hygiene.

The rapid assessment concluded that integration of infection control practices into the annual operation planning process is of critical importance to improving the situation. This is especially true since most infection control leaders are nurses, who are unlikely to be part of hospital senior management. Typically, hospital infection control committees rarely meet, and most hospitals lack reference manuals and standardised infection control training for personnel. Clinicians tend to perceive infection control as a nursing responsibility and therefore do not educate themselves about their role in preventing the spread of disease. The topic is not covered in medical school, although CDC-Kenya has started instructing lecturers at the Kenya Medical Training College on the importance of preparing clinicians to integrate infection control in their regular practice. Poor risk perception and a lack of microbiological information have also been cited as major issues in controlling HAIs (Ndegwa 2009).

Kenya does have policies and guidelines addressing different aspects of infection prevention and control, including the National Infection Prevention and Control Policy (2010), the National Policy on Injection Safety and Medical Waste

Management (2007), the National Standards and Guidelines on Injection Safety and Medical Waste Management (2007), and Guidelines for Tuberculosis Infection Prevention in Kenya (2009) (Ministry of Health 2010). In addition, some health institutions have developed their own documents, such as the 2006 Kenyatta National Hospital Policy Guidelines on Antisepsis, Disinfection, Sterilisation and Waste Disposal. Legislation attached to the National Infection Prevention and Control Policy will establish a national infection prevention and control committee within the Ministry of Public Health and Sanitation, plus institutional, provincial and district infection prevention and control coordinators to advise district and subdistrict facilities, community health centres, and dispensaries. The document calls prevention and control of infections 'essential cornerstones' in addressing the emergence of antibiotic-resistant bacteria and refers to resistance as a 'major problem for patient safety'. It also states that the increase of antibiotic-resistant organisms 'undermines progress made in the fight against infectious disease and poses a serious challenge to healthcare systems'. It cites overuse of broad-spectrum antibiotics as a contributing factor to antibiotic resistance and says that the need to use expensive second-line treatments is a negative economic consequence of drug-resistant HAIs.

The Infection Control Association of Kenya, launched in 1997, promoted education programmes for healthcare providers through workshops on supplies used in infection control and the threat of emerging drug resistance in hospital settings (Kakai and Wamola 2002). According to stakeholders, the association stopped meeting, and education activities shifted to individual hospitals and their nursing staffs. The Nurses Infection Control Chapter is now active on the issue. Other infection control activities include CDC-Kenya efforts at targeting reductions in airborne infections and bloodborne pathogens and NGO activities in educating hospital staff about infection control practices, in particular hand hygiene and safe injection practices (Ndegwa 2009). Infection control actors and agencies within the country have identified low-cost interventions such as respiratory cohorting, hospital isolation rooms, improved healthcare waste management and a reduction of unnecessary injections as important solutions.

Since 2007, the Ministries of Health have been supporting the expansion of capacity to prevent HAIs in public hospitals; however little data on HAI burden exists to inform this effort. In response, CDC-Kenya launched an HAI surveillance project to quantify the burden on the healthcare system and highlight the circumstances in which HAIs occur (Ndegwa, Ellingson et al. unpublished data). With this information, the agency plans to raise awareness of the problem, generate data to design and evaluate infection control interventions (e.g., education campaigns and separating people with infections from those who are not infected), and provide feedback to motivate healthcare workers and hospital administrators to maintain and improve infection control efforts.

Part III. Burden of Disease and Antibiotic Resistance

In countries where infectious diseases exact a high toll, access to effective antibiotics is critical to controlling morbidity and mortality. When antibiotic resistance is common, serious infections emerge, and when cost prevents the use of newer, more expensive therapies, people suffer. Kenya is such a country: both community- and hospital-acquired infections are widespread, and antibiotic resistance is present. Overcrowding, poor sanitation and hygiene and inadequate access to healthcare services favour the spread of resistance in poor neighbourhoods (du Prey, Ford et al. 2004; Haak and Radyowijati 2010). Even though the poor contribute less to the problem in terms of selective pressure through antibiotic use, they are at higher risk of bacterial disease and less able to receive appropriate treatment (Okeke 2010). Young children, the malnourished and the immune-compromised are the least able to clear a bacterial infection without quick and effective interventions. In Kenya, these groups constitute the majority of the population affected by bacterial illness and are the most likely to be living in poverty.

This section reviews the burden of disease and levels of antibiotic resistance in common bacterial infections in human and animal populations in Kenya. Most of the information comes from WHO reports, national surveillance efforts and site-specific case studies. The reliability of data is variable because quality assurance in susceptibility testing is not widespread and some hospitals use obsolete testing methods. The consequences of resistance on clinical outcomes, through either treatment failures or the development of more virulent infections, are largely unknown. Thus, the full burden of antibiotic resistance on health in Kenya remains to be assessed.

National Burden of Disease

According the 2006 WHO mortality report for Kenya, the top five causes of death for all ages are infectious diseases (Table 3).

In one study, malaria is equal in importance to pneumonia and is estimated to cause 20 percent of deaths in young children (Ministry of Health 2004; Ministry of Health 2007). The 20 percent figure for pneumonia was validated in a 2009 WHO study (Cherian 2009).

Malaria is the most common presenting complaint at health facilities, accounting for nearly 30 percent of outpatient visits, 20 percent of inpatient admissions and nearly 26,000 childhood deaths each year (Lin and Tavrow 2000; Ministry of Health 2004; Ministry of Health 2007).

HIV/AIDS consumes 17 percent of general health spending, and AIDS patients occupy more than half the hospital beds in the country (Government of Kenya 2008; Wamai 2009). The National AIDS Control Council estimates that 1.2 million people are infected and about 85,000 people die of AIDS-related complications annually, leaving behind nearly 2.4 million orphans (National Aids Control Council 2010). National HIV prevalence stands at 8 percent, up from 7 percent in 2003 (Ministry of Health 2004; World Health Organization 2006; Government of Kenya 2008). The rate in children is slightly over 1 percent but accounts for

Table 3. Leading Causes of Mortality

Age group	HIV/AIDS	Respiratory infections	Diarrhoeal disease	Malaria	Tuberculosis	Neonatal causes
All ages	38%	10%	7%	5%	5%	Not in top 5
Children under 5	15%	20% (pneumonia)	16%	14%	Not in top 5	24%

Box 1. Urbanisation and health outcomes in Nairobi slums

At the current rate of urbanisation, more than half the population of sub-Saharan Africa will live in urban areas by 2030 (African Population and Health Research Center 2002). Rapid urban growth in an environment of poor economic performance and lack of municipal planning has meant that the number and size of informal settlements—slums—has grown in many African cities. Emerging evidence indicates that the urban poor in Africa have less access to health services and higher mortality rates than others, including rural populations.

Nearly 71 percent of urban residents in Kenya live in slums, characterised by unemployment, overcrowding, insecurity, risky sexual practices and high levels of mobility. Residents earn an average of Ksh3,500 (about US$50) per month. The lack of basic sanitary facilities, conducive to disease outbreaks and giving rise to 'flying toilets', is well known. Officials cite the informal nature of these settlements to justify denying slum communities the provision of water, electricity, garbage collection, law enforcement and fixed health facilities. Health facilities that do exist tend to be located on the outskirts of settlement areas and are generally inaccessible at night because of a lack of security. In the absence of public health services, communities depend mainly on for-profit facilities operating without licence and employing poorly trained staff. While most residents know the symptoms of high-risk illnesses, they tend not seek treatment as a result of high costs and insufficient means (Kwena, Sharma et al. 2008).

The urban poor living in informal settlements have the highest disease burden in the country. Compared with rest of Kenya, health indicators for children under five in slums are the worst (Kyobutungi, Ziraba et al. 2008). The high rate of pneumonia deaths is unsurprising given poor housing conditions and the propensity of residents to sleep in the same room where kerosene oil is used for cooking. Together, pneumonia and diarrhoea account for close to 60 percent of the mortality burden in young children. Among the population aged five years and above, HIV/AIDS and tuberculosis (30 percent of years of life lost and more than 50 percent of mortality burden) and interpersonal violence (13 percent mortality) account for more than two-thirds of all deaths. Nairobi slum residents have been affected by the HIV epidemic more profoundly than most populations in the rest of sub-Saharan Africa. Injuries due to interpersonal violence, the second leading contributor to mortality burden in the five years and older population, reflect high levels of insecurity and the marginalisation of residents of informal settlements. The perceived indifference of the national legal system to citizens living in slums often results in community measures of vigilante and mob justice meted out to those suspected of committing crimes.

15 percent of under-five mortality (Cherian 2009). Finally, malnutrition underlies more than half of all inpatient morbidity and mortality, as a risk factor for a range of infectious diseases in children (Bejon, Mohammed et al. 2008).

As previously described, the country's northern and western regions have the lowest immunisation rates and the highest infant and child mortality rates. Health disparities are likewise evident in rates of infectious diseases. Nyanza province has the highest officially reported HIV prevalence, 15 percent among ages 15 to 49 years (Ministry of Health 2004; Brooks, Ochieng et al. 2006). Since the 1980s, epidemic malaria has been increasing in frequency and severity among densely populated areas of Kenya's western highlands, causing an estimated 25 to 50 percent of childhood deaths (Lin and Tavrow 2000; Phillips-Howard, Wannemuehler et al. 2003). In 2003, acute respiratory symptoms were present in 30 percent of children in Nyanza and Western provinces, compared with 10 percent in the Northeastern province, and diarrhoea was most common in the Western province and least common in the Central province (Ministry of Health 2004).

Bacterial Disease and Antibiotic Resistance in Humans

The data presented here are summarised from WHO and national surveillance efforts, as well as

site-specific case studies. Because illnesses and deaths are not well counted in Kenya, as is often the case in low-resource countries, the picture is incomplete. That such a large proportion of the data come from hospitals—whereas most illness and death occur in the community—is limiting. And separating bacterial from viral diseases requires a level of detail that, in most cases, does not exist. Nonetheless, the available information provides a basic idea of the current situation.

We present information on the epidemiology and burden of disease, current treatment options and antibiotic resistance for each of the following: acute respiratory infections, diarrheal infections, bacteraemia, sexually transmitted infections, and nosocomial infections.

Acute Respiratory Infections

Acute respiratory infections are the leading cause of death for all ages in low-income countries, with the majority of deaths occurring in young children. The most common ARIs range from simple colds, coughs, otitis media, sore throat and laryngitis of the upper respiratory tract, to more serious lower respiratory tract infections—bronchitis, bronchiolitis and especially pneumonia. The pathogens that cause ARIs are varied, including bacteria, viruses, fungi and other organisms. Transmission of pathogens and the likelihood of infection are increased by a range of factors, such as exposure to air pollution, malnutrition and micronutrient deficiencies, and overcrowding. For every death attributable directly to an ARI, respiratory infections contribute to the probability of dying for two or three other patients, since morbidity associated with serious diseases such as malnutrition, measles and malaria are made worse with coinfection, especially pneumonia (HARP 2009).

Acute pneumonia causes most ARI mortality, responsible for 21 percent of deaths in young children in Africa and approximately 2 million deaths each year worldwide—more than AIDS, malaria and measles combined (Ye, Zulu et al. 2009; Adegbola and Saha 2010). Children are the primary victims of pneumonia deaths, but the disease is also important in adults. In Kenya, pneumonia accounts for 20 percent of all invasive bacterial disease in adults, with a mortality rate of 36 percent (Matata, Ondieki et al. 2008).

Pneumonia is of particular concern in areas affected by environmental and disease-related risk factors—the informal settlements of Nairobi and the western region, where HIV infections are highest. For children living in slum neighbourhoods, pneumonia accounts for 23 percent of all years of life lost and is the leading cause of death (26 percent of mortality) (Ye, Zulu et al. 2009). This is possibly due in part to nearly universal household use of kerosene cooking stoves. In rural, western Kenya, all-cause hospitalised pneumonia is greatest among young children and middle-aged adults, the latter reflecting the district's high burden of the national HIV epidemic (Tornheim, Manya et al. 2007). Pneumonia is the most common and deadly initial manifestation of HIV in the country, and the risk of dying from pneumonia in the 20- to 49-year age group increases with a coinfection of either tuberculosis (16 percent) or HIV (22 percent) (Tornheim, Manya et al. 2007). Up to 84 percent of the risk of bacterial pneumococcal disease in the country is attributable to HIV infection, the leading cause of death in adults (Matata, Ondieki et al. 2008).

Incidence is estimated to peak at 698 per 100,000 among children under five, equivalent to one of every 143 children in the district being hospitalised for pneumonia each year. A second peak occurs among 20 to 29 year olds, at 356 per 100,000, with rates twice as high in women as in men ($p < .001$). The incidence of hospitalised pneumonia is highest in infants less than a year old, with rates of 1,370 per 100,000. Pneumonia-associated hospitalisations account for 13 percent of all admissions in the area, ranging by facility from 8 to 19 percent. Of these pneumonia hospitalisations, 44 percent were in young children with an overall case-fatality ratio of 11 percent.

Bacterial infection is believed to play a more significant role in causing pneumonia in developing countries than in industrialised ones (where viral pneumonia is more common). *Streptococcus pneumoniae* (Spn) and *Haemophilus influenzae* type b (Hib) are the prime agents of bacterial pneumonia. Spn commonly 'colonises' the surfaces of the nasal passages without causing disease and

is easily transmitted from person to person (Bartoloni and Gotuzzo 2010). In some cases, an infection begins when the bacteria invade tissue. Spn is the most frequently isolated respiratory pathogen in community-acquired pneumonia and is also a major cause of meningitis and otitis media. A recent hospital study of adults in Kenya documented Spn in more than half of the patients with pneumonia (Kariuki, Muyodi et al. 2003). In 2009, WHO estimated that more than 235,500 cases of Spn illness occurred in young children living in Kenya, including 227,531 cases of pneumonia and 1,342 cases of meningitis (Cherian 2009). Nationally, more than 16,430 deaths in children less than five years of age were caused by Spn disease. The incidence rate for Spn-attributable pneumonia was 4,478 per 100,000 and the case-fatality rate per 100 infections was 7. Meningitis occurs much less frequently, but is fatal nearly two-thirds of the time.

A second important cause of bacterial pneumonia is *Haemophilus influenzae* type b, the burden of which is considerably lessened with vaccination. Among children in sub-Saharan Africa, Hib causes 20 percent of cases of confirmed pneumonia and 40 percent of cases of meningitis (Scott, Mwarumba et al. 2005). As with Spn, pneumonia is about five times as common as meningitis (Akumu, English et al. 2007). In 2001, Kenya was among the first nine countries to receive financial support from Global Alliance on Vaccines and Immunization (GAVI) to introduce routine Hib vaccine. This vaccine has reduced the estimated incidence of Hib meningitis from 71 to 8 per 100,000 children under five, and of Hib pneumonia from 296 to 34. Following the introduction of the vaccine, the hospital incidence of Hib invasive disease dropped from 66 to 8 per 100,000 children. Donor funding for the vaccine was scheduled to end in 2006, but GAVI offered to extend assistance through to 2015, contingent on cost sharing from the government. Without the vaccine, an estimated 27,347 children would experience Hib disease and more than 6,000 would die each year. The Hib vaccine is especially effective during the vulnerable first five years of life, preventing more than 5,400 deaths annually in this age group (4 percent of under-five mortality).

Finally, Spn and Hib also cause more than 90 percent of acute bacterial meningitis outside the neonatal period, a disease with a high case-fatality rate (45 percent) and a 40 to 50 percent risk of neurological sequelae in survivors (Mwangi, Berkley et al. 2002). In 2000, before Hib vaccination had started, the minimum annual incidence rate of acute bacterial meningitis in Kilifi was 202 per 100,000. Spn accounted for 43 percent of the cases, and Hib, 42 percent. Thirty percent of the patients died, and about one-quarter of the survivors developed neurological sequelae.

Treatment. An estimated 60 percent of ARI deaths could be prevented by selective antibiotic use (Kariuki, Muyodi et al. 2003). However, because of the varied sources of infection—viruses and fungi in addition to bacteria—antibiotics are not always appropriate. It is this feature of ARIs that makes them the most common reason for antibiotic prescriptions, appropriate and inappropriate. When rapid diagnostic technology is not available and clinicians treat patients empirically, the challenge is considerable.

The local standard of care for inpatient pneumonia is penicillin alone or penicillin plus gentamicin (Tornheim, Manya et al. 2007; Ministry of Medical Services and Ministry of Public Health and Sanitation 2010). Use of more than one antibiotic is recommended in cases of severe pneumonia (Ministry of Health 2003). In paediatric care, chloramphenicol can be substituted for benzylpenicillin, and cotrimoxazole can replace gentamicin if other drugs are not available. In adult care, erythromycin is advised in the case of penicillin allergy. Amoxicillin, coamoxiclav, ceftriaxone and ceftazidime are recommended second-line treatments, with amoxicillin indicated for cases previously treated with cotrimoxazole. In practice, chloramphenicol is the mainstay of inpatient therapy for pneumococcal infections, and amoxicillin and cotrimoxazole are the most commonly used drugs in outpatient treatment of pneumonia (Mwangi, Berkley et al. 2002). Many healthcare workers also use high doses of penicillin in treating acute pneumonia by many healthcare workers.

Antibiotic resistance. Increasing and widespread penicillin resistance in the bacteria causing most cases of bacterial pneumonia—*Haemophilus influenzae* type b and *Streptococcus pneumoniae*—threatens successful treatment of pneumonia in-

fections and clinicians' ability to save lives. Penicillin-resistant pneumococci first emerged in South Africa in 1977 and then spread globally. In Kenya, resistance of Spn to penicillin was reported at 25 percent in Nairobi in 1996, and by 2003 it was 43 percent (Paul, Bates et al. 1996; Kariuki, Muyodi et al. 2003). In 2005, isolates from children with severe pneumonia were resistant to penicillin half the time (Berkley, Maitland et al. 2008). Resistance to penicillin in HIV-infected patients with pneumonia is unknown but is likely a problem, given the higher exposure of these individuals to hospitals, prophylactic use of antibiotics and patients' propensity to become infected with paediatric serotypes that are antibiotic resistant (Madhi, Petersen et al. 2000; Okeke, Laxminarayan et al. 2005; Pemba, Charalambous et al. 2008).

Penicillin is not the only medicine to which pneumonia-causing bacteria are becoming resistant. Adults with Spn or Hib disease can no longer confidently rely on cotrimoxazole for treatment. Among adults living in Nairobi, 51 to 54 percent of Spn isolates are resistant to cotrimoxazole (Mwangi, Berkley et al. 2002; Kariuki, Muyodi et al. 2003). Hib pneumonia is resistant to cotrimoxazole 66 percent of the time (Kariuki, Muyodi et al. 2003). More than 7 percent of Spn and Hib isolates affecting the adult population in this area are resistant to two or more first-line treatments. The bacteria remain susceptible, however, to chloramphenicol (95 percent) and ampicillin (93 percent) in this population.

Infected children fare worse as chloramphenicol and amoxicillin—among the most prevalent and affordable antibiotics in Kenya—are also compromised by increasing levels of resistance. Among children suffering from severe pneumonia, Spn resistance to cotrimoxazole and chloramphenicol reaches 57 percent and 26 percent, respectively (Berkley, Maitland et al. 2008). In Kilifi, antibiotic-resistant Hib in children has increased over the past decade, and multidrug resistance is common (Scott, Mwarumba et al. 2005). Forty percent of isolates are either wholly resistant or show intermediate resistance to two or more antibiotics. Susceptibility to cotrimoxazole has decreased to 13 percent among children under five years of age ($p = .02$). In children, 44 percent of Hib isolates are resistant to chloramphenicol and 62 percent are resistant to cotrimoxazole. Increasing rates of resistance to first-line antibiotics in childhood infections also raises the cost of treatment. For example, compared with the cost of chloramphenicol plus penicillin for children at the Kilifi District Hospital, US$5.50, second-line treatments with ceftriaxone or coamoxiclav cost US$40 and US$67, respectively.

The Network for Surveillance of Pneumococcal Disease in the East African Region (netSPEAR) published generally similar resistance profiles for Hib and Spn for countries in the East Africa region (Mudhune and Wamae 2009). Resistance to cotrimoxazole had increased from 19 percent of isolates in 2003 to 69 percent in 2009. In contrast, resistance to cefotaxime and erythromycin was low, ranging from zero to 1.5 percent in cerebral spinal fluid and blood samples.

Treatment for respiratory infections is largely empirical because culture results are either unavailable or take longer than 48 hours to develop, by which time more than three-fourths of patients have died (Mwangi, Berkley et al. 2002). According to the data available, treatment with penicillin, cotrimoxazole and chloramphenicol is increasingly compromised by resistance. Ampicillin and erythromycin remain viable substitutes in adults and children, however erythromycin is the only one included in the KEML for regular supply to hospitals and is restricted to adult use in the national treatment guidelines. Second-line alternatives such as ceftriaxone and coamoxiclav, however, are unaffordable for most Kenyans and not available in the majority of health facilities in the country. As mentioned, vaccination for Hib and Spn began in 2001 and 2011, respectively. As vaccine coverage expands, the principal causes of severe bacterial pneumonia will be largely controlled (English and Scott 2008).

Diarrheal Infections

Viruses, bacteria and parasites can cause acute and persistent diarrhoeal infections. A typical disease of poverty, diarrhoea is second to respiratory infections in lost disability-adjusted life years and has the single greatest adverse effect on children's growth and development (Shapiro, Kumar et al. 2001). Globally, it is responsible for 22 percent of

paediatric deaths, 40 percent of them in sub-Saharan Africa (Tornheim, Manya et al. 2009). Regardless of the causative organism, death almost always results from dehydration—the loss of fluid with diarrhoea.

In Kenya, diarrhoea is the third most common cause of death in young children, behind pneumonia and malaria. Even though fatal dehydration is preventable in most cases with oral rehydration therapy (ORT), children die because treatment is not administered, or not used in time. In western Kenya, the country's most affected area, diarrhoea is responsible for more than 11 percent of hospitalisations overall and more than 20 percent in some hospitals (Ministry of Health 2004; Tornheim, Manya et al. 2009). Severe diarrhoea is most common among younger children: nearly 17 percent of hospitalised children under the age of five years have diarrhoea, compared with 9 percent of patients five years and older. In this region of the country, the annual incidence of hospitalisation with diarrhoea is highest for infants under one year of age: 1 in 88 infants. Case-fatality is high (8 percent) and codiagnosis with malaria, pneumonia and HIV is common. Malnourished children are particularly prone to diarrhoea, and infants who do not receive an appropriate diet during a diarrhoeal episode suffer further loss of nutrients, thus exacerbating malnutrition and increasing susceptibility to other infections (HARP 2009).

Rotaviruses have emerged as a leading cause of diarrhoea worldwide. In sub-Saharan Africa it results in 200,000 to 230,000 deaths annually and causes up to 56 percent of all diarrhoea cases in Kenya, exhibiting peaks during the dry months (Kiulia, Kamenwa et al. 2008). Among children under 5 years of age, rotavirus infection causes 19 percent of hospitalizations, 16 percent of clinic visits and around 4, 500 deaths per year (Tate, Rheingans et al. 2009). Bacteria are also important causes of diarrhoeal illness. The leading organisms among children in developing countries are *Escherichia coli*, *Shigella* spp, *Salmonella* spp, and *Vibrio cholerae*. Detailed analyses in patients hospitalised with diarrhoea in western Kenya are ongoing and already indicate high case-fatality ratios for young children infected with bacterial pathogens (Tornheim, Manya et al. 2009).

Shigella spp. Among the bacterial causes of dysentery, *Shigella* spp are highly infectious and are considered the most important (Bartoloni and Gotuzzo 2010). Shigellosis predominates as a cause of sporadic, bloody diarrhoea in rural areas of Kenya (Brooks, Ochieng et al. 2006). Data from the late 1990s suggested high levels of *Shigella* isolates in patients with diarrhoea, of which 21 percent were dysenteriae type 1 (Shapiro, Kumar et al. 2001). In 2003, *Shigella* continued to be the most commonly isolated pathogen in that area, increasing in prevalence with patient age (Brooks, Ochieng et al. 2006). No national incidence rates for shigellosis exist; published data are limited to site-specific analysis in western Kenya.

Salmonella spp. Salmonella enterica serovar Typhi (*S.* Typhi) is the cause of typhoid fever, and other species of *Salmonella* cause a range of diseases (see below). Typhoid fever has almost disappeared from the industrialised world but remains in developing countries with poor sanitation (Bartoloni and Gotuzzo 2010). Globally, typhoid fever causes more than 22 million cases of illness and 200,000 deaths annually (Breiman 2009; Kariuki 2010). Typhoid fever is an endemic disease, but epidemics do occur when water supplies are contaminated or sanitation systems break down. Detailed information on the incidence of *S.* Typhi infections and mortality rates in Kenya are absent, but CDC-Kenya researchers are working on estimates (Breiman 2009). Preliminary results indicate similar trends in the slum areas of Nairobi as found on the Indian subcontinent.

Non-typhi *Salmonella,* as later described, is a leading cause of neonatal sepsis and meningitis in Kenya (Kariuki, Revathi et al. 2006). In developed countries and among the upper classes in developing countries, NTS usually causes self-limited food poisoning, but in poorer households it is also a frequent cause of severe bacterial diarrhoea. Consequently, the organism has received special attention. A highly invasive form of NTS associated with *Salmonella enterica* serovar Typhimurium recently emerged as a major public health problem in Africa, with case-fatality rates around 20 to 25 percent in children and up to 50 percent in adults (Kingsley, Msefula et al. 2009). Multidrug-resistant NTS outbreaks have occurred in the Democratic

Republic of Congo, Rwanda, and Malawi and were the leading cause of septicaemia in children in the former two countries in the early 1990s (Kariuki, Gilks et al. 1996; Kariuki, Revathi et al. 2006).

The estimated incidence of community-acquired NTS in Kenya is 166 per 100,000 people per year for children under five (Mwangi, Berkley et al. 2002; Berkley, Lowe et al. 2005). At Kenyatta National Hospital, 35 percent of all NTS cases in newborns resulted in death, despite hospital care. A significantly higher proportion of NTS admissions at the same facility came from the three main slum areas of Nairobi (38 percent of children with NTS) compared with other parts of the city. Children from slum areas tend to suffer worse health outcomes and are at higher risk of developing an invasive disease with poor prognosis (Kariuki, Revathi et al. 2006). Malnutrition, malaria and HIV are believed to be common risk factors for life-threatening community-acquired NTS infections throughout the country (Kariuki, Gilks et al. 1996; Berkley, Lowe et al. 2005; Kariuki, Revathi et al. 2006; Kingsley, Msefula et al. 2009).

Vibrio cholerae. More than two-thirds of cholera outbreaks in the past decade have occurred in Africa as part of an ongoing pandemic that arrived from Asia in the 1970s (Kariuki 2010; Okeke and Ojo 2010). Since 1971, Kenya has endured several waves of epidemic cholera (World Health Organization 2008). From 1974 to 1989, the country reported outbreaks annually with a case-fatality rate averaging 4 percent. The largest epidemic occurred in the late 1990s and lasted several years, representing 10 percent of all cholera cases reported from the African continent during that time. From 2000 to 2006, 800 to 1,155 cases were reported each year (except for 2002, when 291 cases were reported) (Kiiru, Saidi et al. 2009). More cases have been reported since 2005, and a 2007 outbreak had a case-fatality rate of up to 6 percent, higher than in the previous decade. Studies on the genetic similarity of organisms causing the outbreaks, which ran from the coast to the border with Uganda to the northwest corner of the country near Sudan, suggested that some or all of the outbreaks were epidemiologically linked and associated with rapid spread across vast geographic areas (Mugoya, Kariuki et al. 2008). Two refugee camps in Kenya are also known to be fertile ground for cholera outbreaks. Without quick and effective treatment, the mortality rate for cholera is about 50 percent. Despite the threat of rapid transmission with potentially devastating mortality rates, no national or regional burden data are available for the disease.

Treatment. Although watery diarrhoea should be treated with oral rehydration, bloody diarrhoea (dysentery) often requires antibiotic treatment. As with ARIs, most patients with either type of diarrhoea are treated empirically with antibiotics, whether or not the drugs are necessary. Despite the reduction in mortality associated with enteric infections through the use of first-line agents like chloramphenicol, amoxicillin and cotrimoxazole, acquired resistance to these antibiotics is becoming more prevalent in Africa among *Vibrio cholerae*, *Salmonella* spp, *Shigella* spp and *Escherichia coli* (Okeke, Aboderin et al. 2007).

Shigella spp. Recommended treatment for moderate or severe shigellosis in Kenya is ciprofloxacin, cotrimoxazole or amoxicillin (Ministry of Medical Services and Ministry of Public Health and Sanitation 2010). WHO guidelines recommend the use of ciprofloxacin as first-line therapy for treating bloody diarrhoea (Bartoloni and Gotuzzo 2010). Ceftriaxone is the recommended second-line option, but not in regular supply through KEMSA.

Salmonella spp. From the time of its discovery, chloramphenicol was the first-line drug for treating typhoid. With the emergence of *S.* Typhi strains multiply resistant to ampicillin, chloramphenicol and cotrimoxazole in the 1980s in South Asia and South Africa, fluoroquinolones became the drug of choice (Kariuki, Revathi et al. 2004). The Kenyan national guidelines recommend amoxicillin, cotrimoxazole, chloramphenicol, or ciprofloxacin for typhoid fever in children and adults (Kariuki 2009). Ceftriaxone is used as a second-line alternative in practice, but not stipulated by the national treatment guidelines (Ministry of Medical Services and Ministry of Public Health and Sanitation 2010).

Commonly used antibiotics for NTS in Kenya include a combination of ampicillin and gentamicin or cefuroxime, depending on the point of care (Kariuki, Revathi et al. 2006). Tetracycline, cotrimoxazole and chloramphenicol have also been in-

dicated as common first-line antibiotics for treating serious infection (Kariuki, Gilks et al. 1996). Treatment for NTS is not included in the national guidelines.

Vibrio cholerae. Devastating outbreaks of pandemic cholera continue in Africa, in particular in the east and central regions (Okeke, Laxminarayan et al. 2005). Although treatment is usually based on rapid rehydration, antibiotic therapy can shorten the course of illness in severe cases and break the transmission cycle during epidemics (Okeke, Laxminarayan et al. 2005; Okeke, Aboderin et al. 2007; Bartoloni and Gotuzzo 2010). Antibiotics may also be a life-saving treatment for malnourished and other immune-compromised patients suffering from cholera (Okeke, Aboderin et al. 2007). Erythromycin and doxycycline remain the recommended medicine in Kenya for severe cholera, with chloramphenicol recommended as a second-line alternative (Ministry of Medical Services and Ministry of Public Health and Sanitation 2010).

Antibiotic resistance. In western Kenya, where a high percentage of diarrhoea is caused by bacteria, more than half of all pathogens examined are not susceptible to empirical antimicrobial therapy, and 74 percent of isolates are multidrug resistant (defined by these authors as not being susceptible to three or more agents) (Shapiro, Kumar et al. 2001; du Prey, Ford et al. 2004). However, in other parts of the country, some enteric pathogens remain sensitive to particular agents, or resistance is spreading at a slow pace.

Shigella spp. Shigella strains are responsible for most of the sporadic bacillary dysentery cases in developing countries, with fatalities affecting primarily young children (Okeke, Laxminarayan et al. 2005). *S. dysenteriae* type 1 has been responsible for outbreaks in Africa and is frequently associated with civil conflict and population displacement. Because most shigellosis is treated empirically, an understanding of resistance patterns is important to effective management of cases. Resistance of the bacteria to ampicillin, tetracycline, cotrimoxazole and chloramphenicol has become widespread in Africa, where most of these drugs are still used for first-line therapy despite their high rates of treatment failure. In Kenya, studies reveal a trend of high resistance in *Shigella* to these antibiotics and, increasingly, quinolones in the treatment of dysentery (Kariuki 2009). A 2003 study found that 85 percent of isolates from diarrhoea were resistant to ampicillin, 94 percent to cotrimoxazole, 91 percent to chloramphenicol and 100 percent to tetracycline (Bartoloni and Gotuzzo 2010). In another study on antibiotic susceptibility in *Shigella* spp, all isolates were multiply resistant to ampicillin, cotrimoxazole, chloramphenicol, coamoxiclav and tetracycline (Kariuki, Gilks et al. 1996). Further, the more virulent and multidrug-resistant *S. dysenteriae* type 1, known to exhibit resistance to cotrimoxazole, tetracycline and nalidixic acid, is rapidly replacing the less virulent *S. flexneri* as the main cause of sporadic and epidemic bacillary dysentery in the country (Kiiru Ongoing study 2007-2011). In western Kenya, where *Shigella* predominates as a cause of diarrhoea, 84 percent of patients infected with the bacteria were given ineffective agents, and all dysentery isolates tested were multiply resistant to chloramphenicol, cotrimoxazole, tetracycline, ampicillin and streptomycin (Shapiro, Kumar et al. 2001). From 1997 to 2003, three-quarters of isolates were susceptible to nalidixic acid, and susceptibilities to gentamicin, ciprofloxacin and ceftriaxone were all above 95 percent (Brooks, Ochieng et al. 2006).

Antibiotic resistance, particularly to cotrimoxazole and amoxicillin, substantially limits the utility of available antibiotics for treating shigellosis. Ciprofloxacin and ceftriaxone appear to retain their effectiveness in the majority of patients but are not commonly available and can be relatively expensive.

Salmonella spp. Antibiotic susceptibility in *Salmonella enterica* serotype Typhi (typhoid fever) is not well studied in Africa, but available reports indicate that resistance is present in some areas (South Africa, Ghana, Nigeria, Kenya) but has yet to emerge in others (Okeke, Laxminarayan et al. 2005; Okeke and Ojo 2010). In countries where resistance exists, alternatives to current treatment protocols are often not available or are unaffordable (Okeke, Aboderin et al. 2007).

Resistance has compromised two of the first-line recommendations—chloramphenicol and cotrimoxazole—available in Kenyan public health facilities and certain bacterial strains show increasing resistance to ciprofloxacin (Kiiru Ongoing

study 2007-2011). In western Kenya more than 90 percent of *S*. Typhi isolates tested at St. Elizabeth Mukumu Mission Hospital were resistant to ampicillin and streptomycin, and 79 percent were resistant to cotrimoxazole (Onyango, Machoni et al. 2008). Researchers at this hospital found that all patients with salmonellosis were started on ampicillin for a week, but the majority did not respond and were given other antibiotics available in the essential drug kit. Surveillance for antibiotic susceptibility in *S.* Typhi is complicated by diagnostic deficiencies, however, and prevalence data for resistance are scarce. Researchers at CDC-Kenya are investigating resistance patterns in the Kibera slum (Breiman 2009). Data are forthcoming for this population.

The spread and gradual replacement of drug-sensitive strains of *S.* Typhi with multidrug-resistant (MDR) strains further reduces clinical options for treating typhoid fever. At the end of the 1980s and beginning of the 1990s, strains of *S.* Typhi multiply resistant to ampicillin, cotrimoxazole, chloramphenicol and tetracycline spread through Africa and were associated with increased disease severity (Bartoloni and Gotuzzo 2010). The first MDR typhoid outbreak occurred in Kenya in the late 1990s, with 50 to 65 percent of isolates multiply resistant to antibiotics (Okeke and Ojo 2010). Surveillance at Kenyatta National Hospital indicates that the prevalence of *S*. Typhi resistant to two or more antibiotics has been rising, from 50 percent in 1998 to 70 to 78 percent in 2004 (Kariuki, Revathi et al. 2004; Okeke and Ojo 2010). In a recent study of *S.* Typhi outbreaks over 20 years (1988 to 2008), 60 percent of isolates were multiply resistant to ampicillin, chloramphenicol, tetracycline, and cotrimoxazole. A further 23 percent of isolates were resistant to a single antibiotics, usually ampicillin, cotrimoxazole or tetracycline (Kariuki, Gilks et al. 1997). In data collected from 2000 to 2002 in Nairobi, Embu and Thika, only 14 percent of isolates were fully susceptible to antibiotics tested, whereas 82 percent were resistant to each of the five commonly available drugs—ampicillin, chloramphenicol, tetracycline, streptomycin and cotrimoxazole (Kariuki, Revathi et al. 2004). In laboratory testing, five- and 10-fold higher concentrations (minimum inhibitory concentrations) of nalidixic acid and ciprofloxacin were needed to control 42 percent of isolates than were needed for sensitive strains. In the Nairobi slum of Kibera, emerging nalidixic acid resistance of typhoid isolates suggests a potentially decreased clinical response to fluoroquinolones (Breiman 2009). Following the development of MDR *S.* Typhi with reduced susceptibility to nalidixic acid and ciprofloxacin in Kenya, resistance may soon emerge that renders even high dosages of these powerful drugs ineffective.

For non-typhoidal *Salmonella*, information is more readily available. As previously discussed, multidrug resistant NTS is believed to be an important cause of invasive disease and death among young children, and HIV infection is a significant risk factor for NTS bacteria (Kariuki, Gilks et al. 1996; Kariuki, Revathi et al. 2005; Kariuki, Revathi et al. 2006; Okeke and Ojo 2010). It is also possible that clonal expansion of hypervirulent strains may account for a substantial proportion of such infections (Okeke and Ojo 2010).

Resistance to quinolones increased in Kenya from the early 1990s to 2006 in urban centres but has decreased in the coastal region. In the mid-1990s, NTS isolates were displaying resistance to the antibiotics used in empirical therapy, including ampicillin (48 percent) and cotrimoxazole (46 percent) (Kariuki, Gilks et al. 1996). At the time, only 16 percent of isolates tested were sensitive to all antibiotics. In 2005, researchers published levels of resistance of 94 percent to ampicillin and 67 percent to cotrimoxazole (Kariuki, Revathi et al. 2005). Over the 10-year period, ciprofloxacin was the only antibiotic to which all NTS isolates tested remained fully susceptible.

In contrast, the problem has appeared to reverse in Kilifi, where free treatment and significant health interventions are thought to have reduced the need for antibiotics. Studies from the area demonstrate decreasing prevalence of antibiotic-resistant NTS isolated from children in the district hospital, especially resistance to common antibiotics such as cotrimoxazole and amoxicillin ($p<.001$) during a 10-year period (1994–2005) (Kariuki, Revathi et al. 2006). Rates of resistance for these two first-line agents went from highs of 69 and 68 percent in 1994 to 1997 to 11 and 13 percent in 2002 to 2005, respectively. Significant reductions in resistance to gentamicin and chloramphenicol

were also noted. Other studies reported similar results for NTS resistance trends in gram-negative bacilli in Kilifi (Bejon, Mwangi et al. 2005). The results suggest that most antibiotics remain effective in Kilifi, but the general trend of resistance in the urban population has been upward.

The prevalence of MDR NTS among adults in Kenya rose from 31 percent in 1993 to 42 percent in 2003, including resistance to extended-spectrum cephalosporins and fluoroquinolones (Kariuki, Revathi et al. 2005). Infection with MDR NTS is associated with an increased rate and duration of hospitalisation, a twofold increased risk of death during a two-year period after infection and an increased rate of invasive infection. Most MDR NTS isolates are susceptible to cefotaxime and ciprofloxacin, but these drugs are expensive and unavailable to most of the population (Kariuki, Revathi et al. 2006). At Kilifi District Hospital, treatment for a child for seven days with gentamicin and chloramphenicol would cost US$0.38 to US$2.30 compared with US$108 or US$73 for treatment with cefotaxime or ciprofloxacin (Bejon, Mwangi et al. 2005).

Highly invasive, multiply resistant *S. Typhimurium* isolates in Kenya and Malawi are quickly developing into a public health problem (Kingsley, Msefula et al. 2009). These bacteria kill up to one-quarter of affected children and up to half of affected adults.

Vibrio cholerae. The first MDR strains of *V. cholerae* in East Africa were detected in 1977 in Tanzania and Kenya and quickly spread throughout the region (Bartoloni and Gotuzzo 2010). Isolates from this initial wave were resistant to tetracycline, cotrimoxazole, gentamicin and ampicillin (Okeke, Laxminarayan et al. 2005; Okeke, Aboderin et al. 2007). In all epidemics, tetracycline resistance appeared when the drug was used intensively for prophylaxis as well as treatment (Okeke, Aboderin et al. 2007). By the 1980s, WHO began recommending cotrimoxazole and, later, quinolones. Eventually, strains resistant even to quinolones began to emerge (Bartoloni and Gotuzzo 2010). During the 1998–1999 cholera epidemic in Kenya, 61 strains from 25 outbreaks were resistant to tetracycline, cotrimoxazole and chloramphenicol (Scrascia, Forcillo et al. 2003; Kariuki 2010). This strain appears to have spread to southern Sudan, parts of Somalia, and western and coastal Kenya in 2006. In an outbreak in western Kenya, susceptibility to tetracycline was reported, but no details were provided (Shapiro, Kumar et al. 2001). Resistant strains of *V. cholerae* that were more virulent than susceptible strains led to a large number of deaths in conflict-associated outbreaks in eastern Democratic Republic of Congo (Okeke and Ojo 2010).

Decades-long tetracycline resistance in Kenya, coupled with poor diagnostic capacity, means that empiric treatment frequently employs ineffective drugs. This not only increases the intensity of cholera epidemics but also places more patients at risk of dying.

Commensals. The normal human (and animal) gut harbours hundreds of species of nonpathogenic bacteria in a 'commensal' relationship—beneficial for both host and bacteria. These bacteria also constitute a rich reservoir of genetic material, which may be acquired by other bacteria, including pathogens (Okeke, Aboderin et al. 2007). When commensal bacteria are exposed to antibiotics, resistance genes can develop and transfer to pathogenic microorganisms, causing antibiotic-resistant infections (Nys, Okeke et al. 2004; Okeke, Laxminarayan et al. 2005; Kariuki 2010).

In Kenya, there is concern about growing resistance to the second-line agent ciprofloxacin and common antibiotics like cotrimoxazole, tetracycline and ampicillin in nonpathogenic *E. coli* (Kariuki 2009). In a study to determine the prevalence of antibiotic-resistant *E. coli* in healthy adult volunteers in both urban areas (Kenya, Mexico, Peru and the Philippines) and rural areas (Venezuela, Ghana and Zimbabwe), higher rates of resistance to ampicillin (89 percent) and tetracycline (92 percent) were found in the urban areas of Kenya than in the rural areas of Ghana and Zimbabwe (Nys, Okeke et al. 2004). A 2005 study of diarrhoeagenic *E. coli* in young children in Kenya demonstrated high levels of multidrug resistance to tetracycline (71 percent), ampicillin (66 percent) and cotrimoxazole (68 percent), the leading antibiotics recommended for treatment of bacterial infections by WHO (Bii, Taguchi et al. 2005; Kariuki 2010). Similar rates were found in a control group of healthy children. Tetracycline resistance in children is unusual because the drug is not used in paediatric care, indi-

cating possible contamination from food or water (Kariuki 2009).

To determine the interaction between resistance determinants in *E. coli* from different ecosystems, comparative studies were conducted in central Kenya (Kariuki, Gilks et al. 1999). Nonduplicate strains were obtained from children under five years, and strains were isolated from environmental specimens in the homes of index cases, including from chicken droppings, cattle rectal swabs, and drinking water sources (rivers and boreholes). In the first study, 87 percent of *E. coli* samples from children were resistant to ampicillin, chloramphenicol, cotrimoxazole and tetracycline. Only 26 percent of environmental isolates were MDR, however, suggesting that the normal intestinal flora of children were more exposed to antibiotics than livestock in same setting. In the follow-up study conducted in 2003, isolates from healthy children continued to display high levels of multidrug resistance (89 percent) towards ampicillin, cotrimoxazole and tetracycline.

Finally, a 2005 study on antibiotic resistance in gram-negative bacilli in Kilifi found that *E. coli* exhibited resistance levels as high as 78 percent to amoxicillin, 85 percent to cotrimoxazole and 42 percent to chloramphenicol (Bejon, Mwangi et al. 2005). Isolates, however, were 100 percent susceptible to two rarely used antibiotics in the area, ceftriaxone and ciprofloxacin.

Bacteraemia

Of the 4 million neonatal deaths that occur globally each year, an estimated one-quarter are caused by bacteraemia—severe bacterial bloodstream infections (Newton and English 2007). The most reliable estimates for Kenya come from two complementary studies involving blood cultures of children who were inpatients and outpatients (some of whom were eventually admitted), respectively, at Kilifi District Hospital, a rural facility in the coastal region. The former (Berkley, Lowe et al. 2005) was a large, four-year study (1998 to 2002) of all acute admissions among children up to 13 years of age; the latter (Brent, Ahmed et al. 2006) was a smaller, six-month study in 2003 of 10 percent of outpatient children aged five years and under.

Together, these studies suggest that community-acquired bacteraemia is more common than previously thought and responsible for at least one-third of deaths in infants and one-quarter of deaths in older children, higher than the global figures. These could be underestimates—possibly large—for several reasons: cultures with probable contamination were not included (and those children were categorised as not having bacteraemia); culture positivity increases with the amount of blood available for culture, and amounts for children are small; and previous use of antibiotics, which can be purchased easily, reduces the chances of a positive culture. Furthermore, two-thirds of childhood deaths occur outside hospitals. No major biases work in the opposite direction.

The mix of organisms responsible for bacteraemia changes with age group. In infants under two months of age, the most common organisms were *Escherichia coli* (14 percent), Group B *Streptococcus* (11 percent) and *Acinetobacter* species (10 percent) (Berkley, Lowe et al. 2005). In older children, *Streptococcus pneumoniae* alone was found in a quarter of bacteraemia patients 12 to 23 months old and in about half of patients older than five years. The proportion of cases caused by *S. pneumoniae* or *Staphylococcus aureus* increased with each year of age, and the proportion caused by *Haemophilus influenzae* remained about the same. The proportion caused by NTS fell from 23 percent among those 12 to 23 months of age to 7 percent of those older than five years.

Death from bacteraemia is rapid—within two days of hospital admission, 71 percent of the deaths occurred—but blood culture results take one to two days. The burden and the urgency of treatment argue for prevention with vaccines, which currently can prevent infection with *H. influenzae* and *S. pneumoniae*. Currently, no vaccines exist for NTS.

Treatment. WHO advises treating bacteraemia in infants with ampicillin and gentamicin (Newton and English 2007). In Kenya, ampicillin is replaced by benzylpenicillin in infants under 60 days of age and older children are given benzylpenicillin plus chloramphenicol (Kariuki, Revathi et al. 2006; Ministry of Medical Services and Ministry of Public Health and Sanitation 2010). Ceftriaxone and ceftazidime are indicated as second-line therapies

Box 2. HIV and cotrimoxazole resistance

The AIDS epidemic continues to ravage societies in developing countries. An estimated 22 million of the 30 million people with AIDS live in sub-Saharan Africa. Following WHO recommendations, many of these patients use the broad-spectrum antibiotic cotrimoxazole to prevent 'opportunistic' infections. In addition, WHO recommends that children use cotrimoxazole for 15 months after HIV exposure to lessen the chances of infection. Widespread use of prophylactic cotrimoxazole can complicate efforts to control common infectious diseases (Foster 2010). Use of this antibiotic for HIV/AIDS (though possibly extremely effective) also promotes resistance to cotrimoxazole generally, which is used to treat pneumonia, dysentery and typhoid. Thus, the wider costs of losing this cheap and accessible antibiotic might prove considerable (HARP 2009).

On April 2010, the *Daily Nation*, a popular newspaper in Kenya, ran a story under the headline 'Doctors alarmed about HIV drug', covering the issue of cotrimoxazole resistance and HIV management (Foster 2010; Okwemba 2010). According to the article, the Ministry of Medical Services advises daily cotrimoxazole for HIV patients, regardless of their CD4 counts, to reduce the risk of contracting tuberculosis and pneumonia. Clinicians, however, are worried that this policy could lead to higher costs as resistance emerges in HIV patients and spreads to others in the community. One physician said that, 'with a CD4 count of over 400, it may not add any value to have this person take antibiotics for prophylaxis purposes'.

The relationship of cotrimoxazole prophylaxis to bacterial resistance is not fully understood. Two studies conducted in South Africa shed some light on the risks, however. The first found that reduced susceptibility to penicillin and cotrimoxazole was more common in HIV-positive children (24 percent vs. 6 percent in HIV-negative children, p=.01) (Klugman 2009). Higher levels of resistance to cotrimoxazole were also associated with Spn isolates from children on cotrimoxazole prophylaxis. Similar impacts of cotrimoxazole use on Spn resistance were found in adults. From 2002 to 2003, 61 percent of participants taking cotrimoxazole prophylaxis had isolates resistant to cotrimoxazole compared to 22 percent of those not taking the drug (p=.001) and 30 percent had isolates resistant to penicillin compared to 8 percent of HIV-positive adults not on a cotrimoxazole regimen (p=.014) (Madhi, Petersen et al. 2000).

(Ministry of Medical Services and Ministry of Public Health and Sanitation 2010).

Antibiotic resistance. Reports on antibiotic resistance for bacteraemia in infants and young children are mixed and sparse. Where numbers exist, the results are questionable for several reasons: researchers have not reported gram-positive bacteria to genus and species; they could not determine whether infection was acquired maternally or in the hospital or community, an important characteristic; and because most studies have been conducted in neonatal intensive-care units (IUCs), long hospital stays may have contributed to greater reported resistance rates (in contrast to community-acquired rates) (Newton and English 2007).

A high percentage of gram-negative organisms were reported to be resistant to first-line antibiotics ampicillin (66 percent) and gentamicin (20 percent) in data collected from 1998 (Musoke and Revathi 2000; Newton and English 2007). According to a 2005 report (Berkley, Lowe et al. 2005), all sepsis-causing bacteria (gram-positive and gram-negative) were almost entirely (97 percent) susceptible to ampicillin-gentamicin combination, and 88 percent were susceptible to benzylpenicillin-gentamicin. In malnourished children (21 percent of children with invasive bacterial infections and 38 percent of deaths in children under 60 days of age), susceptibility was lower at 87 percent for amoxicillin-gentamicin and 81 percent for penicillin-gentamicin. Bacteria were resistant to penicillin alone nearly 70 percent of the time in both adequately nourished and malnourished patients.

Sexually Transmitted Infections

More new cases of sexually transmitted infections (STIs) occur in sub-Saharan Africa than any other part of world. Although they are rarely fatal,

bacterial STIs result in significant morbidity, such as infertility and ectopic pregnancy from *Neisseria gonorrhoeae* and *Chlamydia trachomatis* or foetal death from congenital syphilis (Okeke, Laxminarayan et al. 2005). Perhaps most important, STIs increase by 2- to 5-fold a person's susceptibility to HIV infection through sexual contact.

Treatment. At present, regional information for antibiotic resistance exists only for gonorrhoea. *Neisseria gonorrhoeae* remains one of the most common causes of sexually transmitted disease in developing countries (Okeke, Laxminarayan et al. 2005). The emergence of resistance to more affordable drugs, such as penicillin and tetracycline, in Tanzania, Zimbabwe and Ethiopia has greatly compromised treatment (Okeke, Laxminarayan et al. 2005; Bartoloni and Gotuzzo 2010). In the past two decades, newer drugs like ciprofloxacin and ceftriaxone were recommended for the treatment of gonorrhoea as resistance emerged to cotrimoxazole and gentamicin in many parts of Africa (Okeke and Ojo 2010). The 2010 edition of national treatment guidelines recommends first-line treatment with ceftriaxone, ciprofloxacin, or amoxicillin combined with coamoxiclav (Ministry of Medical Services and Ministry of Public Health and Sanitation 2010). When that fails, cefuroxime, azithromycin, ofloxacin or kanamycin are recommended as a second-line treatment. Although ceftriaxone, cefuroxime, and azithromycin are included in the KEML, they are not regularly supplied to hospitals. Ofloxacin and kanamycin are not on the KEML and not available to public hospitals through regular distribution chains. Thus, in practice, if hospitals follow the treatment guidelines, they are limited to ciprofloxacin or amoxicillin with coamoxiclav for treatment and lacking in any viable second-line alternative. This STI, like others, is primarily treated using the syndromic management approach, which can result in substantial over-prescribing of antibiotic agents.

Antibiotic resistance. Data from sub-Saharan Africa indicate that penicillin resistance among gonococci in the region currently exceeds 35 percent, and tetracycline resistance reached 65 percent by the early 1990s (Okeke, Laxminarayan et al. 2005; Bartoloni and Gotuzzo 2010). Some resistance to the more recently recommended alternatives—ciprofloxacin and ceftriaxone—has been reported in Tanzania (Okeke and Ojo 2010). Although susceptibility testing has not been reported for *N. gonorrhoeae* in Kenya, these regional observations indicate that gonorrhoea is becoming more difficult to treat and that third-generation cephalosporins may eventually cease to be effective against it.

Nosocomial Infections

Little information exists on the burden of HAIs in African countries, but WHO estimates that 10 to 30 percent of all hospital admissions in the region result in an infection (Ndegwa 2009). Bacteria are the most common pathogens of nosocomial infections, and failures in the healthcare system are typically responsible for the spread of disease in hospitals. At present there are no national figures on the rates and burden of HAIs in Kenya; however, several hospital-based studies indicate that the problem is severe.

The prevalence of viral HAIs identified in various studies suggests that a substantial proportion of patients may not require antibiotic treatment, often empirically prescribed for HAI patients (Ndegwa, Ellingson et al. unpublished data). In their preliminary findings, the CDC-Kenya and Ministries of Health documented that at least one-third of respiratory HAIs in three public hospitals were caused by viruses, including adenovirus (15 percent) and influenza A (13 percent). Although clinicians remark that viral HAIs are common and incorrectly treated with antibiotics, there is little documentation on the issue outside the CDC-Kenya study.

Three studies examine the importance of bacterial HAIs in neonatal units and ICUs in Kenyan hospitals. At Kenyatta National Hospital in 2000, 17 percent of hospital-born neonates acquired sepsis, and of those, 41 percent died (Musoke and Revathi 2000). According to the researchers, this is likely an underestimate of the hospital's neonatal nosocomial infection rate because surveillance was inconsistent. The high infection rate is presumably linked to overcrowding and poor infection control.

A study published in 2006 identified common bacteria from infected patients in the Kenyatta National Hospital ICU (Ngumi 2006). Patients with longer than a two-day stay were at risk of infection, with no organisms found up to two days fol-

lowing admission, a few found by the third day, and more than one organism isolated from the majority of patients by the end of the first week. The most commonly isolated bacteria were *Klebsiella* spp, *S. aureus*, *S. pneumoniae*, and *E. coli*. The incidence of nosocomial infections within the ICU was 40 to 50 percent of all patients. Determinants of infection included age, underlying disease, and status of immunological defences, with HIV patients tending to contract bacterial opportunistic infections. Patients staying in the ICU were infected with bacteria that had previously been cultured from ward equipment, floors, sinks and other patients. Factors contributing to the cross-infection of patients included shared suction machines, use of the same catheter several times within a 24-hour period, and one nurse caring for multiple patients. Overcrowding was also an issue, since the 20-bed ICU is used for general paediatric, adult, surgical and medical patients who can't afford private facilities; it admits nearly 1,200 patients a year.

A study of common postoperative infections, conducted at Moi Teaching and Referral Hospital, found that *S. aureus* was the most prevalent bacterium infecting wounds (55 percent of isolates examined, $p < .05$) (Andhoga, Macharia et al. 2002). *Pseudomonas* and *E. coli* accounted for 12 and 2 percent, respectively. Researchers discovered an association between the level of contamination and pathogens isolated, with *S. aureus* dominating the heavily contaminated (59 percent) and septic (48 percent) wounds; *E. coli* increased in prevalence the more contaminated the wound. Contamination was categorised as 'clean', 'clean-contaminated', 'heavily contaminated' or 'septic', based on physical examination. Indicators for each level focused on inflammation of the tissues involved and the surrounding bone and muscle, the presence of pus or other draining fluid, and the colour and smell of the tissues.

Staphylococcus aureus. Although it is responsible for illnesses ranging from bacteraemia to infections of the central nervous system and respiratory tract, the frequency of *S. aureus* has not been reported for the majority of African countries (Kesah, Ben Redjeb et al. 2003). In a retrospective clinical lab study at Aga Kahn University Hospital between 2003 and 2008, 34 percent of bloodstream infections were caused by *S. aureus* (Omuse 2009). A surgical site infection study in 2008 at the same hospital revealed that *S. aureus* was the most prevalent causative agent of infected wounds (32 percent). The study is in progress, and final results have not yet been published.

Antibiotic resistance. The intensive use of antibiotics and consequent selective pressure placed on bacteria make hospitals and healthcare facilities 'hotbeds for evolution' of resistant organisms (Miralles 2010). Transmission of resistant infections can easily spread between patients and from patients to hospital staff when standard infection control precautions are lacking, hindering the ability of hospitals to prevent deaths and cure disease. In some developing countries, up to 60 percent of all nosocomial infections are due to resistant bacteria (Kakai and Wamola 2002).

In Kenya, organisms of concern include *S. aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and enterococci. MDR strains of typically benign bacteria such as *E. coli* and Acinetobacter are now associated with invasive infections among immune-compromised hospital patients and those staying in the ICU (Kiiru Ongoing study 2007-2011). Hospital transmission of community-acquired resistant organisms, such as shigella and pneumococcus, has also been increasingly documented (Okeke, Laxminarayan et al. 2005).

Methicillin-resistant *S. aureus* outbreaks are becoming a challenge for infection control professionals (Bartoloni and Gotuzzo 2010). Data in western Kenya reveal high levels of resistance to common antibiotics in *S. aureus* isolates collected from healthcare facilities (nearly 25 percent for all antibiotics tested) (Kakai 2009). In 1997, documented rates of MRSA in Kenya were 28 percent of all *S. aureus* tested in city hospitals (Kesah, Ben Redjeb et al. 2003). A separate study during the same year on the public health threat of bacterial infections and antibiotic resistance at Kenyatta National Hospital found the prevalence of MRSA to be 40 percent of all *S. aureus* infections (Omuse 2009). In 2006, MRSA was found in 33 percent of *S. aureus* isolates at Kenyatta National Hospital (Ngumi 2006).

Data concerning the antibiotic susceptibility patterns of MRSA in sub-Saharan Africa are

extremely limited, and few studies on it have been conducted in Kenya. One investigation of eight African hospitals noted comparatively higher levels of MDR MRSA in Kenya, Nigeria and Cameroon, with more than 60 percent of isolates exhibiting resistance to at least three antibiotics (Kesah, Ben Redjeb et al. 2003). According to the same study, MRSA susceptibility to gentamicin and tetracycline were extremely low, at 15 and 8 percent, respectively.

Outbreaks of infections caused by *Klebsiella* strains resistant to third-generation cephalosporins have been reported. Extended spectrum beta-lactamase–producing strains of *K. pneumoniae* present a therapeutic challenge because the majority are resistant to commonly used antibiotics. At Kenyatta National Hospital, *K. pneumoniae* isolates in neonatal wards were uniformly resistant to ampicillin, tetracycline, cephradine, cefuroxime, cefotaxime, carbenicillin and ceftazidime (Musoke and Revathi 2000; Kariuki 2010). They remained susceptible to streptomycin, cotrimoxazole, gentamicin and nalidixic acid.

Tables 4 and 5 list statistics related to the burden of bacterial disease and antibiotic resistance.

Antibiotic Resistance in Domestic Animals

The use of antibiotics for growth promotion in livestock and the treatment and prevention of animal diseases accounts for considerable amount of global antibiotic consumption, which may lead to the development of resistant bacteria in animals with possible transmission to humans through the food chain (Kariuki, Revathi et al. 2005; Okeke, Laxminarayan et al. 2005). The consequences of antibiotic resistance in food-borne pathogens on human health are yet to be seriously evaluated in most of sub-Saharan Africa (Okeke, Laxminarayan et al. 2005). In Kenya, like most of the African continent, there is no formal system for surveillance of antibiotic resistance in bacterial isolates from food animals or their products and the impact on selective pressure from antibiotic use in agriculture is generally not investigated. Where studies exist, the results are mixed. While one Nigerian report found that resistance was more common in *E. coli*

Table 4. Mortality Rates and Incidence of Bacterial Disease per 100,000 Population

	Bacteraemia	Respiratory infections		Diarrhoeal disease			STIs	Nosocomial infections	
Inc-Mort	All bacteria (1, 4)	Spn (2)	Hib (2)	Shig	Salm (NTS) (3)	V. chol	N. gon	Neonatal (KNH, sepsis) (5)	ICU (KNH – HAIs) (6)
Infants	2,440 cases; 1/3 of all deaths	No data	No data	No data	No data	No data	No data	16.9% rate	No data
Young children	1/4 of all deaths	235,500 cases; 16,430 deaths	34	No data	166	No data	No data	No data	No data
All ages	No data	No data	No data	No data	No data	No data	No data	No data	40–50% infection rate

Abbreviation: KNH = Kenyatta National Hospital.

Sources: Brent, Ahmed et al. 2006 (1); Cherian 2009 (2); Mwangi, Berkley et al. 2002 (3); Berkley, Lowe et al. 2005 (4); Musoke and Revathi 2000 (5); Ngumi 2006 (6).

Table 5. Antibiotic Resistance in Kenya by Organism and Location

Disease	Organism	Resistant drugs (percentage resistant)	Sensitive drugs (percentage susceptible)	Location
Bacteraemia	All bacteria	Amp Pen (70)	Pen-Gent (88) Amp-Gent (97) Less susceptibly in malnourished children	—
Pneumonia	Spn	**Children (severe):** Chlorm (26) Cotrim (57) **Adults:** Doxy (24) Pen (43–50) Cotrim (51–54)	—	Nairobi
	Hib	**Children:** Chlorm (44) Cotrim (87)	—	Kilifi
		Adults: Cotrim (66)	Amp (93) Chlorm (95)	Nairobi
Diarrhoea	*Shigella* spp	Amp (85) Chlorm (91) Cotrim (94) Tet (100)	Nal Acid, Cipro, Gent, Ceftri	Nairobi and Western Kenya
	NTS	Cotrim (67) Amp (94)	Cefo and Cipro	Nairobi
		—	Cotrim (87) Amp (89)	Kilifi
	S. Typhi	Amp (90) Cotrim (79) Amp, Cotrim, or Tet (23 in 88-08) **MDR:** Amp, Chlorm, Tet, Strep, Cotrim (82 in 2000-2002) Amp, Chlorm, Tet, Cotrim (60 in 88-08)	Nal Acid and Cipro: Increasing resistance to both reported (42 with elevated MICs)	Nairobi and Western Kenya
	V. cholerae	Tet, Cotrim, Gent, Amp, Chlorm	—	—
	E. coli	Amp (66 –87) Cotrim (68–87) Tet (70–87) Chlorm (87)	—	Nairobi
		Chlorm (42) Amox (78) Cotrim (85)	Ceftri and Cipro	Kilifi

Table 5. Antibiotic Resistance in Kenya by Organism and Location (continued)

Disease	Organism	Resistant drugs (percentage resistant)	Sensitive drugs (percentage susceptible)	Location
STI	*N. gon*	Pen (35) Tet (65)	Ceftri and Cipro	SSA Region
HAIs	*S. aureus*	MRSA (40) Gent (85) Tet (94)	—	Kenyatta National Hospital, Nairobi
	K. pneumonia	Amp, Tet, Ceph, Cefuro, Cefo, Carben, Ceftaz	Strep, Cotrim, Gent, Nal acid	Kenyatta National Hospital, Nairobi

Abbreviations: Amp = ampicillin, Amox = amoxicillin, Carben = carbenicillin, Cefo = cefotaxime, Ceftaz= ceftazidime , Ceftri – ceftriaxone, Cefuro = cefuroxime , Ceph – cephradine, Chlorm = chloramphenicol , Cipro = ciprofloxacin , Cotrim = cotrimoxazole, Doxy = doxycycline, Gent = gentamicin, MRSA = methicillin-resistant S. aureus, Nal Acid = nalidixic acid , Pen = penicillin, Strep = streptomycin, Tet = tetracycline.

samples from poultry farms engaged in high levels of antibiotic use, data from Kenya suggests that animal isolates of *E. coli* are unaffected by selective pressure. Studies on the contribution of food-borne pathogens to the spread of bacteria within the human population are limited in number and restricted to sentinel-site research conducted with hospital patients. Furthermore, challenges such as inadequate specimen collection, as well as incubators and autoclaves of insufficient quality, undermine data analysis (Mitema 2009). Without a coordinated and routine data collection system in place, national risk assessments and the advancement of sound policies to address the possible threat to human health from antibiotic resistance in animals remain elusive.

Salmonella spp

Farm animals are a major reservoir of NTS, a common cause of bacteraemia among infants and the immune-compromised in Kenya (Kikuvi, Schwarz et al. 2007). Outbreaks of NTS infection in humans have been associated with food-borne transmission from poultry, milk and other dairy products, and MDR salmonella strains are believed to be increasing in part from antibiotic pressure in veterinary medicine. In slaughtered pigs, cattle and chicken, salmonella was found in 6 percent of the samples, with a higher prevalence (19 percent) in carcasses than in faeces (9 percent). In pork alone, 79 percent of carcass samples are culture-positive. This suggests severe cross-contamination during slaughtering and indicates poor hygienic conditions during subsequent dressing activities. In 18 percent of positive pork carcasses, the same salmonella serovar was also isolated from faeces samples, posing a direct threat to consumer health through the transfer of pathogens from faeces to carcass meat. An estimated 36 percent of salmonella isolates are resistant to common antibiotics, including ampicillin, tetracycline, streptomycin and chloramphenicol. All isolates are fully susceptible to gentamicin, cotrimoxazole and nalidixic acid. Around 7 percent of isolates are multiply resistant to streptomycin and tetracycline or ampicillin, tetracycline and streptomycin. Although ampicillin, tetracycline and streptomycin are relatively inexpensive and easily available to farmers for therapeutic and prophylactic applications, chloramphenicol is not approved for use in food animals in Kenya. Researchers propose that resistance is acquired either from horizontal gene transmission from water contaminated with human sewage or from illegal use of the drug in livestock production.

Although a variety of foods, including pork products, may serve as reservoirs of drug-resistant salmonella and are thus implicated as vehicles of drug-resistant NTS transmission to humans, Kenyan studies fail to show any significant genotypic association between NTS isolates in animals

and humans in close contact (Kariuki, Revathi et al. 2005; Kariuki, Revathi et al. 2006). Rather, one study revealed that a significant number of NTS isolates in children (7 percent) shared the same serotype and resistance profiles as those isolated from siblings and parents (Kariuki, Revathi et al. 2006). No major animal or food reservoir of NTS was discovered in the homes of infected children. The full importance of human-to-human transmission of NTS is unknown, but the authors hypothesise that it is the major mode of infection in Kenya (Kariuki, Revathi et al. 2005). The role of foodborne transmission of MDR *S. Typhimurium*, an important cause of invasive NTS infection, is also unclear, and studies have yet to address this question (Kariuki, Revathi et al. 2006).

Escherichia coli

Four studies in Kenya have investigated the presence of antibiotic-resistant *E. coli* in animal products, including poultry and milk. Household poultry farming is common in the country, and a large proportion of the population lives in close contact with chickens. Given these conditions, there is a possibly high risk that resistant bacteria can spread from poultry to humans. A pilot study on small-scale farms in Thika, where farmers practice intensive commercial chicken farming, found that a significant proportion of *E. coli* isolates were resistant to tetracycline (72 percent) (Kariuki, Gilks et al. 1997). All isolates, however, were sensitive to neomycin and apramycin. As previously mentioned in the discussion of commensals and resistance in humans, comparative studies were conducted to determine possible environmental sources of *E. coli* infection in children (Kariuki, Revathi et al. 2006). The results of these studies suggested that drug-resistant *E. coli* in children was the result of human antibiotic exposure, rather than transmission from livestock or food products.

A separate study in 2000 assessed the risk of infection with *E. coli* from unpasteurised milk (Arimi, Koroti et al. 2005). The sale of unpasteurised milk to consumers, either directly or through small-scale traders, has increased since the liberalisation of the milk market in 1992; an estimated 80 percent of all milk sales in Kenya are conducted through such informal channels. Given the potential for transmission of *E. coli* from cattle to humans via the consumption of unpasteurised milk, the study investigated the presence of the bacteria in raw milk products found in rural and urban households in central Kenya during the dry and rainy seasons. *E. coli* was isolated in 35 percent of the milk samples obtained from consumers, with 0.8 percent testing positive for 0157:H7. The prevalence rate of 0157:H7 translates into a potential risk of exposure to this rare but virulent strain about three times each year for a daily consumer of raw milk. The risk is even greater among the Maasai people and other communities that frequently consume raw milk from open-grazed herds. The majority of urban households (96 percent), however, and a large number of rural households boil milk before consumption in the process of making tea, reducing the chances of exposure to live pathogens. The study did not investigate resistance profiles of the bacteria in milk samples or demonstrate its link to human *E. coli* infections.

Besides those reports, virtually no other data illuminate the role of milk or poultry in the transmission of *E. coli* disease in Kenya. There are no studies on the extent of drug resistance in normal flora *E. coli* in other often-consumed animals, such as goats or cows.

Staphylococcus aureus

S. aureus is an important mastitis bacterium in Kenyan bovines and is the most frequently isolated pathogen from mastitic milk. One study conducted in the Rift Valley compared the prevalence of MDR *S. aureus* in milk products between large dairies (> 200 cows) and small producers (< 50 cows), assuming that possible differences in antibiotic use within the two producer categories would manifest in the resistance profiles of *S. aureus* isolates (Shitandi and Sternesjö 2004). The overall prevalence of *S. aureus* in milk was 31 percent, with a significant difference in the average resistance profiles of large-farm (7 percent) and small- farm (15 percent) isolates ($p < .05$). The prevalence of multidrug resistance likewise differed significantly between isolates from small farms (34 percent) and those from large farms (18 percent). Isolates from small farms were also more likely to demonstrate resistance to penicillin and tetracycline than large

farms, possibly the result of selection pressure for these antibiotics in small-scale milk production. There are no other studies investigating the role of herd size as a risk factor in the development of antibiotic-resistant bacteria in the country.

Surveillance for Bacterial Disease and Resistance

National surveillance efforts for notable infectious diseases are relatively common in sub-Saharan Africa; however, similar systems for the burden of antibiotic resistance have been harder to establish (Tornheim, Manya et al. 2007). Despite the heavy burden of bacterial disease on the population, scarcity of resources, inadequate infrastructure and the imperative to focus on basic services preclude the development of local resistance profiles or the ability to track resistance trends. Few countries in the region have adopted the WHONET system for data management, including Kenya (Vlieghe, Bal et al. 2010). The country's large geographical and topical areas from which no data are available evidence the difficulty of quantifying the burden imposed by antibiotic resistance on public health. Where lab facilities exist for site-based surveillance, they are characterised by a lack of quality control, inadequate supervision and unreliable reagents. As a result, clinicians find it difficult to optimise empiric antibiotic treatment for common infections, national treatment guidelines advise the use of medicines with dangerously high resistance levels, lower-level health facilities are restricted by the Kenyan EDL to increasingly ineffective antibiotics, and decisionmakers struggle to design and monitor control measures of drug-resistant diseases.

Several efforts within Kenya seek to address this information gap with quality surveillance on the resistance trends in clinically significant pathogens, including programmes within CDC-Kenya, KEMRI-Wellcome Trust Research Programme, the Kenya Medical Research Institute, the Department of Veterinary Services and major hospitals. Although Kenya lacks a national database on healthcare-associated infections and has not developed a standardised methodology with which to undertake data processing, CDC-Kenya has partnered with the government health ministries to collect, analyse and disseminate data on HAIs as part of infection control capacity building within the country (Ndegwa, Ellingson et al. unpublished data). The initiative aims to generate quality data on antibiotic resistance patterns for HAIs on a regular basis and produce facility-level reports on local resistance profiles to support empirical treatment decisions. The reporting system will be integrated into the country's health management information system to enable district, provincial and national health agencies to extract epidemiological data on HAIs and drug resistance (Ministry of Health 2010). CDC-Kenya is additionally engaged in sentinel-site and population-based surveillance of influenza in the eight provincial hospitals, two refugee camps, and residential areas of Nairobi and Kisumu (Katz 2009). A joint project with the government, this programme aims to provide an early warning system for pandemic flu, characterise strains of influenza in Kenya and better describe the epidemiology and burden of influenza disease in the country. The population-based sites in Kisumu (25,000 people) and Nairobi (Kibera, 28,000 people) gather biweekly information from households on episodes of pneumonia, diarrhoea and fever. Pneumonia specimens collected in this study are tested for bacterial and viral origins, as well as drug susceptibility profiles.

In 2003, KEMRI – Wellcome Trust Research Programme established the netSPEAR project through GAVI to better inform the development and use of pneumococcal vaccines at the country level (Mudhune and Wamae 2009). The initial scope was limited to Kenya, Uganda, Tanzania and Ethiopia and focused on data collected from young children. The project sought to enhance the representativeness of the data collected by increasing the number of sites in each country, improve completeness of the data by ensuring that sites had the technical ability to isolate pneumococci and elevate the role of local data in formulating policy. The network's initial project appears complete, and netSPEAR will be integrated into WHO-AFRO activities. The plan is for country level networks to continue after the handover.

Aga Kahn University Hospital, a tertiary referral and post-graduate teaching hospital in Nairobi,

seeks to use its advanced laboratory capacity to perform resistance surveillance within its own operations. The microbiology division has internal quality management systems in place and is a registered participant in the United Kingdom National External Quality Assessment Service program. Data generated from its system are used to update guidelines for syndromic treatment, reassess the drug formulary, and identify the need for infection control measures and impact evaluations for various interventions. The microbiology department and infection control teams manage the system. High-risk areas, such as the ICU, surgical wards and the neonatal unit, are targeted for specimen collection, as determined by physicians. Previously, the hospital used WHONET for information management, but individuals involved in data entry found this system difficult to navigate and technologists switched to storing data in Excel spreadsheets (Makau 2009). The department is currently developing a more sophisticated and user-friendly database. Deficient clinical information on patients remains a challenge, and the dictation of culture requests and sample collection by physician choice results in unsuitable and unpredictable numbers and case mix of specimens for analysis. At present, the hospital is conducting an MRSA carrier study of healthcare workers and typing for hospital- and community-acquired origins (Omuse 2009). Studies on community prevalence of ESBL-producing enteric bacilli, surgical site infections and community acquired pneumonia have just been concluded. Researchers are also assessing virulence factors in MRSA strains in the hospital environment.

In 2004, the Department of Veterinary Services began monitoring antibiotic residue in agricultural products as a means for ensuring safe food and verifying the effectiveness of preharvest control practices (Gichia 2009). Plans were designed according to their potential for affecting international trade. Central Investigatory Labs at the University of Nairobi, Bora Biotech Ltd. and the Kari Trypanosomiasis Research Centre perform residue analysis while the sampling of milk, honey, and red and white meats is performed by Department of Veterinary Services staff with assistance from the Department of Public Health and Toxicology at the University of Nairobi. Officials from the Department of Veterinary Services report that surveillance will eventually include the presence of resistant bacteria in agricultural products, and the department intends to examine strategies to prevent the transmission of bacteria, especially salmonella and *E. coli,* to the human population.

Part IV. Antibiotic Use and Supply Chain

Antibiotic resistance is driven by numerous factors, many of which are associated with inappropriate and excessive antibiotic use. The regulatory environment, economic incentives, and the knowledge and expectations of drug providers and patients influence medicine consumption. Furthermore, antibiotic misuse is exacerbated by the impoverished living conditions characterizing the majority of patients suffering from bacterial infections, including poor healthcare delivery and unreliable access to medicines. Antibiotics are also misused in the livestock industry. After reviewing consumption levels and the patterns and drivers of use in both human healthcare and livestock production, this section examines the supply chain for antibiotics.

Antibiotic Use in Human Health

This section reviews information available on factors leading to antibiotic use in human health in Kenya. It begins with a presentation of overall national consumption, followed by patterns of use by particular distributors for specific conditions. It concludes with a presentation of the incentives and drivers of antibiotic prescribing and consumption in patients, hospitals and pharmacies.

National Consumption

National estimates on antibiotic use are derived from importation licenses and manufacturers' records held at the Poisons and Pharmacy Board (PPB) and the Ministry of Trade (Mitema and Kikuvi 2004). Using these data and incorporating prescription patterns, Mitema and Kikuvi (2004) described the consumption of drugs in kilograms converted into defined daily doses per 1,000 inhabitants per day for 1997 to 2001. This study is the only existing official report on national antibiotic use.

Trends during the study period displayed a decrease in total annual antibiotic consumption except in 2000, when there was a 4 percent increase during a severe famine early in the year. Average annual national antibiotic use was 20 DDD per 1,000 people a day. According to the authors, penicillins are the most prescribed antibiotic class, possibly because of their relative affordability and broad-spectrum activity on both gram-positive and gram-negative bacteria (Mitema 2010). Penicillins accounted for an annual average of 6 DDD per 1,000 people a day and 31 percent of the overall mean, of which 68 percent were extended-spectrum forms (Mitema and Kikuvi 2004).

Trends in consumption of tetracyclines, cotrimoxazole, chloramphenicol and the fluoroquinolones were varied. Tetracycline use fluctuated with no specific trend except in 1998, when the authors registered a 37 percent decrease. At the time of the study, tetracyclines were the second most frequently consumed antibiotic class, at an annual average of 5 DDD/1,000, of which doxycycline was the most popular. Cotrimoxazole consumption increased in from 1997 to 1999, possibly in response to preventing and treating pneumonia in the growing HIV-positive population, and represented 4 DDD/1,000 of annual average antibiotic use. More than 75 percent of chloramphenicol consumption (1 DDD/1,000 on average) for the entire study period was recorded in 1997, during an increase in typhoid fever episodes following the El Niño rains. The expiry of the patent period for innovator fluoroquinolones in 1998 and the consequent increase in generics may account for the decrease in chloramphenicol use for typhoid treatment after 1997. Indeed, the authors found that the use of fluoroquinolones increased 18-fold during 1997 to 1998 following the release of generics on the market, and the drug represented 0.8 DDD/1,000 people a day of the yearly average.

Aminoglycoside consumption also rose steadily after 1999, of which gentamicin accounted for 78 percent of the mean annual amount. While macrolide use remained stable after 1999, the popularity of rifampicin grew in response to new tuberculosis combination regimens and increased treatment of tuberculosis as a secondary infection among HIV patients. During the study, average annual use of first-generation cephalosporins (0.2 DDD/1,000)

was high compared with the second-generation (0.03 DDD/1,000) and third-generation (0.003 DDD/1,000) drugs. It is worth noting that first-generation cephalosporin use spiked from 0.3 DDD/1,000 in 1999 to 0.7 DDD/1,000 in 2000 but dropped to 0.04 DDD/1,000 in 2001. The authors of the study offered no explanation for these sharp variations.

The published numbers may be low in part because of the declining socioeconomic status of a substantial proportion of the population during the study period, as well as the deterioration of the healthcare system and drug supply chain prior to the reforms of 2002. For example, no essential drug kits were distributed in 2000, leading to a severe shortage of antibiotics in public health facilities in 2001 (Ministry of Health 2003).

Patterns of Use

Resistance develops in part as a result of poor prescribing and dispensing practices, as well as inappropriate use by patients. Weak pharmaceutical management and inadequate regulation lead to the proliferation of unlicensed outlets selling prescription-only antibiotics and the indiscriminate use of antibiotics in hospitals and official healthcare facilities. Additionally, the lack of precise diagnostics and quality lab facilities spurs empiric prescribing of antibiotics to treat viral infections when the etiology of a disease cannot be determined and when different conditions manifest with similar symptoms, such as malaria and pneumonia.

An estimated half of all medicines in Africa are irrationally used, including up to two-thirds of antibiotics (Ecumenical Pharmaceutical Network 2009). In Kenya, antibiotics are available from a range of providers with varying degrees of medical training—from family members and friends to physicians, healthcare workers, pharmacists and pharmacy clerks. Patterns of antibiotic dispensing for the same condition can differ depending on the source, and the source of treatment can differ depending on the symptoms and illnesses for which patients are seeking care. For example, according to a recent report, whether patients went to a healthcare facility for antibiotic treatment in the case of respiratory disease was based on the perceived severity of the condition and experience with prior treatment. In cases where patients felt confident in their knowledge about the efficacy of a particular antibiotic prescribed to them on previous occasions by a healthcare worker, they tended to visit a retail chemist to self-medicate or stock up on drugs for repeat conditions in the future (Blum 2008). If symptoms worsened, the patient would seek help in a health centre or area hospital.

Patterns by provider. Unfortunately, the majority of studies on prescribing and dispensing patterns do not compare trends in antibiotic source by disease or investigate patient choice of provider by symptom. The information that current research does provide is primarily limited to the number of antibiotics dispensed by a particular site (hospital or pharmacy) for one specific condition, such as diarrhoea or fever. The picture emerging from these reports is that both retail pharmacies and public health facilities prescribe and dispense medicines that are not indicated for particular infections, and they provide insufficient regimens of correct drug choices.

Retail pharmacies, frequently operating without a licence, appear to be more accessible to patients: they are located within the community, do not charge consultant fees, have shorter waiting times and are willing to negotiate treatment protocols to meet the financial needs of clients (Ross-Degnan, Soumerai et al. 1996; Okeke and Ojo 2010). Around a quarter of the entire Kenyan population and more than a third of Nairobi residents use retail pharmacies as the first site for outpatient care (Kakai and Wamola 2002; Kwena, Sharma et al. 2008; Thoithi and Okalebo 2009). In the rural, western region of Kenya, up to 54 percent of ill persons visiting the Lwak Hospital had previously sought care from informal drug sellers and up to 24 percent with an ARI symptom had already purchased an antibiotic without a prescription (Bigogo, Audi et al. 2010). According to new research by Synovate, more than 70 percent of pharmacies in Kenya dispense medicines without a prescription as required by law. In the study, antibiotics were the most frequently abused (Karambu 2011).

Drug retailers also appear to be an important source of information about illness in general (Ross-Degnan, Soumerai et al. 1996; Ram 2008). In an investigation of ORT use in treating diarrhoea,

caregivers of young children emphasised their reliance on both chemists and healthcare workers to guide them in diagnosing the problem and preparing treatments at home (Ram 2008). Pharmacy employees were relied upon for advice on childhood diarrhoea and case management by a third of caregivers interviewed. Inconsistent recommendation of ORT led to confusion about whether it is appropriate for all cases of diarrhoea and resulted in a reduction of home-based rehydration techniques.

Dispensaries, clinics, and hospitals remain an important source of antibiotics for a range of illnesses; however, they do not necessarily dispense antibiotics more rationally than retail pharmacies. In 2003, only four in 10 public healthcare facilities prescribed according to the national treatment guidelines at least 90 percent of the time (Ministry of Health 2003). A general assessment of inpatient paediatric care in all district hospitals (first-level referral care) in 2004 found that case management was often not in line with national or international guidelines. Prescribed doses per kilogram bodyweight of gentamicin, penicillin and chloramphenicol, the most frequently prescribed parenteral antibiotics, showed considerable variation, with evidence of worrying degrees of overdosing for chloramphenicol and underdosing of gentamicin in respiratory tract infections (English, Esamai et al. 2004). Likewise, in 2000, prolonged (73 percent) and sometimes unjustified (42 percent) use of antibiotics in the Kenyatta National Hospital neonatal unit were contributory factors of increased antibiotic resistance in hospital-acquired infections (Musoke and Revathi 2000). Approximately one-third of all monthly admissions to the unit were given antibiotics, and nearly half of those patients were not investigated with a laboratory evaluation of sepsis or confirmation of drug susceptibility. Of those investigated, only 22 percent had lab results noted in their case files. Even in the country's leading referral hospital, all sick newborns were presumed infected until proven otherwise, leading to indiscriminate, prolonged and inappropriate use of antibiotics in children. Another study found that of the more than 70 percent of patients on antibiotics during their stay in the Kenyatta National Hospital ICU, only 26 percent were on an appropriate treatment (Ngumi 2006). Drug sensitivity discs were not always available in the hospital lab, and thus patients often received antibiotics assumed to be effective.

Patterns by condition. A study conducted in 2004 investigated antibiotic recommendations made for common infections by primary healthcare providers, including physicians, nurses, pharmacists and pharmacy clerks in rural and urban centres (du Prey, Ford et al. 2004). Providers were asked for treatment recommendations in seven case scenarios depicting bronchitis, strep throat, common cold, cystitis, shigella dysentery, malaria and acute otitis media. Recommendations were then judged for concordance with Kenya's national clinical guidelines for indication of antibiotic treatment and specific drug choice. According to the author, primary healthcare workers recommended antibiotic treatment 67 percent of the time for acute bronchitis and 48 percent of the time for common colds, neither of which are indicated for antibiotic use by the national guidelines. When antibiotics were recommended for conditions requiring such treatment, drug choice was evaluated. In 28 percent of cases of acute otitis media and 58 percent of cases of strep throat, drug choices were inappropriate. Recommended antibiotics for cystitis and dysentery were almost always incorrect. Though national guidelines specify treatment with cotrimoxazole and amoxicillin or ampicillin, patients were treated with combinations that included metronidazole in 84 percent of cases for both conditions.

Inappropriate prescribing is perhaps most common for ARIs and enteric diseases for which demand for treatment is high, clinical care is widespread, and in which there are both viral and bacterial causes. In district hospitals, nearly 71 percent of the antibiotics prescribed for pneumonia were for very severe cases even though only 16 percent of recorded admissions fit into this category (English, Esamai et al. 2004). In 2003, more than 30 percent of public health facilities were using first-line antibiotics in fewer than 25 percent of pneumonia patients requiring first-line treatment (Ministry of Health 2003). Clinical treatment for pneumonia is further complicated by high rates of malaria infection and their similar symptomatic manifestations. In western Kenya, more than three-fourths of children visiting rural health facilities were diagnosed

with malaria and/or respiratory infections (Phillips-Howard, Wannemuehler et al. 2003). Penicillin constituted 61 percent of all prescriptions for sick children, either alone or with chloroquine. Half of the children given a sole diagnosis of measles or pneumonia were prescribed chloroquine (malaria medication) and 22 percent of children with a sole diagnosis of malaria were given penicillin.

Diarrhoea rarely requires antibiotic treatment, yet antibiotics remain a popular choice of empiric therapy (Kariuki, Revathi et al. 2006; Kariuki 2010). There was a 32 percent decline in ORT use in Kenya from the late 1990s to 2003, partially because healthcare workers were perpetuating inappropriate antibiotic use (Ram 2008). Although national guidelines and WHO standards stipulate that young children should be treated with ORS for most types of diarrhoea, more than half of cases were given one or more antibiotics (Ministry of Health 2003). Fewer than three of 10 public facilities use ORS for the management of at least 90 percent of diarrhoea cases. In contrast, one in four facilities uses antibiotics for at least 90 percent of cases in children. In health clinics, antibiotics were prescribed in 67 percent of visits for diarrhoea in 2006 (Brooks, Ochieng et al. 2006). Levels of antibiotic use in clinics were higher in western Kenya, at 76 percent, for all cases of gastroenteritis, diarrhoea and dysentery (Shapiro, Kumar et al. 2001). In the same region, one study found that of the antibiotics prescribed for diarrhoea, only 27 percent were appropriate for the condition (Ram 2008). Comparatively, only 40 percent of patients in the area received any form of ORT. In 56 percent of that region's district hospitals, cotrimoxazole alone was prescribed for nonbloody diarrhoea (Phillips-Howard, Wannemuehler et al. 2003) (English, Esamai et al. 2004).

Limited availability of ORS in pharmacies and shops may also drive antibiotic treatment for diarrhoea in areas where caregivers have difficulty accessing formal healthcare facilities that provide ORS for free (Ram 2008). In a 2008 survey, ORS packets were available in only 68 percent of pharmacies and 10 percent of shops surveyed; antibiotics, contrast, were available in 98 percent of pharmacies and 43 percent of shops. Diminished efficacy of cheap and available antibiotics resulting from all causes of injudicious use poses a serious problem when antibiotics are necessary, especially for cases of dysentery, cholera, and invasive NTS disease.

Drivers of Use

Although the total amount of antibiotic consumption is an important issue, perhaps of greater concern in Kenya, where the need for antibiotics exceeds available stocks, is the way these drugs are used (Okeke, Aboderin et al. 2007). Inappropriate antibiotic use is a multidimensional problem, and an understanding of the incentives behind prescribing, dispensing and consumption of drugs is necessary for designing effective policies to curb resistance. As demonstrated in the section above, self-medication is widely practiced and appears to be a typical behaviour for treating common diseases. Factors of irrational antibiotic use related to patients' self-medication include motivations to save money by purchasing insufficient dosages and avoiding the consultation fees of formal healthcare facilities. Other factors involve geographic inaccessibility of formal healthcare facilities (covered in Section II), noncompliance with prescribed regimens by prematurely ending treatment when symptoms subside, sharing of medication with family members and friends, and hoarding drugs for future use. Patterns of drug purchase according to who has advised the person are largely unknown.

Provider-related factors for inappropriate antibiotic use range from profit incentives and financial gains associated with sales of unneeded or newer and more expensive second-line antibiotics to a lack of diagnostics, improper training and legitimate fears of bad treatment outcomes in cases of critical illness. Some pharmacies hold commercial contracts with physicians or are physician-owned, and thus the clinicians derive direct financial benefits from drug prescriptions and sales. The exact number of these contracts or ownership patterns in Kenya and their effect on antibiotic sales is not documented.

Institutional factors of irrational drug use are also important. As previously discussed, healthcare facilities are frequently overcrowded and lack thorough infection control practices. Where antibiotics are cheaper than implementing infection control measures, they may replace standard hygiene

and sanitation as a prophylactic against the spread of disease. Other facility-related factors include limited publicly supplied antibiotics, legislation on malpractice and prescribing, and the unavailability of national treatment guidelines in lower-level health facilities.

The lack of literature on such determinants for Kenya creates a significant gap in public understanding of what influences antibiotic consumption in the general population and prescribing among healthcare workers. In particular, the perceptions and motivations of providers and consumers and their responsiveness to behaviour change interventions have received little attention.

Economic incentives. How much profit goes to a healthcare facility from drug sales, and what portion of these sales belongs to antibiotics? Are expensive, second-line antibiotics prescribed more for insured patients versus uninsured patients? Do patients themselves demand newer antibiotics when their prescriptions are covered by insurance? Are dispensing clinicians who directly benefit from drug sales more likely to prescribe antibiotics than nondispensing clinicians? Many questions remain about the economic motivations behind antibiotic use and possible responses to changed incentives (Mwabu 2009). Although economic factors for prescribing, dispensing and purchasing of particular drugs are often discussed in theory, few papers carefully investigate these drivers of antibiotic use (Haak and Radyowijati 2010). Information is not available for many issues in Kenya: the demand and supply response to prices of antibiotics versus alternative treatments, payment mechanisms available to consumers by dispensing agents (insurance, credit and exemption schemes), healthcare workers' incomes and facility financing mechanisms, and norms governing intrahousehold distribution of resources and control of income. Studies on consumer perceptions on the relationship between quality of care and treatment expense are also lacking, in particular whether low-cost solutions are perceived as inferior care in situations requiring consultation fees or hospital attention (Omuse 2009; Haak and Radyowijati 2010). Clinicians' response to these perceptions has likewise not been investigated.

Patients' incentives for antibiotic use. Consumer demand for antibiotics is shaped by beliefs about disease, medication and drug strength, and one's own and others' past experiences with different treatments for illness. People frequently believe that antibiotics are stronger and more powerful agents than alternatives and may expect health providers to recommend specific antibiotics for particular symptoms, often resulting in unnecessary prescriptions (Franco-Paredes and Santos-Preciado 2010). The reputation of antibiotics can also drive up prices compared with other drugs, leading to the procurement of partial therapies from dispensers willing to provide suboptimal amounts of drugs in accordance with customers' ability to pay (Haak and Radyowijati 2010).

Popularity. Antibiotics are popular for several reasons, including the relative ease with which they can be purchased and their ability to quickly stop symptoms. In one study on STI treatment in Kibera, approximately 45 percent of pharmacy customers specifically requested antibiotics (Kwena, Sharma et al. 2008). Mothers of young children in Kibera often expect health facilities and pharmacies to provide antibiotics to reduce the volume of diarrhoea or stop it completely (Ram 2008). In fact, when surveyed, mothers preferred antibiotics despite their relative high cost compared with ORS packets—Ksh162 (US$2.31) for oral medications versus Ksh10 (US$0.14) for a single packet of ORS or Ksh30 (US$0.42) for a full regimen of ORS. When asked why they did not demand ORS treatment, caregivers reported that rehydration couldn't end diarrhoea immediately, an understandable concern in an area with poor sanitation and limited facilities for washing a child. Demand for various forms of treatment was also associated with consumer risk perception. If caregivers had a heightened sense of risk because they had known a child who died from diarrhoea, they were more likely to request ORS treatment over antibiotics.

Ease of purchase. Populations most affected by infectious disease in Kenya often cannot afford to consult properly qualified clinicians for diagnosis and treatment of illness. Even when fees are waived, as in the case of treating young children and HIV-positive individuals, lower-income patients face high patient-to-clinician ratios in their commu-

nities and may have to forfeit income from work while waiting for care (Okeke 2010). Usually, it is cheaper and faster to self-medicate with unregulated purchases of antibiotics. A survey of mothers in the slum areas of Nairobi indicated that although caregivers correctly perceived pneumonia and diarrhoea as serious health problems with fatal outcomes, the lack of financial resources prevented them from seeking professional healthcare services (African Population and Health Research Center 2002). Rather, their first point of care was chemists and shops in the community that sold them drugs over-the-counter without demanding a consultation fee or requiring long waits and time away from work. Costs related to accessing treatment were also cited as barriers to using ORS therapies in rural areas, where distances to healthcare facilities were so great that the caregiver would have to spend an order of magnitude more for transportation to see a clinician for free ORS packets than it would cost to purchase treatment at a pharmacy near home (Ram 2008). Frustrating stock-outs of ORS at public facilities were also reported by caregivers, discouraging them from future consultation after facing the challenge and expense of arriving at a health centre only to discover that ORS treatment was not available. Cost, however, was not cited as a barrier in antibiotic use, even though the direct price of antibiotics was more expensive than ORS for the customer. As mentioned in Section II, 50 percent of the population is within an hour's walking distance to a public health facility, but more than 80 percent is within an hour of a retail chemist (Ministry of Health 2003). Cost-sharing policies in public facilities also pose a financial burden to patients. Thus, even though public facilities may offer more affordable essential medicines, private pharmacies offer a more practical option in terms of time and overall cost of care. In many cases, self-medication through drug shops is the only means of accessing treatment for infections, appropriately dispensed or not.

Drug prices. Drug prices are related to problems in treatment compliance, the failure of which has possible repercussions for the development of antibiotic resistance. When a patient misses doses, surviving pathogens are exposed to subinhibitory drug concentrations, which likely increase the possibility that the bacteria will acquire resistance (Amabile-Cuevas 2010). In Kibera, three-quarters of pharmacies report that their customers either cannot afford full regimens or have difficulty raising money for medicines recommended to them for treatment (Kwena, Sharma et al. 2008). As a result, 94 percent of pharmacy staff in an STI treatment survey agreed to provide partial treatment to patients who did not have money for a full antibiotic regimen. Additional compliance issues associated with drug prices include storing antibiotics for future use and sharing prescriptions with family and friends struggling to pay for their own medications.

Providers' incentives for antibiotic use. Not much is known about the influence of drug prescribers and dispensers, including clinicians, nurses, pharmacists, pharmacy assistants, and small shop owners and counter staff, on antibiotic use in Kenya. A few studies have examined the extent of providers' knowledge in different contexts and the prescription or recommendation of antibiotics in practice. Other influences appear to drive supply, however, since even practitioners who understand the correct treatment may inappropriately prescribe antibiotics. Inadequate or underutilised diagnostics can cause uncertainty about the best treatment and fear about the outcome if the healthcare provider withholds antibiotics, leading not only to an overprovision of antibiotics in general, but also to a heavy reliance on broad-spectrum drugs.

Perhaps even less is known about the financial incentives in the private sector versus the public sector and by type of supplier. For example, hospital clinicians in Kenya are reportedly held to different prescribing standards, depending on their status as either consultants or hospital staff and the consequent amount of revenue they bring into the hospital. The ways in which hospital departments are incentivised to bring in money and the scale of their profits derived from drug sales are also unknown. A desire to satisfy patients' demands and adjust sales according to their ability to pay appears to have some influence on dispensing and dosage levels, but how much has yet to be fully evaluated. Studies of prescribers' and dispensers' behaviour in the country have not investigated how they view their status as health professionals in promoting community well-being, what diseases they feel confident diagnosing and treating

without laboratory support, and how they perceive the usefulness of laboratory diagnostics and antibiotic sensitivity tests to their practice.

Knowledge. In many developing countries, healthcare providers and drug dispensers fail to recognise bacterial infections and as a result provide inappropriate treatment for a range of illnesses (Kakai and Wamola 2002). Pharmacy clerks and attendants, typically handling the daily activity of a pharmacy, tend to have minimal education levels compared with clinicians and pharmacists, yet they are often regarded as equally knowledgeable by patients. Even high education levels do not necessarily mean improved quality of care. In 2008, an evaluation of the characteristics of retail pharmacies in Kibera found that although 90 percent of respondents had at least three years of medical training, only 10 percent of pharmacists offered treatment for gonorrhoea as indicated in the national treatment guidelines (Kwena, Sharma et al. 2008). Of the pharmacists who correctly diagnosed gonorrhoea in surrogate patients, only 27 percent offered a regimen that included government-recommended antibiotics.

The level of clinicians' knowledge is variable. As according to studies described earlier, irrational prescribing occurs in health centres and hospitals. For example, although IMCI replaced vertical programmes for controlling diarrhoeal and respiratory infections in 2000, by 2007 only about 15 percent of health workers had received IMCI training (Ram 2008). In a survey of providers' knowledge about treatment for watery diarrhoea, clinicians cited antibiotics as among the most effective treatments more frequently (71 percent) than community health workers (49 percent). Misinformation among health workers regarding the antiviral properties of common antibiotics was also common, with 73 percent of clinicians reporting that antibiotics kill viruses causing diarrhoea.

Deficient knowledge is also reported among community health workers, who are frequently supported by NGOs to provide care for sick children in rural areas and refer severely ill patients to health facilities (Kelly, Osamba et al. 2001). In an assessment of performance with IMCI guidelines in western Kenya, community health workers often made mistakes interpreting symptoms and prescribing correct types and doses of medication. Only 33 percent accurately instructed patients to take cotrimoxazole for pneumonia, and 61 percent prescribed something other than ORS for children with cases of watery diarrhoea. The authors concluded that the primary cause of suboptimal care to be inadequate understanding and knowledge of IMCI guidelines.

In response to this problem, a variety of education interventions have been implemented by civil society organisations in Kenya and East Africa generally, in the hope that correct knowledge will lead to more appropriate antibiotic use in health facilities, pharmacies and small shops. The reality, however, is more complex. Greater years of experience and reported levels of education among pharmacy workers have been associated with more, not less, antibiotic provision for uncomplicated childhood diarrhoea (Ram 2008). An earlier study (1996) also found major discrepancies between knowledge of correct treatment and observed behaviour among a sample of pharmacists in Nairobi, Nakuru, Thika, Ruiru and Kisumu (Ross-Degnan, Soumerai et al. 1996). Although 87 percent of pharmacists understood that fluid loss and replacement was critical during cases of childhood diarrhoea and 66 percent of pharmacists said they would treat a simple case of short-duration watery diarrhoea with ORS, only 33 percent of pharmacies with ORS packets actually sold them for such cases during surrogate patient visits. The reverse was true for antibiotics, with reported use at 33 percent and actual practice at almost 50 percent. When focus groups examined reasons for the divergence, respondents reported that they and their customers wanted something 'stronger' to stop diarrhoea. Pharmacy staff also mentioned that leaflets were available for other drugs in their facility but not for ORS, and that they wanted to be perceived as competent practitioners who contributed to national health programmes. Apparently, treating diarrhoea with antibiotics was considered the more scientific method. A separate study on staff knowledge and the quality of retail pharmacy prescribing for childhood diarrhoea could not find a consistent relationship between the clinical knowledge of pharmacy assistants and quality of prescribing (Goel, Ross-Degnan et al. 1996). Rather, controlling for correct knowledge, the determining factor appeared to be the socio-

economic status of the neighbourhood in which the pharmacy was operating. The odds of prescribing ORS treatment were higher in pharmacies located in high- or middle-income neighbourhoods, whereas location in a low-income neighbourhood was associated with inappropriate forms of treatment. Thus, this study suggests that in Kenya the location of a retail pharmacy, not the knowledge of pharmacy workers, is associated with the propensity to correctly prescribe ORS over antibiotics for childhood diarrhoea. The economic incentives and patterns of customer demand in each location were not investigated by this study.

The discrepancy between knowledge and practice is not limited to pharmacy staff. Among surveyed clinicians, considerable variation exists between actual treatment and hypothetical recommendations for watery diarrhoea (Ram 2008). In theory, only 12 percent of health workers prescribed antibiotics alone, but in practice this number was 20 percent. None of the knowledge parameters used by the researchers in this study was statistically associated with treatment choices made by health workers.

Fear of negative outcomes. Dispensers may fear negative outcomes if they fail to provide antibiotic treatment, resulting in a dissatisfied customer and increased health risks if an infection is not addressed. One study in western Kenya highlights this problem in relation to limited diagnostics and high rates of malaria and pneumonia (Phillips-Howard, Wannemuehler et al. 2003). Because of the overlap in clinical presentation of malaria and respiratory illness, penicillin was given as a safeguard treatment for possible pneumonia in more than a fifth of the children with a sole diagnosis of malaria. The consequences of not treating a potential pneumonia infection were felt by clinicians to be far worse than the unjustified use of antibiotics.

Imprecise diagnostics and weak laboratory capacity. Antibiotic prescriptions are largely empirical and lack laboratory investigation for either etiology of disease or drug susceptibility. In East African countries, lab services have been established as part of national health structures, from the central referral hospitals down through each level of healthcare delivery, sometimes even to the dispensary level (Kakai and Wamola 2002). They suffer, however, from unreliable access to clean water or electrical power, a shortage of equipment and supplies and little supervisory support from administrators. Consequently, the majority function below capacity.

Insufficient surveillance data on local causes of infections and prevailing antibiotic susceptibility patterns complicates empirical diagnosis and treatment. Difficulty in determining the causative agent spurs irrational use of antibiotics, in particular clinically convenient broad-spectrum agents. Narrow-spectrum antibiotics could reduce unnecessary selective pressure but are difficult to use without adequate diagnostic support (Okeke and Ojo 2010). A better understanding of antibiotic susceptibility patterns in the country could inform empiric treatment guidelines to reduce injudicious use of broad-spectrum antibiotics and thus preserve the utility of available medicines (Brooks, Ochieng et al. 2006). This would not necessarily have a large impact on overall clinical outcomes, however. Some studies show that despite high levels of in vitro antibiotic resistance, many patients eventually recover (Andhoga, Macharia et al. 2002). Thus although improved antibiotic susceptibility testing may help limit the use of broad-spectrum antibiotics, it is unclear what effect it would have on patient health.

Although a lack of quality lab services and diagnostics is regarded as a vital driver of irrational antibiotic prescribing, the availability of lab facilities does not necessarily motivate clinicians to use them (Kakai and Wamola 2002; Haak and Radyowijati 2010). Healthcare practitioners and hospital lab personnel assert that clinicians do not appreciate the role lab services have in improving diagnosis and rationalizing drug use. Beyond conversational anecdotes, however, there are no data in Kenya on lab use by clinicians or the effect of lab results on treatment decisions. The long-term benefits of improved diagnosis are unknown, as are the necessary motivations for better use of lab services in routine clinical practice.

Demand by patients and profit motives. Prescribers and dispensers say that clients' demands are an important determinant for provision of antibiotics. Pharmacy workers in particular defer to customers' preferences in treating illness. A re-

ported 45 percent of pharmacy clients arrive without prescriptions and request specific medications (Kwena, Sharma et al. 2008). Dosages are also given according to customers' demands, as evidenced by the frequency with which chemists in Kibera were willing to sell smaller doses of antibiotics for STI management at the request of the patient (94 percent). In a survey on ORS use, the majority of caregivers mentioned that 'oral drugs', including antibiotics, were their preferred treatment for childhood diarrhoea, and drug providers said that patients' demand for antibiotics influenced their prescription decisions (Ram 2008). Health workers and pharmacy staff stated that parents wanted a medication that would go beyond addressing dehydration and stop diarrhoea completely. Some feared customers would take their business elsewhere if those expectations were not met (Haak and Radyowijati 2010).

Compared with other profit motives, however, the true influence of patients on antibiotic provision is not clear. The ORS study found an association between higher drug prices and treatment recommendations, with a median cost of antibiotics at Ksh150 (US$2.13) among those who sold antibiotics for diarrhoea treatment compared with about Ksh75 (US$1) for antibiotics among those did not (Ram 2008). Thus, the more expensive the drug in stock, the more likely the dispenser was to recommend it. Interestingly, health workers reported that they were less likely to recommend antibiotics because of the cost to the patient. Further investigation on profit motives behind antibiotic prescribing revealed more concern about immediate availability of cash from a sale than overall profit. Although the markup for the retailer on average was higher for ORS (nearly 100 percent) than for antibiotics (33 to 300 percent), an ORS packet put only about Ksh10 in the till, compared with Ksh75 to Ksh150 for antibiotics. More research on the economics of antibiotic prescribing is needed to understand the role of drug prices, patients' demand, and profit to the facility in the treatment recommendations of providers.

Antibiotic supply and stock-outs. National treatment guidelines and treatment policies are impossible to implement without an ensured supply of essential drugs, including safe and effective antibiotics. For antibiotics listed as 'vital' on the KEML, very few are currently supplied to hospitals. At Thika District Hospital, for example, KEMSA only supplies 6 of the 13 injectable antibiotics listed by the KEML as 'vital' or 'essential' (benzyl-penicillin, benzathine-penicillin, gentamycin, metronidazole, chloramphenicol, and ceftriaxone). Further, the quantities of these that are supplied are inadequate to meet the demand, resulting in stock-outs. A critical finding in the ORS report was the widespread unavailability of ORS packets at shops, pharmacies, healthcare facilities and with community health workers. Stock-outs of ORS in public facilities were reported by caregivers in Kibera and rural Asembo, leading to antibiotic use as an alternative. This study indicates that a prescriber's ability to provide correct treatment may be limited by the absence of indicated medications. Conversations with health professionals also reveal that public facilities purchase second-line antibiotics pushed by private distributors when government supplies run dry. There are no studies on the consequences of this problem in Kenya.

Institutional drivers of antibiotic use. Inadequate human resources, poor infection control guidelines and practice, health system financing arrangements, and weak regulatory environments constitute institutional drivers of antibiotic use. In Kenya, financing the supply of medicines relies on cost-sharing and revolving drug funds, which have the potential to create perverse incentives for overprescribing of antibiotics and create additional barriers to access for patients. The transmission of highly pathogenic and drug-resistant bacteria within hospital settings and, eventually, to communities increases the need for antibiotic treatment. Failure to implement and follow infection control practices is partly due to reliance on antibiotics as a low-cost prophylactic alternative in high-risk hospital departments like the ICU, surgical ward, and neonatal unit. When patients bear the cost of prophylactic antibiotic use, the hospital is further incentivised not to fund infection control practices. Few regulatory bodies oversee prescription practices by healthcare workers, and hospital administrators rarely enforce guidelines. In Kibera, nearly all retail pharmacies, private health clinics and drug-dispensing small shops report that they operate with formal licenses. Upon investigation

by health researchers, however, few had official licenses from authorised agencies (African Population and Health Research Center 2002). Additionally, nearly 72 percent did not have any working guidelines or prescription protocols informing their practice. In some Nairobi hospitals, staff and consultant doctors within the same facility are held to different prescribing standards, depending on the amount of revenue they generate for the hospital. Finally, the breakdown of drug storage and transportation systems within healthcare facilities affects the quality of antibiotics used by clinicians and infection control nurses. Detailed information on these institutional drivers of antibiotic use has not been documented in the country.

Antibiotic Use in Agricultural Production

Antibiotic use in agriculture and livestock has the potential to affect human health in several ways. Incorrect use of veterinary drugs can lead to the accumulation of antibiotics in animal products sold for human consumption, as well as to the development and spread of antibiotic-resistant bacteria through the food chain (Irungu, Bett et al. 2007). Challenges to rational antibiotic use in agriculture include limited surveillance on the intersection of animal and human health and insufficient veterinary services to ensure detection and response to drug-resistant bacterial infections in livestock (Blum 2008). This section reviews what is known and documented about national trends in antibiotic use in agricultural production and patterns of use by livestock sector, application and farm size. It concludes by reviewing drivers of antibiotic use in livestock and their possible consequences for human health. The extent of antibiotic use in animals and how it contributes to drug resistance in humans is largely unknown in Kenya, however, and few studies investigate the matter.

National Consumption

Using data on the quantities of active substance classes imported for agricultural production from Poisons and Pharmacy Board records, Mitema et al. (2001) published a report on national antibiotic use for food animals for 1995–1999 (Mitema, Kikuvi et al. 2001). This is the only study documenting national antibiotic consumption in livestock. The analysis was developed to encourage the monitoring of veterinary drug use in Kenya and to provide a baseline against which to evaluate trends in antibiotic consumption and bacterial resistance. Mean antibiotic use for the five-year study period was 14,594 kilograms (± 1,457 kg) per year. Although no specific trend was identified in the quantities of antibiotics consumed, the study revealed that tetracyclines, sulfonamides, nitrofurans and aminoglycosides were the most commonly used drugs in livestock production in the country. Tetracycline, popular for its broad-spectrum activity and relative affordability, accounted for 55 percent (7, 975 kg) of average antibiotic use, followed by sulfonamides at 21 percent (3,103.96 kg). Aminoglycosides (7 percent), beta-lactams (6 percent), quinolones (0.6 percent), macrolides (0.2 percent) and tiamulin (0.2 percent) constituted the majority of the rest.

Antibiotic use in poultry alone accounted for nearly 20 percent of mean consumption per year (2,906 ± 127 kg). The rest was shared among cattle, sheep, pigs and goats (10,989 ± 357 kg) or used in both large animals and poultry (699 ± 427 kg). Resistance to tetracycline and sulphonamides has been observed among chicken and swine bacterial isolates, possibly related to the intensive conditions in which these animals are housed and the greater potential for the spread of disease. Because of their low cost and easy availability, these drugs are used for both therapeutic and prophylactic applications (Kariuki, Gilks et al. 1997). Cephalosporins and quinolones, important therapies in human health, were hardly used compared with other classes of antibiotics (Mitema, Kikuvi et al. 2001). During the study period, only one fluoroquinolone—enrofloxacin, which accounted for less than 1 percent of annual mean consumption—was used in animals. Compared with tetracycline and the sulfonamides, however, this drug is expensive and difficult to access.

Patterns of Use

Purpose. Growth promotion does not appear to be an important application of antibiotics in livestock production in Kenya. Rather, antibiotics

in veterinary practice and livestock production are typically used for therapeutic and prophylactic purposes. Therapeutic application accounts for 90 percent of antibiotic purchases (13,178 kg a year on average), followed by prophylactic use at 10 percent (1,411 kg ± 246 kg a year on average). Further investigation is necessary, however, since at first glance these data would indicate that antibiotics are mainly used to treat disease, not prevent it. In contrast, the majority of farmers say they rely on antibiotics to treat illness in their animals 'rather than implement proper hygiene and feeding practices' (Kariuki, Gilks et al. 1997). There is a possibility, therefore, that even though antibiotics are not explicitly used to prevent disease, they are used in replacement of standard disease prevention activities.

Sector. Some information is available for antibiotic use in cattle and poultry, but studies investigating drug use in swine and goats, as well as in aquaculture and horticulture, are absent. Irungu et al. (2007) found extensive improper usage of veterinary drugs in cattle owned by farmers in Kajiado and Narok Districts (Maasailand), which constitute the major sources of red meat supplied to Nairobi and its environs (Irungu, Bett et al. 2007). In regards to antibiotics, incorrect dosing and use of antibiotics for nonindicated diseases were common. Oxytetracycline was underdosed at all concentrations in all classes of cattle except for 20 percent oxytetracycline hydrochloride in adult bulls. Additionally, several farmers treated trypanosomosis using antibiotics. The route of drug administration, an important part of a drug's pharmacokinetic properties, also differed from appropriate use. Up to 37 percent of farmers administered injectable drugs intravenously, contrary to instructions on the label or package insert. In the case of antibiotics like oxytetracycline and dihydrostreptomycin sulphate, which should be administered intramuscularly, intravenous administration was noted. A large proportion (92 percent) of farmers used oxytetracycline hydrochloride to dissolve or mix trypanocidal drugs, the effect of which is unknown and not advised in practice. In all cases where oxytetracycline hydrochloride was used, it was substituted for water as a diluent for trypanocides.

Concern has also been raised regarding the indiscriminate or unnecessary use of antibiotics in dairy cows, with *S. aureus* being the main target in treating mastitis. Although the large-scale dairy producers reportedly adhere to recommended disease management protocols and document histories of antibiotic usage in their livestock, they contribute only 30 percent of the produced milk in the country (Shitandi and Sternesjö 2004). The remaining 70 percent comes from small-scale farms, which operate with fewer financial and human resources and may be less likely to follow recommended regimes when using antibiotics. The discrepancy between antibiotic use on large- and small-scale dairy farms manifests in the higher prevalence of drug residue in the milk produced by small-scale farms. Penicillin is the most common residue in milk, with levels often exceeding the limits (4 mg/kg) by twofold. Dairy farmers have expressed a need for more affordable residue tests and for information on disease prevention management, correct preparation of antibiotics, and public health concerns associated with agricultural antibiotic use.

Poultry farming is a critical aspect of household economies in Kenya, especially as cash-producing assets (Blum 2008). An estimated 80 percent of the country's 30 million domestic chickens are raised in small numbers and allowed free range in and around homes. Most grandparent egg stocks are imported, but several breeder farms in Kenya hatch chicks to produce the parent stock. The majority of free-range poultry is concentrated in the eastern and western provinces. Commercial farming, a well-developed industry in Nairobi, Mombasa, and Nakuru, consists of multiple companies that slaughter and process thousands of chickens on a daily basis. Conditions on these farms are generally good, and the companies typically employ full-time veterinarians to ensure that biosecurity measures are followed. Workers on these farms tend to be well informed and have access to ongoing training in livestock production and management.

Backyard and small-scale farmers reportedly treat sick birds at home with a range of indigenous remedies (aloe vera, pepper, garlic and water, cactus and herbs) or allopathic medicines purchased at a local chemist's without a prescription; tetra-

cycline is the most commonly used antibiotic in rearing chickens. In a recent survey about avian influenza, farmers reported using antibiotics only for treating sick chickens and as a prophylaxis when poultry disease outbreaks occur in their area or during transport. Commercial farmers listed vaccines and sanitation practices as their primary means of preventing disease in flocks, without any mention of antibiotics. Although the rate of resistance to tetracycline in chicken *E. coli* isolates is estimated at 72 percent, there are no published records or studies on the extent of antibiotic use in either small-scale or commercial poultry production (Kariuki 2010).

Fish farming plays an increasingly important role in the national economy and sector growth is estimated at over four percent (Mwangi 2008). At present, antibiotic use in fisheries is not monitored. As the industry expands, however, a better understanding of the motivations for antibiotic use in fish production is needed.

Drivers of Use

Drivers of antibiotic use in agriculture are rarely mentioned in reports on antibiotic resistance for the sector. A study on antibiotic residues in milk found that farmers' priority need (34 percent) was information on implementing and managing disease prevention practices to minimise reliance on antibiotics as a prophylaxis, followed by affordable tests to control residues in milk (23 percent), instruction on the preparation of antibiotics for treatment of disease (20 percent) and education on public health concerns related to antibiotic use in milk production (11 percent) (Shitandi and Sternesjö 2004). This indicates that a lack of knowledge and insufficient training are major drivers of antibiotic use in dairy farming, as are technological gaps in the production process.

Another issue driving unauthorised antibiotic use involves veterinarians. The survey on avian influenza found that backyard chicken farmers were suspicious of veterinarians and find the costs of veterinary inputs prohibitive, hence they prefer treating livestock themselves (Blum 2008). Irungu et al. (2007) report that the government prohibition on community animal health workers and the relative scarcity of veterinarians in rural areas motivate cattle farmers to purchase drugs from retail chemists (Irungu, Bett et al. 2007). Economic reforms in the 1990s led to greater privatisation of professional veterinary services, which were previously publicly provided, placing drug procurement and administration in the hands of untrained farmers. With around 670 public veterinarians in the entire country and the majority of the 1,500 private veterinarians located in urban centres, it is unsurprising that cattle herders in the marginal and rural areas resort to practices that run contrary to government restrictions on the use of veterinary drugs by nonprofessionals (Gichia 2009). Additionally, high rates of illiteracy among cattle herders compromise their ability to correctly use veterinary medicines: they are unable to read drug labels and package inserts containing information on the dosage, drug preparation and route of administration. Further statistical analysis suggests that advancement in formal education has reduced herders' tendency to misuse antibiotics.

The relationship between correct knowledge on containment and treatment of animal disease and actual practice is complicated in the agricultural sector, as it is in human healthcare, and studies in other countries have shown that widespread understanding of appropriate methods does not necessarily translate into behaviour modification (Blum 2008). It is therefore important that researchers and health advocates concerned with drug resistance investigate what motivates antibiotic use and where barriers to change exist, including risk perception, trust in officials and economic and livelihood conditions.

Supply Chain of Antibiotics

This section reviews the supply chain and management systems for antibiotics in Kenya. It discusses national policy documents and their role in drug supply and distribution, the position of antibiotics in therapeutic guidelines and dispensing regulations, and the current status of pharmaceutical management. It concludes by identifying areas of the supply chain where weaknesses or inefficiencies lead to irrational antibiotic use and their effect on the development of drug resistance.

Kenya Essential Drugs List

In 1981, the Kenya Essential Medicines List (KEDL), one of the first comprehensive essential drugs lists in Africa, was developed to guide rational drug use within the country. It served to complement the Essential Drugs Programme, structured on kit distribution for rural health facilities. When the government consolidated its programmes in the field of essential drugs in 1994, it formulated the Kenya National Drug Policy. The goals of this policy include using 'available resources to develop pharmaceutical services to meet the requirements of all Kenyans in the prevention, diagnosis, and treatment of diseases using efficacious, high quality, safe and cost-effective pharmaceutical products' (Ministry of Health 1994). Availability and affordability of drugs and the facilitation of rational drug use through sound prescribing and dispensing are also listed as specific objectives. In an effort to best manage pharmaceutical services in the country, the government and pharmaceutical stakeholders have revised this policy and the corresponding KEML five times since 1994 according to a planned review schedule. The KEML continues to be the basis for public sector procurement, prescribing and dispensing activities. Drugs not on the KEML are procured only if they fit into the categories of treatment for diseases not addressed by the list or are intended for use in institutions with specialised medical personnel (Ministry of Health 1994; Ministry of Medical Services and Ministry of Public Health and Sanitation 2010). Antibiotics on the current KEML and their recommended uses are listed in Table 6.

Two sets of treatment guidelines—the *Handbook for Rural Health Workers* and *Clinical Guidelines for Diagnosis and Treatment of Common Hospital Conditions in Kenya*—form the basis for revisions to the KEML as well as for various training programmes on rational drug use. The former lists the standard treatments for Kenya's health centres and dispensaries; the latter contains guidelines for diagnosis and treatment at provincial, district and subdistrict hospitals. The guidelines give priority focus to the inpatient management of major causes of childhood mortality and are primarily derived from WHO standards and the Integrated Management of Childhood Illnesses (IMCI) manual (Ministry of Medical Services and Ministry of Public Health and Sanitation 2010). The national referral hospitals and private hospitals also follow treatment guidelines based on WHO models (Kariuki, Revathi et al. 2006).

Medicines on the 'Core List' of the KEML represent the priority needs for the healthcare system. This status is designated by the letters A (core) or B (supplementary) under the category 'procurement priority'. All the antibiotics contained the KEML are considered 'core' priorities with the exception of clarithromycin, azithromycin and ampicillin. The Core List status implies these medicines should be routinely available in health facilities (primary care facilities and up, or Level 4 and up, as indicated above) and affordable to the majority of the population (Ministry of Medical Services and Ministry of Public Health and Sanitation 2010). Finally, all antibiotics on the KEML, with the exception of ampicillin, are considered 'vital' in their therapeutic importance. This means they are considered crucial for the provision of basic health services.

Pharmaceutical Management

The Pharmacy and Poisons Board (PPB) oversees pharmacy operations and trade in pharmaceutical products, as provided for by Chapters 244 (Pharmacy and Poisons Act) and 245 (Dangerous Drugs Act) of the Laws of Kenya (Ministry of Health 2004; Export Processing Zones Authority 2005). Established in 1957, PPB has a mandate to regulate pharmaceutical services, ensure the quality, safety and efficacy of human and veterinary medicines and medical devices, and advise the government on all aspects of drug regulation (Ministry of Health 2007). Within PPB, the Department of Pharmacovigilance was created in 2005 to monitor the quality and safety of medicines in Kenya, develop appropriate systems for detecting and reporting adverse drug reactions, and implement postmarket surveillance. The National Quality Control Laboratory, PPB's technical arm, is responsible for assessing the quality of medicines. At the request of PPB or on behalf of the government, it tests imported and locally manufactured drugs and determines whether they comply with national standards. The laboratory is pursuing WHO prequalification;

Table 6. KEML Antibiotics and Standard Treatment Guideline (STG) Indications

Antibiotic category	Antibiotic name	Level of Use	Therapeutic Priority	Procure-ment Priority	STG Indications
B-lactams	Penicillin	2	Vital	A	**1st line**: pneumonia (alone and with gentamicin); sepsis; meningitis; syphilis
	Ampicillin	4	Essential	B	Not indicated for use in the guide-lines
	Amoxicillin	2	Vital	A	**1st line**: typhoid; dysentery (shi-gella); gonorrhea; UTI (uncompli-cated); otitis media (pediatric) **2nd line**: pneumonia (when previ-ously treated with cotrimoxazole)
	Co-amoxiclav	4	Vital	A	**1st line**: gonorrhea (adult) **2nd line**: pneumonia (severe)
	Cefuroxime	4	Vital	A	**2nd line**: gonorrhea (adult) **Other**: Mentioned for UTI
	Ceftriaxone	4	Vital	A	**1st line**: gonorrhea (adult) **2nd line**: pneumonia (severe); dysentery (shigella); sepsis; menin-gitis
	Cefixime	2	Vital	A	Restricted for treatment of uncom-plicated gonorrhea
	Flucloxacillin	2 – cap 4 – inj	Vital	A	**2nd line**: acute rheumatic fever **Other**: Recommended for staphy-lococcus
	Ceftazidime	5	Vital	A	Restricted for specialist 2nd line use only (KEML) **Other**: Mentioned for Level 4 and above facility use in 2nd line treatment of pediatric pneumonia, meningitis and sepsis
Macrolides	Azithromycin	4	Vital	B	**2nd line**: gonorrhea (adult) **Other**: Restricted for mass treat-ment of trachoma (KEML)
	Erythromycin	2	Vital	A	**1st line**: cholera; otitis media (pediatric); pneumonia (if penicillin allergy)
	Clarithromy-cin	4	Vital	B	Not indicated for use in the guide-lines
Other Classes	Cotrimoxa-zole	2	Vital	A	**1st line**: pneumonia (mild); dysen-tery (shigella); typhoid; otitis media; UTI (uncomplicated) **Other**: Used in prophylactic treat-ment of HIV positive individuals or HIV-exposed infants

Table 6. KEML Antibiotics and Standard Treatment Guideline (STG) Indications (continued)

Antibiotic category	Antibiotic name	Level of Use	Therapeutic Priority	Procure-ment Priority	STG Indications
Other Classes	Chloram-phenicol	4 – cap and oral liquid 2 – PFI	Vital	A	**1st line**: pneumonia (severe-pediatric); typhoid; sepsis; meningitis **2nd line**: cholera (pediatric)
	Vancomycin	4	Vital	A	Restricted for use in endocarditis and other serious infections caused by MRSA (KEML)
	Doxycycline	2	Vital	A	**1st line**: cholera
	Nitrofuran-toin	4	Vital	A	**Other**: Recommended for UTI
	Ciprofloxacin	2	Vital	A	**1st line**: dysentery (shigella); typhoid; gonorrhea (adult) **Other**: Recommended for UTI
	Gentamicin	2	Vital	A	**1st line**: pneumonia (severe); sepsis

Sources: Kenya Essential Medicines List *(Ministry of Medical Services and Ministry of Public Health and Sanitation 2010);* Clinical Guidelines for the Management and Referral of Common Conditions in Kenya *(Ministry of Medical Services and Ministry of Public Health and Sanitation 2010); papers reviewed in Section IV.*

when necessary, PPB uses a WHO-qualified lab in South Africa for evaluating drugs.

Distributors. An estimated 9,000 pharmaceutical products have been registered for sale in Kenya, channelled according to outlet categorisation as free sales or over-the-counter, pharmacy dispensable, or pharmacy dispensable or prescription only (Export Processing Zones Authority 2005). The Kenya Medical Supplies Agency (KEMSA), a former division of the Ministry of Health and autonomous since 2003, is responsible for procuring and distributing pharmaceuticals primarily to public health facilities. It is the largest purchaser of drugs (manufactured locally and imported), buying nearly 30 percent of the medicines on the market through an open-tender system in competition with other suppliers and private wholesalers. The Mission for Essential Medicine and Supplies (MEDS) and private sector retailers and wholesalers provide medicines for private facilities, including NGOs, mission sector hospitals and for-profit clinics. Kenyatta National Hospital was established as a state corporation and undertakes independent procurement of medical commodities for its own use (Ministry of Medical Services 2009). Anti-infectives (primarily antibiotics and antimalarials), analgesics, antipyretics and cytotoxic drugs (mainly for cancer treatment) account for the bulk of government and private sector purchases of medicines in Kenya (Export Processing Zones Authority 2005). Recently, a series of activities aimed at strengthening transparency and accountability in the public health sector was proposed by the Ministry of Medical Services and KEMSA to improve service in the commodity supply chain and procurement system (Ministry of Medical Services 2009). The activities are to be implemented under the Millennium Challenge Account Threshold Program, as provided by an American foreign aid body, the Millennium Challenge Corporation.

Manufacturers. Pharmaceutical manufacturing is an important aspect of Kenya's industrial sector, and the country is currently the largest producer of pharmaceutical products in the Common

Market for Eastern and Southern Africa, supplying half of the region's market through 45 manufacturing operations—local companies, large multinational corporations, subsidiaries and joint ventures (Ministry of Health 2004; Export Processing Zones Authority 2005; Thoithi and Okalebo 2009). Products manufactured within Kenya for local and international markets include antibiotics, antiamoebics, analgesics, antidiarrhoeals, antacids, vitamins and tranquillisers. Anti-infectives, of which antibiotics are a part, constitute 40 percent of pharmaceuticals produced in Kenya. The industry primarily compounds and packages medicines, repacks formulated drugs and processes bulk drugs into doses using predominately imported active ingredients, the majority of which are nonsterile, over-the-counter drugs. More than 95 percent of the raw material used in the production process is imported. To increase domestic supply of production materials, the government has supported research into the use of local natural resources and into supplementing allopathic drugs with herbal treatments. The development of the industry has been enhanced by the decision of GlaxoSmithKline PLC to license Cosmos Ltd, a Kenyan company, to produce generic versions of its AIDS drugs zidovudine and larnivudine. Government budgeting and development strategy documents assert that manufacturing of generic pharmaceuticals is a 'major force in the economics of medicine use in Kenya' (Export Processing Zones Authority 2005). Patent protection of pharmaceuticals is based on the African Regional Industrial Property Organisation patent system, created by the Lusaka Agreement in 1976 (Ministry of Health 2004; Export Processing Zones Authority 2005). In 2001, the government passed the Kenyan Industrial Property Bill, which allows Kenya to import and produce more affordable medicines for HIV/AIDs and other priority diseases. It is unclear whether antibiotics fall into this category.

A recent report on medicine prices and supply in Kenya asserts that even though the basic structures necessary for implementing the Kenya National Drug Policy are in place, implementation remains incomplete and progress is slow (Ministry of Health 2004). There is no strict framework for enforcing adherence to the therapeutic and supply management requirements of the policy. Additionally, there are no national guidelines for pharmacy inspections, and enforcement of compliance with the regulations is insufficient. In 2003, only 20 percent of the samples collected for monitoring drug quality were actually tested by the National Quality Control Laboratory, and of the prescribed medicines reviewed in the document, a mere 10 percent were properly labelled. Treatment guidelines were found in only 13 percent of public health facilities, indicating that prescribers lack the therapeutic information necessary to adhere to drug policy guidelines. Although PPB's operations have improved, there is insufficient human capacity to handle illegal and unethical activities occurring in the purchasing and distribution of pharmaceuticals, including the manufacturing and importation of substandard and counterfeit drugs and the operation of pharmacies by unauthorised persons (Thoithi and Okalebo 2009). An estimated two-thirds of pharmacy retail outlets could, by law, be closed for operating without a license. Moreover, there is limited ability within the government to generate data on health system performance. This affects all aspects of pharmaceutical management, including drug selection (requiring epidemiological data on disease profiles), the procurement of appropriate quantities of medicines, tendering and contracting (data on past supplier performance and price comparisons), distribution (data on stock movement and loss due to damage or expiry) and monitoring of drug use (dispensing records) (Miralles 2010).

Affordability of drugs has been given little attention, and a more reliable medicine pricing policy is needed. Although Kenya is a member of the World Trade Organization and has modified its industrial property bill to be compliant with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), the government has not used any of the TRIPS public health protections or flexibilities to promote greater availability of cheaper essential drugs. In particular, the 'Bolar' provision, sometimes referred to as the regulatory exception, has not been fully exploited. The provision allows developing countries to manufacture generic versions of patented drugs without the patent owner's permission and before patent protection has ended (World Trade Organization 2006). The generic producers can then market their versions as soon

Table 7. Medicine Policies and Statistics

Indicator	Figure
National Drug Policy	Enacted in 1994, currently under review
Kenya Essential Medicines List	Last revised in 2010
National Standard Treatment Guidelines	Last revised in 2010
Government per capita spending on medicines (2004 US$)	40.51
Number of registered pharmacists (2008)	2,775
Number of registered pharmacy technicians (2009)	2,324
Number of registered retail pharmacies (2009)	1,700

Source: A Survey of Medicine Prices in Kenya *(Ministry of Health 2004);* FIP Global Pharmacy Workforce Report *(Thoithi and Okalebo 2009)*

as the patent expires, which speeds the introduction of generic medicines to the market. Parallel imports (the importation of a patented drug from one country into another without the approval of the patent owner) and compulsory licensing (the permission of a government to produce a patented product without the consent of the patent owner) are also neglected, but helpful, provisions within the TRIPS agreement. There is no clear policy on cost recovery for drugs in public health facilities or what percentage of the costs of drugs the government can recover through patient fees and other cost-sharing measures (Aronovich and Kinzett 2001). Clarity on this issue is critical because cost recovery, a factor in the total resource envelopes available for the districts, determines what medicines district-level facilities can procure and the final drug prices faced by patients.

Table 7 summarises medicine policies and pharmaceutical sector indicators.

Stakeholders in Pharmaceutical Supply

The provision of health commodities in Kenya involves a complex supply chain with numerous stakeholders. KEMSA, NGO and private distributors, donors and civil society organisations are particularly influential in the management and use of antibiotics.

Ministries of Health and other government agencies. For the management and distribution of health commodities, four primary vertical programmes operate on parallel logistics systems within the Ministries of Health. These include Reproductive Health (family planning and condoms, STI drug kits, HIV tests), Kenya Expanded Program of Immunization, the National Leprosy and TB Program, and the essential drugs programme. Together, these systems cover the six high-priority care packages identified by the NHSSP-I (Aronovich and Kinzett 2001). The Kenya Bureau of Standards inspects imports and disseminates information about the standards of goods sold, including prescription and over-the-counter drugs.

KEMSA. KEMSA is a semi-autonomous institution within the Ministry of Medical Services charged with managing the procurement and logistics of the public sector healthcare supply chain (World Bank 2009). It was transformed into a parastatal organisation to apply private sector management techniques as part of government health reforms through the NHSSP-I (Aronovich and Kinzett 2001). It uses a tendering system that is open to both local and foreign manufacturers and distributors and sells commodities to health facilities according to requested needs ('pull system'). Essential drugs, however, are allocated through a kit approach ('push system'), and the type and amount of drugs are based on the type of facility receiving the kits. For the past seven years KEMSA has implemented a centralised supply chain network and uses outsourced transport for scheduled deliveries to more than 4,000 customers. Although all major cities and towns are connected by a road network and can be reached within one day's drive (about 250 kilometres), the rural areas are harder

to reach, especially during the rainy seasons. Three Nairobi warehouses and eight regional depots are owned by KEMSA, and orders are received and delivered every two months to major provincial hospitals and quarterly to the subdistrict hospitals and health centres. Lead-time variability is estimated at three weeks or more. Transportation and warehousing costs account for the bulk of expenses (41 percent and 40 percent, respectively).

KEMSA receives funding from Ministry of Medical Services, which obtains an annual budget from the Exchequer for drugs and medical supplies based on estimates of the national public health medicinal requirements. Public health facilities receive a total resource envelope for each district according to government allocation, which together with donor contributions and the collection of user fees (cost-sharing) are used by clients to prioritise needs and purchase medicines from KEMSA. According to a 2009 report by the World Bank on the public sector healthcare supply chain in Kenya, KEMSA functions are hampered by a lack of appropriate funding for the procurement of drugs to meet the demand of clients (World Bank 2009). An earlier report in 2001 found that although family planning and tuberculosis drugs were generally maintained at an appropriate level, essential drugs in high demand (e.g., penicillins) were consistently undersupplied, and those in low demand (e.g., IV fluids) were oversupplied (Aronovich and Kinzett 2001). The kit system used for essential drugs had not been updated since the mid-1980s, and what was supplied did not take into account variations in disease and treatment patterns around the country. Field research indicated that district-level facilities were using cost-sharing money to buy certain drugs from private wholesalers as a result of kit system failures. According to the most recent figures available (2009), the public sector supply chain is meeting about 21 percent of clients' demand, suggesting chronic shortages of nearly all major items (World Bank 2009). Shortages of antibiotics include co-amoxiclav, ampicillin drops, ceftriaxone and benzylpenicillin injections, and chloramphenicol and cotrimoxazole tablets. If KEMSA were to ensure a 100 percent fulfilment rate, the estimated warehouse space required would need be two to three times the current amount, and inventory on hand would need to increase by 20 percent.

In a project supported by USAID and the Millennium Challenge Corporation, KEMSA has been undergoing a process of restructuring, capacity improvement and distribution support. The KEMSA board was dissolved in 2008 and the CEO was sent on compulsory leave over concerns of declining performance (KEMSA Task Force 2008). The minister of Medical Services appointed a nine-member task force to analyse the situation, with main recommendations targeting KEMSA's legal framework, governance and warehousing, distribution and financing functions. Although KEMSA was found to provide a more competitive procurement price for drugs than other agencies, its warehouses did not meet the good distribution practices recommended by WHO, thus compromising the quality of medicines stored by the agency. Furthermore, a rising number of parallel programmes are using up to 75 percent of KEMSA warehouse space. The outsourced transport system also failed WHO Good Distribution Practices. Compared with its competitors, KEMSA is high for transport lead-time and costs as percentage of actual turnover.

NGOs and private distributors. NGOs account for nearly 40 percent of the essential drugs distributed in the country (Aronovich and Kinzett 2001). MEDS, a Christian not-for-profit organisation based in Nairobi, was founded in 1986 after a WHO feasibility study identified an opportunity to provide affordable drugs to underserved groups (World Health Organization 2004). Previously, church health facilities had purchased pharmaceutical products from government-run central medical stores. During stock-outs, government health facilities were given priority for the delivery of supplies, and church groups grew frustrated. Originally established as a revolving drug fund supported by church donors abroad, MEDS is now autonomous and does not rely on outside funding for routine operations. It is a joint service of the Kenya Episcopal Conference and the Christian Health Association of Kenya. Its two broad objectives are (1) to provide a reliable supply of essential drugs of good quality at affordable prices and (2) to improve the quality of patient care through training in all aspects of health and general management, with a specific emphasis on the rational use of essential drugs. It serves a client base of nearly 1,000 healthcare providers in various categories, includ-

ing 723 church health facilities, and operates on a strict cash-and-carry basis (Aronovich and Kinzett 2001; World Health Organization 2004).

Donor-funded public health projects and about 150 NGO relief agencies such as AMREF, World Vision, ICRC and MSF also purchase drugs from MEDS (World Health Organization 2004). Government institutions account for about 20 percent of medicine sales. MEDS stocks 580 products chosen from a list that is reviewed by a committee of experts within the government, WHO and elsewhere. More than 90 percent of the products are sourced locally, and 70 percent of the local products come from Kenyan manufacturers. Overseas suppliers provide 5 percent of the drugs purchased by MEDS. Mission hospitals tend to have more reliable drug stocks because of their MEDS affiliation, which maintains warehouses specifically for buffer supplies to avoid stock-outs. Customer feedback and a quality assurance system are used to guarantee that stocks meet international standards. Visits are paid to manufacturing plants of local suppliers, and a pharmaceutical technical committee screens all products at the tendering and delivery stages. Stored products are randomly sampled for chemical analysis on a routine basis to verify their continued efficacy. In 2002, failure rates in stock received by tender were quite low, at 3 percent, compared with 37 percent for the same products available on the market through other distributors.

The success of NGOs in the market is attributed to their low mark-ups for generics (e.g., MEDS permits mark-ups of 10 to 20 percent whereas there is no mark-up limit for drugs provided by the government) and swift, effective service (Aronovich and Kinzett 2001; World Health Organization 2004). AMREF, which serves clients in areas considered too remote by KEMSA, purchases the majority of its drugs from MEDS. Additionally, two pharmaceutical companies in Kenya, Cosmos and Surgipharm, sell essential drugs directly to public and private health facilities and KEMSA.

Donors. Although donors have historically been associated with the health sector in Kenya, their roles have changed from supporting national programmes to a decentralised approach focused on district-level care (Aronovich and Kinzett 2001). The following donor projects assist in the management and supply of essential drugs:

- USAID works with the DELIVER project to forecast and coordinate donor procurement and distribution of STI kits. It also supports Management Sciences for Health in advocating rational drug use policy in Kenya and assessing the financial sustainability of medicines.
- DIFD provided essential drugs in the past and supports the SWAp approach to health system improvement in Kenya.
- DANIDA provided a substantial number of essential drugs and the bulk of vaccinations prior to decentralisation. DANIDA currently supports districts in determining what drugs they require and can purchase within their total resource envelopes. Support is conditional on government-matched funds.
- The Belgian government provides funds for essential drugs through a revolving drug fund established in the Nyamira district through the Belgian Technical Cooperation.
- SIDA provides support to districts in determining how to use their resource envelopes and the quantity of drugs required beyond what is provided through KEMSA's essential drug kits. SIDA also supports districts in establishing revolving drug funds through cost-sharing.
- UNICEF acts as the primary provider of vaccines in Kenya. Additionally, the agency provides some essential drugs to KEMSA. UNICEF has expressed concerns that the use of drug kits has hindered the development of expertise in the country for the procurement of loose drugs. It also views KEMSA as unresponsive

to possible epidemics or outbreaks by neglecting buffer stocks.

- WHO piloted revolving drug funds in three districts; the funds were of similar structure to those produced by SIDA. The WHO office in Kenya also promotes the secure supply of generic, affordable and high-quality essential drugs for the treatment and prevention of common diseases.
- The World Bank provided a US$50 million loan to the government for the procurement of health commodities, including IMCI treatments and essential drugs.

Civil society organisations. The Ecumenical Pharmaceutical Network, a Christian organisation with membership in some 30 countries, works with USAID and Management Sciences for Health to support church health facilities in providing and promoting quality pharmaceutical services (Ecumenical Pharmaceutical Network 2009). In recent years, this mandate has involved promoting access to and advocating the rational use of antibiotics in Kenya. In recognition of the growing problem of antibiotic resistance, the Ecumenical Pharmaceutical Network organised a five-day workshop in Tanzania attended by experts from 11 countries in Africa (Ecumenical Pharmaceutical Network 2008). Participants evaluated studies and evidence on the extent of the problem in the region and concluded that urgent action was required by all affected countries. Additional work includes public forums hosted around the country to promote correct use of antibiotics, stress the importance of infection control and highlight the role of diagnostics in containing resistance. The organisation also distributes fliers, posters and fact sheets to health professionals with basic messages about antibiotic resistance and appropriate prescribing practices.

The PPB issues licenses to pharmacists and ensures that drug store managers are members of the Pharmaceutical Society of Kenya (Export Processing Zones Authority 2005). The Society, in collaboration with the PPB, enforces standards, promotes training for pharmacy personnel, advocates the proper distribution of pharmaceutical products and raises queries when members are believed to be committing malpractice. In April 2008, the society published a series of articles in the Pharmaceutical Journal of Kenya on challenges arising from the inappropriate use of antibiotics (Pharmaceutical Society of Kenya 2008). The articles note that antibiotics are often used unnecessarily, and when antibiotics are appropriate for treatment, the wrong one is frequently prescribed. The society advocates the creation of a national antibiotic use policy that prioritises improved legislation on essential drug supply and prescription standards.

Pharmaceutical Workforce

Kenya has endeavoured to strengthen the pharmaceutical workforce through increased training and regulation as guided by the Kenya Health Policy Framework Paper and the NHSSP-I and II (Thoithi and Okalebo 2009). The Kenya National Drug Policy, currently under review and renamed the Kenya National Pharmaceutical Policy, proposes a human resource development plan to improve the supply and skills of pharmaceutical personnel. At present, there are three schools of pharmacy and 18 colleges offering pharmaceutical diplomas. The number of pharmacists has increased from 1,866 in 2002 to 2,775 in 2008. Technologists have increased nearly 66 percent, from 1,399 in 2002 to 2,324 in 2009. Since 2005, the number of pharmacology graduates from the University of Nairobi has grown from 25 per year to 80 in 2008. Despite these improvements, both public and private health sectors are understaffed in pharmacy and lab departments, which fail to meet government staffing targets. Kenya has about eight pharmacists for every 100,000 people; for the country to meet its health-related MDGs, an estimated 28 percent annual growth in the pharmacy workforce must occur between 2010 and 2015. Furthermore, the workforce is heavily skewed towards urban areas and unevenly distributed between public and private sectors, with only 13 percent (382) of pharmacists and 9 percent (227) of technicians employed in the public sector, even though government facilities constitute 58 percent of health facilities in Kenya. Retention is also problematic, with 20 pharmacists, or 25 percent of new graduates, applying to migrate abroad every year.

Supply Chain Issues: Drug Quality Control and Stock-Outs

Drug quality control. Developing countries tend to struggle with enforcing regulations on medicine distribution and maintaining drug quality, particularly for antibiotics, which are in demand and whose active ingredients degrade in high temperatures and humidity (Okeke and Ojo 2010). Despite more than 50 years of pharmaceutical practice in Kenya, surveillance on drug quality started only in the 1980s (Thoithi and Abuga 2008). Drugs analysed by the National Quality Control Laboratory have a failure rate of about 20 percent (2001–2007), with quality varying by drug type and whether the drug is manufactured locally or imported (Ministry of Health 2007). Therapeutic classes with the highest failure rates are anti-infective agents, including antibiotics (15 to 30 percent failure rate during the past three decades). Counterfeits have also been discovered, including co-amoxiclav (Augmentin) tablets without any clavulanate potassium and ciprofloxacin tablets missing active ingredients (Thoithi and Abuga 2008). Raw materials purported to be amoxicillin and ampicillin, imported for domestic manufacturing, were also found to contain no active ingredients.

Reasons for the circulation of substandard drugs are several and include heat and humidity. Studies in Burkina Faso showed that ampicillin, erythromycin, trimethoprim and chloroquine lost more than 10 percent of their active ingredient during two years of storage (Newton, Fernández et al. 2010). The authors recommended that these drugs not be stored for more than one year in a tropical climate. As previously discussed, a 2009 World Bank study found that KEMSA failed WHO storage and warehousing standards. A 2003 investigation carried out by WHO found that only 30 percent of public health facilities met more than 70 percent of the minimum criteria for adequate drug conservation conditions (Ministry of Health 2003). Further, the shelf life and packaging of most antibiotics are not adapted to preserve drug potency in the tropics or mark their degradation (Okeke, Aboderin et al. 2007). Legitimate antibiotics whose properties have been altered by adverse climate conditions and counterfeits with little or no antibiotic properties may contain less than the stated dose, thus failing to kill the bacteria and allowing the patient to continue transmitting the pathogen to others. The subtherapeutic concentrations of low-quality antibiotics and counterfeits also favour the development of resistant organisms (Amabile-Cuevas 2010; Okeke and Ojo 2010). Surveillance of degraded antibiotics and counterfeits remains poor, and the extent of this problem in Kenya is unknown.

Stock-outs. Shortages of quality medicines contribute to poor access to medicines and irrational use of what is supplies, as well as increase the likelihood that expired or counterfeit drugs will enter the supply chain (Okeke and Ojo 2010). As noted, only 21 percent of demand for essential medicines, including antibiotics, is currently met by KEMSA and only a portion of the medicines listed by the KEML as 'vital' or 'essential' is ever supplied. WHO found regular stock-outs lasting longer than a month in public facilities and recorded statements from district-level health workers saying that unpredictable supplies of essential drugs led to purchases from private sector wholesalers. The same report found that noncompliant patients cited stock-outs or the unavailability of drugs at a public healthcare facility as the second most frequent reason for failing to take the complete dose of medicines recommended to them by a healthcare worker. The full effect of stock-outs on the supply chain, including the substitution of publicly provided first-line treatments with privately procured second-line drugs and the introduction of counterfeit or damaged medicines, is often raised anecdotally but has not been documented.

Antibiotic Prices

As discussed in Section II of this report, access to affordable essential drugs is critical to ensuring the provision of quality healthcare. According to the Ministry of Health's Public Expenditure Review 2008, medicines contributed to 28 percent of nonpersonnel costs of Kenya's 2008 health budget, compared with 50 to 90 percent for most developing countries (Ministry of Medical Services 2009). With relatively low budget allocations for healthcare commodities, the burden of paying for essential drugs shifts to the patient through cost-sharing. In a 2003 WHO survey of the pharmaceuti-

cal sector, the most frequently cited reason for not taking all medicines as recommended by a healthcare provider was cost: either the price of drugs was considered too high or the patient did not have enough money to make the purchase when the drug was prescribed (Ministry of Health 2003). While the government spent only 9 percent of its total health budget on medicines in 2007, households spent an estimated 69 percent of their total out-of-pocket outpatient expenditure on medication. Prices also vary by sector, with higher prices reported at private facilities that are more numerous and better stocked than public health facilities (Ram 2008). The average prices for common first-line and second-line drugs are reported in Table 8.

Prices by sector. The prices of antibiotics can influence prescribing and consumer purchasing behaviour in different ways. Practitioners, for example, may overprescribe to generate revenue, and consumers may purchase lower doses than recommended or hoard prescriptions for future use. Although there are no direct taxes or tariffs on essential medicines, multiple and substantial mark-ups are applied along the distribution chain. A comprehensive review of antibiotics prices by healthcare sector, private and public, has not been conducted, but some information is available:

- In 2004, WHO and Health Action International–Africa surveyed medicine prices in Kenya using a sample of essential drugs that included antibiotics.
- PharmaSupport Services publishes a guide to pharmaceutical product prices based on information provided by distributors and manufacturers, including wholesale and suggested retail prices. The most recent edition was published in 2006.
- In 2009, Millennium Challenge Corporation through the Millennium Challenge Account Threshold Program supported KEMSA and the Ministry of Medical Services to compare prices of KEMSA and other distributors to determine whether KEMSA is 'providing value for money in publicly-funded commodity procurement' (Ministry of Medical Services 2009). This report, however, did not account for final mark-ups applied by the healthcare facility after purchasing drugs from the distributor.

Those reports provide some insight into the antibiotic market, but they do not document the prices paid by patients for the same drug at different drug suppliers or the mark-ups to antibiotics applied by different distributors. Together, however, they paint a general picture of the situation and can inform market-based approaches to rationalizing antibiotic use.

According to WHO, in a Ministry of Health survey, patients' out-of-pocket expenses for medicines vary from the more affordable mission sector (Ksh36) and the public sector facilities (Ksh55) to high-priced private pharmacies (Ksh120) (Ministry of Health 2003). The price for accessing medicines in a health facility increases when consultation fees, estimated at around Ksh46 in the public sector and Ksh12 in private health clinics, are added. The affordability of treatment also varies with age, since consultation fees are waived for children under five years. For example, the number of days' wages needed to purchase amoxicillin for pneumonia in adults (based on the lowest government salary) in public facilities was 1.1, whereas only 0.5 day's wages were needed to treat a child with cotrimoxazole. The average cost of a visit, not including lab fees, was Ksh86. In contrast, the cost is higher in private pharmacies: 1.7 days' wages to purchase pneumonia treatment for an adult and 0.9 for a child. In private pharmacies, however, no consultation fee was charged.

At the distributor level, procurement prices for the public and mission sectors were 61 percent and 74 percent of the international reference prices in 2004, respectively (Ministry of Health 2004). According to a government review conducted in 2009, KEMSA prices for most items are generally more competitive than those quoted by other suppliers on the market. For example, KEMSA prices for ciprofloxacin tablets, at Ksh1, are nearly 429 percent lower than those sold by the private wholesaler, Cosmos Ltd, at Ksh4.50 (Ministry of

Table 8. Average Prices of Antibiotics in Kenya

Category	Name	KEDL	Dose range (low–high)	Wholesale price (KSh)	Retail price (KSh)
B-lactams	Penicillin	Yes	500mg 100s	450	—
	Ampicillin	Yes	1MU 1s	15	—
			5MU 1s	18	—
	Amoxicillin	Yes	125mg/5ml 100 ml	263	351
			500mg 100s	1,985	2,647
	Co-amoxiclav	Yes	156mg/5ml	702	878
			1.2gx10 vials	7,346	9,793
	Cefuroxime	No	250mg 10s	440	586
			500mg 12s	1,008	1,343
	Ceftriaxone	Yes	250mg, vial	345	459
			1gm vial	1,079	1,435
Tetracyclines	Tetracycline	Yes	15g, hcl 3%	17	—
	Doxycycline	Yes	100mg, 10x10s	85	—
			100mg, 1000s	2,400	3,600
Quinolones	Nalidixic Acid	Yes	500mg, 100s	400	—
			500mg, 500s	2,250	3,000
	Ciprofloxacin	Yes	500mg 10s	75	100
			100mlx200mg 5 vials	16,396	21,856
Peptides	Vancomycin	No	500mg 1 vial	670	804
			0.5g	2,192	2,923
Chloramphenicol	Chloramphenicol	Yes	10ml	12	—
			250mg 1000s	2,415	—
Aminoglycosides	Streptomycin	No	Inj, 1g vial	12	16
	Gentamicin	Yes	80mg	6	—
			80mg/2ml, 100 Amps	400	—
Sulfonamides and Trimethoprim	Cotrimoxazole	Yes	240mg/5ml 50ml	42	52
			480mg 100x10blis	1,028	1,285

Source: The Greenbook *(PharmaSupport Services 2006)*

Note: 1 US dollar = 72 Kenya Shillings (KSh) in 2006.

Medical Services 2009). MEDS tender prices were lower for amoxicillin syrup (Ksh23, versus KEMSA price Ksh26) and benzylpenicillin injections (Ksh3.8 versus KEMSA price Ksh3.9), but KEMSA tender prices were cheaper for 67 percent of items reviewed. Compared with the international reference price, KEMSA drugs were cheaper for 88 percent of indicator items (10 items, six of which were antibiotics). This suggests that KEMSA is procuring medicines at prices below those available on the international market.

These low procurement prices, however, are not necessarily passed on to patients. Retail prices of a sample of essential drugs indicate large markups of 287 percent in the public sector and 385 percent in the mission sector (Ministry of Health 2004). Retail prices in the private sector were more than three times the international reference

price for the lowest-priced generic and nearly 17 times the international reference price for the most expensive innovator brands. Comparatively, retail prices in the mission sector displayed a much smaller range, with the lowest-priced generic also at three times the international reference price and the most expensive innovator brand at an average eight and a half times the international reference price. International reference prices for this analysis were taken from the 2003 Management Sciences of Health International Drug Price Indicator Guide, which tends to be low because data were pooled from the price lists of large, nonprofit generic medicine suppliers.

Traditional medicines. Traditional medicine use goes almost completely undocumented in Kenya. Traditional and herbal medicines, which incorporate plants, animals and minerals, are frequently used by Kenyans to diagnose, treat and prevent illnesses (Export Processing Zones Authority 2005). In Africa, up to 80 percent of the population is estimated to use traditional medicine for primary healthcare and seeks formal sector solutions only when traditional routes fail. Information regarding the exact properties of these medications and proportions mixed with antibiotics or other mainline treatments is lacking, as are data on the supply chain and costs of such remedies. The government does offer licenses to healers from China and India to open traditional Asian healthcare practices, but the majority of Kenyan healers operate on the periphery, unlicensed and unregulated. According to some experts in antibiotic research in Kenya, antiinfectives are frequently mixed into herbal tonics and powders at unknown dosages, and people are subject to antibiotic exposure without their knowledge. The extent of this problem has not been investigated, and information that does exist is neither officially recorded nor published.

Part V. Government Policies and Regulatory Environ-

Although several laws and parliamentary acts are in place to manage antibiotics, it is not clear whether government regulation is effective or meaningfully enforced by officials. This section briefly reviews important aspects of the antibiotic regulatory environment in Kenya and its success in meeting particular objectives.

Access to Antibiotics and Prescribing Guidelines

Access

With more than half the population living at or under US$2 a day, cost-sharing and consultation fees make visiting health facilities financially impossible for a large number of Kenyans. Substantial mark-ups applied along the distribution chain contribute to the difficulties Kenyans face in obtaining affordable treatment. Additionally, only 30 percent of the population has regular access to essential medicines due to frequent stock-outs. By most estimates, the national drug policy's goal—to 'meet the requirements for all Kenyans in the prevention and treatment of diseases'—seems not to have been achieved (Ministry of Health 1994; Ministry of Health 2004).

The annual operational plan of the NHSSP-II for 2007–08 aims to facilitate the delivery of the Kenya Essential Package for Health and is the main instrument by which the government 'brings to life the aspirations and targets' of the NHSSP-II (Ministry of Health 2007). Priorities of the plan include improved adherence to clinical guidelines, utilisation of data and surveillance information by healthcare decisionmakers, and enforcement of public health standards. Some critical aspects of antibiotic management fall within these categories, but none of the service delivery indicators or targets includes access to effective antibiotics. Childhood illness indicators focus on measles vaccination, malaria treatment, deworming and growth monitoring. The importance of antibiotics in treating neonatal sepsis, pneumonia and bacterial diarrhoea is never mentioned.

Prescribing guidelines

In response to the frequency of empiric diagnosis and treatment in Kenya, the government issued national guidelines to compliment the KEDL. However well intentioned the documents, national treatment policies appear to percolate slowly down to the periphery and are missing from the majority of rural health facilities (Phillips-Howard, Wannemuehler et al. 2003). The guidelines insufficiently address the needs of clinicians in situations where seriously ill children meet criteria for multiple clinical syndromes or when clinical manifestations of different diseases overlap, as for malaria, pneumonia, bacteraemia and meningitis (Phillips-Howard, Wannemuehler et al. 2003; Berkley, Lowe et al. 2005).

Agricultural Sector and Livestock Production

Several laws regulate the use of drugs in food animals, including the Pharmacy and Poisons Act (Cap 244), Animal Disease Act (Cap 364), Food Drug and Chemical Substances Act (Cap 254), Meat Control Act (CAP 356), Pests Control Products Act (Cap 346) and Fertilizer and Animal Foodstuffs Act (Cap 345). According to representatives in the Department of Veterinary Services, however, actual measures to enforce these policies and monitor antibiotic use in agricultural and livestock production is hampered by inadequate financial and human resources and unequipped laboratories. A national livestock policy, promulgated in 2008, provides for the separation of management of veterinary and human medicines; however, veterinary medicines continue to be regulated by the Ministry of Health through the Poisons and Pharmacy Board (Kenya Veterinary Association 2009). Although PPB recognises its inability to fully regulate veterinary medicines as mandated in Cap 244, the ministry in charge of the livestock industry has no authority or

control over registration and distribution of veterinary medicines. As a result, inadequate monitoring and enforcement of protective legislation, drug adulteration, lack of postmarket testing and unprofessional repackaging of veterinary medicines are major challenges in the sector. A recent study conducted by the Kenya Veterinary Association, a nonprofit organisation of veterinary professionals in the country, found that approximately 33 percent of antibiotics available for use in animals were substandard and/or counterfeit. The same study found that people not considered legally qualified for the position operate 78 percent of veterinary medicine outlets in Kenya. Contributing to problems of inappropriate antibiotic use in livestock production, there is no clear regulatory body to streamline the importation, distribution and use of veterinary vaccines. As ordinary animal diseases proliferate, antibiotics are used in greater amounts for both bacterial and nonbacterial infections.

Recently, legislators drafted the Veterinary Medicines Bill, which provides for the establishment of a veterinary medicines and poisons board similar to PPB, the registration of premises for the manufacture, storage, distribution and sale of veterinary medicines, and full documentation of all medicines available for use in agricultural production. The Kenya Veterinary Association and other stakeholders believe that enactment of this bill will not only facilitate implementation of the national livestock policy but also improve supervision of the use of antibiotics in livestock and enhance quality assurance of drugs available in the market. The Department of Veterinary Services also recognises the importance in addressing the threat of antibiotic resistance, as underlined by a joint FAO-WHO meeting on critically important antimicrobials held in 2007 (Gichia 2009). Department officials believe that modern food production should be designed to ensure that exposure of food animals to veterinary drugs does not pose a risk to human health.

Part VI. Recommendations: Interventions against the Development and Spread of Resistance

Antibiotic resistance has garnered international and local attention in recent years. In Kenya, media interest spiked when World Health Day 2011 was dedicated to the theme of antimicrobial resistance. Public and government concern about the issue increased, with radio forums where the curious could ask questions about resistance directly to a representative of the Pharmacy and Poisons Board, and public pronouncements from the minister for Public Health and Sanitation calling for 'concerted efforts to take responsibility for drug resistance'.

However, choosing which 'concerted efforts' to make is not as straightforward as stating their need. Evidence for the potential impact of different interventions is scarce, and where information exists, it cites policies already instituted in Kenya. This includes the familiar litany of good management protocols for essential medicines and healthcare staff, such as the creation of standard treatment guidelines and essential medicines lists and the establishment of infection control and medicine and therapeutic committees in hospitals, to the adoption of important vaccines for bacterial pneumonia and regulatory prohibitions against over-the-counter sales of antibiotics and the use of critical antibiotics to promote growth (as opposed to therapeutic uses) in livestock.

Some of these initiatives have been implemented successfully in Kenya, but none comprehensively addresses the fundamental drivers of resistance—inappropriate use of antibiotics and the incentives affecting their consumption. In settings where guidelines and policies exist to support antibiotic stewardship, the challenge primarily lies in changing behaviour and developing innovative approaches to institutional failures. Additionally, communication between those on the frontlines of resistance and the policymakers they call upon to act needs improvement. Because science-based evidence on the medical and economic benefits of different strategies is scant—not just in Kenya, but globally—pilot studies and impact assessments will be of immense help to the government, healthcare administrators and others in prioritising solutions and identifying those most likely to produce results.

In March 2011, the Global Antibiotic Resistance Partnership (GARP)–Kenya Working Group, in collaboration with the Center for Disease Dynamics, Economics & Policy (CDDEP), convened a policy development workshop of government and civil society representatives, researchers, and health professionals to identify ways stakeholders across diverse sectors and specialties could respond to the emergence of antibiotic resistance. The outcome, presented in the summary table at the end of this report, outlines specific policy actions, their benefits and feasibility. Ongoing collaboration and discussion will be vital to determining implementation strategies for each recommendation. Facilitating consultations with stakeholders and updating recommendations as necessary will be an important aspect of the next phase of the GARP–Kenya agenda.

Focus Areas

The options discussed in this report respond to the two basic approaches to slowing the spread of resistance—*reducing need* for and better *targeting* of antibiotics. Both approaches should lower overall demand for antibiotics. Within this framework, policy actions target five critical areas of disease management and access to effective treatment:

- surveillance and monitoring;
- training and education;
- vaccination;
- quality control and supply chain improvements; and
- veterinary use of antibiotics.

The specific policy actions suggested within these areas in the tables below involve some measure of overlap. Training in hospital infection control, for example, should include information on the

rates of hospital-acquired infections at the facility and antibiotic resistance profiles obtained from regular surveillance and monitoring, for maximum impact. The categorisations in this report are meant to provide the structure for discussion and research, not detract from links across sectors or across focus areas. Indeed, for policy implementation to be successful, it should harness the synergies between approaches and build upon the connections.

Surveillance and Performance Monitoring

Several policy actions recommended in this report underline the need for antibiotic resistance surveillance and performance monitoring. Although these activities do not themselves produce change, without knowing the levels or trends of antibiotic resistance or how key actors are performing, it is impossible to make rational recommendations or monitor the effectiveness of interventions. The prevalence of resistance, influenced by a host of local factors, varies within the country and between pathogens. Without a clear picture of these patterns, designing meaningful interventions can be futile and ultimately waste scarce resources. Further, the lack of systematic data may also lead to the use of ineffective medicines in places where prescribers are unaware of local resistance patterns. This is particularly worrying in countries like Kenya, where the majority of infectious diseases are empirically diagnosed and patient management often depends on early, appropriate antibiotic administration.

Regular monitoring and surveillance offer several opportunities. Monitoring prescriptions and providing feedback on prescribing rates and resistance levels could reduce antibiotic use through behaviour change, especially in facilities where health workers believe—perhaps erroneously—that resistance rates are low and their costs are minimal. As shown in the EPN study (Ecumenical Pharmaceutical Network 2010), many healthcare workers in Kenya believe that antibiotic resistance is a national problem—just not in their own facility. Who can fault them when actual resistance rates and levels of antibiotic use within a hospital are rarely seen?

Where antibiotics are required, timely and locally relevant information about resistance trends can improve treatment and patient management, as well as prompt administrative support for stronger enforcement of antibiotic use and infection control policies. Nationally, information about antibiotic use and resistance can inform the training of health workers and the development of standard treatment guidelines, antibiotic procurement strategies, and regulatory policies. When the system is hosted on a data-sharing network for multiple audiences, such as policymakers and researchers, it can raise resistance as a public health priority. Ultimately, routine surveillance and monitoring serve to reduce costs and curb the mortality threat of resistant organisms.

Strategies to consider

Surveillance and monitoring can be conducted in a variety of ways, depending on the institutional goals of the system and the outcomes of interest (Aiken 2010). Every system has its strengths and weaknesses. These must be weighed according to the resources available and the priorities of each facility—in the case of national surveillance, the Ministries of Health.

Several models and strategies have been proposed for different types of monitoring and surveillance in developing countries:

International Nosocomial Infection Control Consortium (INICC) (Rosenthal et al. 2008). Infection surveillance is particularly useful for improving administrative support for infection control and prevention (ICP) activities and in changing behaviour of health workers. A possible model to follow in Kenya is the HAI surveillance performed by INICC during its device-associated infection monitoring in developing countries. The targeted performance feedback for hand hygiene and CVC, ventilator and urinary catheter care reduced the incidence of ICU-acquired infections in many participating hospitals.

Latin American Antimicrobial Resistance Monitoring/Surveillance Network. In 1996, the Pan American Health Organization (PAHO) launched a program to identify bacterial susceptibility to antimicrobial drugs. The network of 20 countries comprises more than520 sentinel sites in provincial, hospital and private laboratories. In addition to reporting raw data to national reference laboratories,

the sites also send in samples for identification and susceptibility testing. Surveillance data are used to report trend data for the region, as well as to inform the treatment of individual patients, national policies such as treatment guidelines, and public awareness campaigns about appropriate drug use. Despite limited external financing, the PAHO network has continued for more than14 years and could likely be replicated in other regions.

Collaboration across existing networks. In Kenya, several disease programs have their own surveillance activities and laboratory, notably focused on TB and HIV/AIDS. The Center for Global Development recommends that groups focused on antibiotic resistance collaborate with these existing networks to make best use of scarce resources and identify resistance across diseases of interest (Nugent et al. 2010).

Mobile diagnostic clinics. One suggested (but not evaluated) approach is intermittent use of mobile diagnostic 'clinics' that can perform testing in the community and at health facilities (dispensaries, clinics, hospitals) that lack laboratories or cannot run the required tests (Cheng et al. 2008).

Drug resistance index (DRI). The contours of the antibiotic resistance issue have not been well communicated to policymakers in low- and middle-income countries. Although a policymaker may easily grasp that medicines used to treat malaria are failing, it is far more difficult to understand the complexity of bacterial resistance to antibiotics. To address these communication gaps, a DRI (actually a family of indices) has been created (Enserink 2010). The DRI relies on low-cost models of resistance surveillance that will (1) indicate overall trends in resistance; (2) inform policy decisions, especially in formulating national treatment guidelines; and (3) permit resistance trend comparisons across countries. The system will build on a DRI that has been developed and applied to several (mostly higher-income) countries; the index marries data on antibiotic resistance with data on the mix of antibiotics in use in a given place.

Training and Education

Training and education interventions are another method of improving antibiotic use by targeting specific knowledge gaps and perceptions. In Kenya, chemists and private pharmacies are often a first source of health advice and treatment because they offer dependable supplies, reasonable cost, and convenience compared with the services from the formal health sector. But while they are a popular source of information, the workers who staff many private drug shops have little or no background in clinical care.

Training and education can also target healthcare staff at hospitals and dispensaries. Clinicians and other prescribing health workers rarely receive systematic continuing education on the topic of drug resistance. Further, even though the development of standard treatment guidelines (STGs) and essential medicines lists (EMLs) in Kenya is cited as a model example, up-to-date guideline revisions are poorly communicated and the documents are hard to access within facilities. When coupled with educational interventions, however, guidelines can improve prescribing.

A global survey (Fresle and Wolfheim1997) confirmed the need for public education about medicines; information for consumers can be included in government essential drug programs and NGO and consumer organization projects. Training farmers and agrovets in standard hygiene and sanitation and appropriate use of antibiotics in veterinary medicine could reduce demand for antibiotics in livestock production. Confined animal husbandry can increase the risk of disease exposure and transmission and thus lead to greater antibiotic use than would otherwise be the case. The effect of education programs on livestock antibiotic use, however, is poorly documented, and results from educational interventions in human antibiotic use cannot be easily generalised.

Strategies to consider

Approaches to education and training interventions vary from individual sessions and small-group discussions to formal seminars and workshops, printed materials and mass media campaigns. Specific country models of these methods include:

Drug-resistance curricula in Zambia. The creation of a national task force on drug resistance coincided with the government's effort to reform the medical curriculum in Zambia (Nugent et al. 2010). Members of the task force, from the University of

Zambia and other institutions, included aspects of drug resistance in the new curricula. Although Kenya may not undergo a similar change soon, this initiative highlights the importance of seizing the opportunity as it does arise—a likely scenario in Kenya.

Ghana National Drugs Programme. Established in 1997, this programme made promoting rational drug use its core goal. In addition to passing a national drug policy and developing and distributing standard treatment guidelines, the government required training for clinical pharmacists and medicines and therapeutics committees. Five years after the programme launched, antibiotic use among patients at public health facilities had dropped from around 56 percent to 42.5 percent (2002) (Nugent et al. 2010).

Monitoring-training-planning. Approaches that incorporate monitoring and feedback with training are the most effective educational interventions. In a monitoring-training-planning approach, a hospital or and dispensary establishes a team to identify priority problems and plan a series of meetings involving those contributing to the problem. Targets for improvement are set and problem-solving steps agreed on. Studies from Asia suggest that three to five meetings are required to address a single problem, and that this approach can be effective in addressing inappropriate antibiotic use (Nugent et al. 2010; Norris 2007).

Vaccination

Every year, millions of children in Africa die before reaching their fifth birthday from treatable illnesses such as pneumonia and diarrhoea. The primary causes of most cases of these diseases—pneumococcus, *Haemophilus influenzae* type B (Hib) and rotavirus—are now preventable through vaccination. The health gains from these vaccines are unmatched by any other interventions. As a secondary benefit, vaccination can also decrease the use of antibiotics by reducing the need for them. In some cases, such as acute diarrhoea, vaccines may reduce unnecessary and inappropriate antibiotic use. A major constraint to introducing new vaccines or increasing coverage is financing, which will not be resolved in relation to antibiotic use or resistance.

The approaches to enhanced vaccination are well established, as are the challenges.

Quality Control and Supply Chain Improvements

The problem of antibiotic resistance cannot be addressed through interventions aimed solely at reducing antibiotic use. In countries where the burden of infectious diseases remains high and barriers to treatment are common, ensuring greater access to effective antibiotics is important. For Kenya, interventions in this area target quality control of antibiotics and improving the supply chain of essential medicines.

The prevalence of substandard antibiotics in Kenya is unknown, yet the issue of poor-quality medicines is widely discussed in the media and inside government ministries. One review suggests that older antibiotics, such as penicillin, tetracycline, co-trimoxazole and chloramphenicol, are among the most common counterfeited antibiotics in Africa, and WHO estimates that 30 percent of all medicines sold in Africa are substandard. In Kenya, antibiotics have failure rates of 15 to 30 percent, and co-amoxiclav, ciprofloxacin, amoxicillin and ampicillin have all been associated with counterfeiting (see Part IV). Monitoring the flow of antibiotics across international borders is a difficult task, one often constrained by severely limited resources (Nugent et al. 2010). Poor-quality manufacturing, packaging, transportation and storage conditions, as well as counterfeiting, can result in widespread circulation of substandard antibiotics. Without adequate staffing and funding, the Pharmacy and Poisons Board and other regulatory agencies in Kenya have little capacity to enforce medicine quality standards. As a result, counterfeit and low-quality legitimate antibiotics are common and can lead to the emergence and spread of resistance—by failing to control pathogens, allowing transmission to continue or exerting subinhibitory selective pressure.

Access to effective treatment also encompasses adequate financing and supply of essential antibiotics. The majority of people who lack access to antibiotic treatment are often those who face the highest burden of infectious disease: people struggling with extreme poverty or living in remote areas. Even if patients can afford medicines and reach a facility, a large number of 'vital' antibiotics listed on the Kenya essential drugs list are absent or in short supply in dispensaries and hospitals. The majority

of health facilities in Kenya lack the second-line antibiotics necessary for treating a resistant infection. The failure of KEMSA to deliver on the approved list of essential medicines in a formal healthcare setting contributes to irrational use of those antibiotics that are available at retail pharmacies.

Strategies to consider

Several new and creative models exist for improving medicine quality control, the supply chain of essential antibiotics, and overall access to effective treatment:

mPedigree screening. mPedigree allows consumers to send a code via text messaging to the government, which determines whether the code comes from a legitimate package. The text also sends information on the manufacturer and expiration date. The system is free for customers and is paid for by pharmaceutical companies and governments. The platform, recently adopted in Ghana and Nigeria, is currently being piloted in Kenya and has been endorsed by the minister of Medical Services (Taylor 2010). The campaign has not yet been fully evaluated.

World Bank distribution methods in Zambia. Two distribution methods were tested in Zambia (World Bank 2010) and found successful; both involved a district-level commodity planner to manage orders for public health center supplies at the village level. The commodity planner directly addressed breakdowns in the supply chain that left boxes of critical medicines to 'gather dust for weeks at a district storage facility' while being unavailable at public health centers. Both methods also relied on bulk ordering, improving the ability of village health centers to count their stock and order medicines according to patient demand. One method—the dramatically more successful of the two—simply docked drug shipments at district storage facilities without unpacking and repacking them.

National health insurance review. High out-of-pocket costs tend to increase over-the-counter sales of antibiotics, purchase of suboptimal doses, sharing of medicines with family and friends, hoarding of antibiotics for future use and inappropriate treatment of non bacterial conditions with antibiotics. The recent expansion of NHIF may reduce out-of-pocket spending on medicines at dispensaries, clinics and hospitals, improve access to formal health care and thus lead to lower rates of self-medication. Capitalizing on this change could enhance any effect through an information campaign or other intervention designed around the new policy.

Reducing Veterinary Use of Antibiotics

Increased access to quality vaccines benefits livestock producers by reducing the mortality and costs associated with animal diseases. The demand for these benefits was especially evident during the campaign for government approval of the vaccine protecting cattle against East Coast fever. This initiative sprang from the determination of Kenyan pastoralists intent on protecting their animals and spread to include a range of local and international veterinary organisations. An additional benefit of animal vaccines is their potential to reduce appropriate and inappropriate use of antibiotics—in particular, antibiotics for treating and preventing diseases. No studies were found evaluating the effect of vaccines on antibiotic use in livestock, but certain vaccination initiatives in Australia are said to have achieved an enormous drop in therapeutic antibiotic use in the poultry industry (NAS 1999). The literature review did not produce any published material on the coverage rate for recommended animal vaccines in Kenya, including any recommendations for vaccines that target diseases frequently treated with antibiotics. Without this information, it is difficult to determine whether access to vaccines is a policy area warranting attention or identify other topics that deserve priority. Thus, an assessment on the type of and coverage rate for government-endorsed vaccines is advised.

Since 2010, the Kenyan government has prohibited the use of chloramphenicol and nitrofurans in food-producing animals, including for use in growth promotion. It would be helpful to investigate whether producers follow the ban, how they interpret it, and whether education and training interventions could affect compliance with the ban. It may be that livestock producers confuse prophylactic application of antibiotics and their use in growth promotion: in some conversations with farmers, it was apparent that they did not understand the difference between the two because preventing disease is viewed as a way to encourage

growth, and vice versa. Further, depending on the type of feed that is used, the addition of antibiotics to feeds is said to be prophylactic as well as growth promoting. The literature review did not produce any evidence of interventions that work to address these specific problems. To better understand the effect of current laws in Kenya and how to improve them, an assessment of the ban is advised.

Antibiotic substitutes in livestock production

In addition to strategies to improve hygiene practices and increase vaccination, the use of substitutes for treatment, prevention and growth promotion could reduce antibiotic use in livestock. These range from cattle anabolics to Chinese herbal medicine to probiotic and 'competitive-exclusion products' (to reduce gastrointestinal stress). Some proposed benefits of normal gut flora and probiotics are improved survival of offspring, reduction or prevention of diarrhoea, increased growth rate and enhanced immune response.

The actual promotion strategy is unclear, and this approach has not yet been evaluated for cost or effects on antibiotic use.

Additional Strategies

Three additional strategies would support the four critical areas described above—monitoring and surveillance, training and education, vaccination, and quality control and supply chain improvements—but require further development and detail before being recommended. All may be addressed in the next phase of GARP.

- improved microbiology services and rapid diagnostic testing;
- chemist accreditation; and
- stronger medicine and therapeutic committees in hospitals.

Each is described briefly below.

Improved microbiology services and rapid diagnostic testing

Hospital clinicians most often diagnose infections empirically, which can result in unnecessary antibiotic use and in use of inappropriate antibiotics. Improving diagnostic information may improve antibiotic targeting. Although the effect on antibiotic prescribing has not been evaluated in sub-Saharan Africa, studies in China and Nepal show a decrease in antibiotic prescribing when cultures are performed (Shankar et al. 2003; Hu et al. 2002).

In Kenya, several barriers to laboratory diagnostics exist (Revathi personal communication, 2010). First, patients often find lab cultures cost prohibitive. Second, hospitals lack the facilities and qualified personnel to perform cultures. Third, clinicians may fail to appreciate the information provided by a lab diagnosis and not use the facility even if it is available. Fourth, the time required for a culture result may prove too long in urgent cases needing immediate attention. All of these barriers can be addressed.

Several rapid tests have become popular with clinicians in private sector hospitals in Kenya: Immune-chromatography techniques, with a testing time of 15 to 20 minutes:

- Rota-Adeno virus antigen detection in stool (US$4 to 5 per test)
- *H. pylori* antigen detection in stool (US$7)
- *Salmonella* Typhi antigen in stool (US$8)

Latex agglutination tests, with a testing time of 15 minutes to 1 hour:

- Cryptococcal antigen in cerebrospinal fluid and plasma (US$15)
- Bacterial antigens in cerebrospinal fluid to detect *S. pneumoniae, S. agalactiae, N. meningitides, E. coli* and *H. influenza* type B

Rapid detection of streptococcal antigen in throat swabs is also moderately popular, but is preferably done along with culture and thus more costly. *Chlamydia trachomatis* rapid antigen detection tests are also available for testing female genital swabs.

Urine dipsticks are used in all clinics and hospitals and are potentially the most effective tools for rapid diagnosis of acute urinary tract infections. Because 40 to 60 percent of outpatient antibiotic

prescriptions for adults are said to be for suspected urinary tract infections, urine strips could play an important role in reducing this aspect of antibiotic overuse. The cost is US$0.25 to $0.35 per strip, and results are available in less than 5 minutes.

Chemist accreditation

A few African initiatives suggest that incorporating informal retail pharmacies and drug shops into formal networks may be more effective than relying on regulatory enforcement mechanisms (Alphonse 2008; Center for Pharmaceutical Management 2008; MSH 2008; MSH 2009)

In Tanzania, where an estimated 60 percent of the population uses private pharmacies and drug shops as first-line care, the U.S. Agency for International Development's Rational Pharmaceutical Plus Program explored chemist accreditation schemes. The initiative is called the Accredited Drug Dispensing Outlets programme and has been in effect since 2006. Administered by the Tanzanian Food and Drugs Authority, it created retail medicine outlets called *Duka La Dawa Mu himu* that must adhere to product and service quality standards to achieve and maintain government accreditation. The certification allows consumers to differentiate quality services with particular 'brands' of chemist shops.

In 2000, a similar effort was undertaken in Ghana and Kenya through a franchise model in which community health workers operate shops selling essential drugs and nurses operate health clinics. Both the shops and the clinics are managed by the franchisor, the Health store Foundation, and the outlets are reimbursed on the basis of maintaining standards of service.

An assessment of the programme in Tanzania did not show whether the accreditation scheme reduced over-the-counter purchases in target communities or improved dispensing quality for patients with a prescription. Cost of maintaining the program appears high, though no cost-effectiveness studies have been conducted on the intervention. The cost-effectiveness of the franchise initiative in Kenya and Ghana has not been evaluated.

Strengthening medicine and therapeutic committees

The effectiveness of medicines and therapeutics committees (MTCs) in monitoring and promoting quality use of medicines has been generally accepted in developed countries. There has been little evaluation of their effectiveness (clinical or economic) in developing countries. However, most papers reviewing the topic recommend the establishment of MTCs at each referral and at general hospitals within developing countries.

An MTC has two critical tasks: to develop and revise facility-level standard treatment guidelines, and to maintain the institution's essential drugs list or formulary. MTCs can also establish systems for reviewing patient records, performing prescription audits and providing education to prescribers and hospital pharmacists. Where databases are not in place, clinical and pharmacy records can be manually reviewed for audit and feedback reports.

Operations research is needed in hospitals to determine how MTCs can function most effectively. Publication of the results of establishing MTCs and the success of their various approaches to antibiotic management may help improve performance. Other suggestions include creating performance indicators so that MTC activities can be monitored, with an emphasis on self-assessment. Administrative support and buy-in on MTC activities is critical to performance but difficult to obtain without data on their benefits to the hospital.

Since MTCs involve their members in a heavy workload, they are most effective in health systems with sufficient and well-trained staff, performance incentives and accountability.

Summary Table of Policy Actions

Addressing antibiotic resistance requires action by hospitals, the community, livestock producers, health workers and the government. The table below presents the major action items recommended by the GARP–Kenya Working Group and additional stakeholders. These will be taken up in the next phase of GARP, when 'critical paths' will be developed for those policies with the highest likely impact and feasibility.

Action area	Intervention, policy	Notes	Feasibility
Hospital Infection Control			
Surveillance and monitoring	Conduct HAI surveillance, with public reporting. Document rates of HAIs and, where possible, consequences (mortality, extended hospital stay, attributable cost, resistance).	Useful where HAI rates are mistakenly perceived as low and ICP is presumed good. Studies in other countries show improved infection control practices following outcome surveillance. Could discourage patient transfers and referrals.	Hospitals lack ability to determine HAIs. Referral system makes it difficult to determine origin of infections.
Education and training	Incorporate ICP into all curricula. Base curricula on national ICP guidelines and include activities and projects in hospitals to increase learning. Rely on professional associations to provide schools and trainings. Support IPC curricular development and coordinate across schools and training opportunities through MoH.	Doctors and other clinical staff may not consider themselves part of hospital ICP system. Inadequately trained members of ICCs may lack knowledge or motivation. No studies show long-term improvement in practice from education interventions alone.	Not expensive, but difficult to maintain over time. Members of ICCs and professional associations generally express interest in ongoing education. Requires administrative support to develop curriculum and ensure use in educational settings.
Hospital Antibiotic Use			
Surveillance and monitoring	Conduct resistance and antibiotic use surveillance, with public reporting and STGs based on regional susceptibility data. Document and report resistance rates and, where possible, the consequences (mortality, extended hospital stay, attributable cost). Include antibiotic use rates by department.	Useful where HAI rates are mistakenly perceived as low or without consequence. Potential to address appropriate medicine use, as well as capture emergence and spread of resistance.	Hospitals lack human resource capacity, infrastructure and financial means to perform resistance surveillance. Labs are underutilized.
Education and training	Educate and train all providers on STGs and antibiotic use. For prescribers, focus on new (2010) STGs and antibiotic use and resistance. Conduct audits on prescribing patterns to monitor intervention effect. Include feedback from handouts, group discussions and peer review, or from refresher courses.	Helpful where STGs exist and standards are known but not followed. Studies show that training on STGs plus audits, feedback and peer review reduce antibiotic use. Training alone has little effect; audits and feedback are critical.	At hospital level, not expensive to implement. May be difficult to implement monitoring and feedback at regional or national scale. Hospital administrators must be motivated to adopt practice. Collecting prescribing data is challenging in district-level hospitals.

Community Use			
Vaccination	Improve long-term financing for vaccines against bacterial pneumonia (Hib and PCV-10). Build capacity of local manufacturers to produce vaccines for domestic market at reduced prices through technology transfers and private-public partnership.	Can decrease antibiotic use by reducing the need to treat bacterial disease. Long-term financing concerns for national immunization program could be eased by producing vaccines locally at lower cost.	Strategy is relatively untested. Good strategy and implementation models do not exist.
Education and training	Train staff at private pharmacies and provide certification for training. Use one-on-one sessions to train chemist shop owners in antibiotic use, resistance and STGs and laws on prescribing. Follow with small-group training for counter attendants. If possible, collect feedback or conduct sales audits for private pharmacies and chemists.	Study found that one-on-one meetings with pharmacists, followed by small-group training sessions with attendants, improved use of oral rehydration therapy and antibiotics in short term. Long-term effects and generalizability to other health conditions (e.g., acute respiratory infections) are uncertain. No studies show long-term improvement in practice after workshops.	Not expensive to implement. Organizations capable of providing training are available. Unlicensed chemist shops concerned about being discovered and shut down may be reluctant to participate. Turnover of trained staff would undermine effectiveness.
Education and training	Conduct broad public awareness campaign about antibiotic use, coupled with small-group training for mothers about medicines; involve community advocacy groups. Use popular media (radio, TV, newspapers) and gatherings (village market days, mamas groups, community leader meetings) to disseminate messages about antibiotic use, antibiotic substitutes (e.g., oral rehydration therapy), and dangers of self-medication. Consider use of package inserts in literate communities.	Broad media campaign launched with package inserts was effective in Indonesia with small groups of mothers taught to review inserts.	Not difficult to plan or implement. Can replicate models used for other public health campaigns in region.

Insurance	Review expansion of NHIF by committee within PPB or MOMS pharmaceutical division. Consider how NHIF expansion can help or hinder community access to clinical diagnosis and full courses of appropriate antibiotics.	High out-of-pocket costs drive OTC sales of small doses of antibiotics and sharing and hording of drugs; insurance may offset this.	NHIF expansion must reach those most in need. Unclear whether mandate will cover those who now buy small doses of antibiotics OTC.
Livestock Use			
Surveillance	Establish national surveillance system for antibiotic resistance and use in livestock production.		
Education and training	Train farmers in alternative methods of disease prevention (e.g., herd and flock hygiene). Consider demonstration booths or lecture sessions on market days, village demonstrations on agricultural hygiene and sanitation, and small-group training sessions with agricultural cooperatives at district or village level.	Education interventions have not had sustainable effect on practice in human medicine. Effect on animal husbandry is unknown.	Unclear who should conduct training for farmers. Cost is unknown: inputs are not expensive, but reaching farmers in rural areas may be costly. Farmers may require demonstration of economic benefit.
Supply chain and vaccines	Review current recommendations for vaccines and rates of vaccination for poultry, cattle and hogs. If necessary, update recommendations to include vaccines that prevent diseases commonly treated with antibiotics. Review and improve coverage of vaccines.	Animal vaccination may reduce therapeutic use of antibiotics by reducing incidence of disease.	DVS policy on vaccinations is unclear. Farmers' access to vaccines is unknown, as is cost of vaccination compared with antibiotic prophylaxis and treatment. Field assessments show that demand for vaccines is high and farmers want to learn more.
Government Regulation and National Health System			

Quality control	Enhance anticounterfeit and medicine quality control efforts. Consider education for judiciary, improved reporting channels, public information campaigns, routine surveys of medicine quality, blister packaging, and mPedigree platform.	Options listed have shown some effectiveness in case studies. Legal measures have not proven significant.	Enforcing regulations would be difficult. Such interventions lack funding support from donors and international agencies.
Education	Create national antibiotic guidelines ('guideline of guidelines for antibiotics') listing clinical situations in which antibiotics can be used and describing economic and health costs of resistance. Provide training for health workers on using guidelines.	Can be used as advocacy tool with government and as assessment tool at facility level. Guidelines have shown little effectiveness without training and education.	Feasible and relatively simple to produce but will take time to develop.
Supply chain improvement	Place price or mark-up controls on antibiotics to increase access. Legislate a maximum retail price on essential antibiotics, based on constitutional right to have access to essential medicines. Institute measures to improve prescribing and dispensing of antibiotics in formal and informal health sectors.	Could be effective, but examples and case studies are few. Experiences from other countries should be assessed as models to follow or mistakes to avoid.	Possible EAC implications and backlash from retailers and hospital administrations.

Abbreviations: DVS = Department of Veterinary Services; EAC = East African Community; HAI = Hospital-Acquired Infection; ICC = Infection Control Committee; ICP = Infection Control Practice; MoH = Ministry of Health; MOMS = Ministry of Medical Services; NHIF = National Health Insurance Fund; OTC = over-the-counter; PPB = Poisons and Pharmacy Board; STG = standard treatment guideline

Part VII. Summary and Conclusions

This report has focused on understanding the status of antibiotic use and antibiotic resistance in Kenya, the result of antibiotic use largely within the country, with some influence of global use. Much of the antibiotic use has been therapeutic and some of it life-saving. But as is the case in every country, antibiotics are overused in various circumstances and by particular segments of the population. In hospitals, antibiotics typically substitute for better infection control, and in the community (particularly in somewhat better-off areas), they may be used for every cold and sniffle, just in case they work. The direct costs of overuse have been minimal, and the indirect costs—factoring in the cost of inducing resistance—have not been considered, in Kenya or any other country. That there is a cost is becoming more apparent, however, particularly in hospitals. Second- and third-generation antibiotics are needed to cure staph and strep infections, and the gram-negative bacteria often associated with surgery are ever more difficult to treat effectively.

Drivers of Antibiotic Resistance: Current Indications

Major drivers of antibiotic resistance in Kenya have not been well investigated. Current indications, however, suggest that a combination of behavioural factors and economic incentives motivate prescribing, dispensing and purchasing of antibiotics when they are inappropriate for treating the condition, in amounts inappropriate to the situation or both. On the patient side, demand for fast eradication of symptoms, particularly in diarrhoea cases, leads to requests for antibiotics. Because of the high cost of drugs relative to the incomes of most patients suffering from infectious diseases, people purchase partial doses, share drugs with others or hoard them for future use. Cost and time constraints also encourage patients to self-medicate at retail pharmacies for familiar symptoms or diseases rather than visit a healthcare facility for a diagnosis and prescription. For clinicians and dispensers, the drivers stem from incomplete knowledge of either the correct usage of antibiotics or the exact cause of an infection, leading to misuse of antibiotics in viral conditions or an overuse of the right drug at the wrong dosage. Ill-informed empiric treatment is thus as a major driver of resistance. Even where knowledge exists, however, irrational application of antibiotics persists—the result of strong underlying beliefs about the power of antibiotics, pressure to meet clients' demands, financial rewards from the sale of antibiotics or the simple availability of antibiotics when other indicated treatments, such as ORS packets for diarrhoea, are not present.

Two other institutional factors may be contributing to rising levels of antibiotic resistance in Kenya, though neither has been explored for its effect on the problem. First, the quality of antibiotics on the market is largely unknown, but it is suspected that a significant proportion—up to 30 percent—would fail tests for labelled potency. This is partially the result of weak distribution and warehousing systems, as well as the possible infiltration of counterfeits. Second, hospital infection control practices are generally ineffective, possibly failing to prevent the spread of bacterial disease within facilities, raising the amount of antibiotics used to treat infections and elevating the selection pressure for resistance on bacteria in the environment.

Information Gaps and Research Opportunities

The extent and consequences of antibiotic resistance in Kenya, including the full burden of resistance on human health and the economic costs to society and individual patients, are largely unknown—as they are for every other country, both developed and developing. Research is hampered by institutional factors, leading to three major information gaps. First, without a systematic national surveillance system, data on levels of bacterial disease and drug resistance in common pathogens

are limited and drawn primarily from hospital-based studies. Isolates used for analysis in these reports are usually available only when a clinician orders a test, an infrequent and unpredictable occurrence. When clinicians do order cultures, it is typically late in the course of a disease and limited to higher-level referral care (district hospitals and above). Both situations lend themselves to a greater prevalence of complicated cases and elevated antibiotic exposure in the patient, likely biasing study results for resistance levels in various bacteria. Second, without national standards for reporting data, comparing trends over time and among regions is difficult, and microbiology labs are ill equipped for assessing the effects of resistance. Capital equipment may be lacking or in poor condition, and consumables may be of poor quality or insufficient in quantity. Finally, information on the clinical outcomes of resistance is difficult to obtain and rarely collected. Without a coordinated and routine data collection system, national risk assessments and the advancement of effective policies to address the threat to human health from antibiotic resistance remain elusive.

Thorough studies investigating the drivers of antibiotic misuse in Kenya are almost entirely absent. No documented information exists concerning barriers to behaviour change in irrational drug prescribing, dispensing and purchasing in hospitals and the community, including the risk perceptions of various actors and the influence of economic incentives and livelihood conditions of patients and healthcare providers. Furthermore, although CDC-Kenya is investigating several interventions in hospital infection control practices, interventions aimed at reducing unnecessary antibiotic consumption have been neither fully implemented nor evaluated. For example, it is unclear what quick and reliable surrogate diagnostic tests are available for bacterial disease and whether they are affordable or cost-effective in Kenya. The effect of infection control committees on decreasing antibiotic use and controlling drug-resistant disease in the hospital is unknown, including which characteristics have determined success or failure. Questions also remain about the influence of training curricula on antibiotic use among prescribers and dispensers in the long-term.

Annex. Health Facilities and Human Resources

Facilities. There are approximately 5,129 health facilities in Kenya, including private clinics, nursing homes, hospitals, health centres and dispensaries (Ministry of Health 2005). Rural health facilities (health centres and dispensaries) constitute the majority, at 2,904 of the total (1,962 public, 718 mission or NGO, 224 private), followed by 1,743 private clinics, 227 hospitals and 191 nursing homes. This is an increase from 4,767 facilities in 2004.

The provincial and district levels of healthcare provision vary in geographic size and population, as well as facility distribution (Table A-1).

Facilities are distributed unevenly across the seven provinces and Nairobi (Ministry of Health 2004; Ministry of Health 2005; Wamai 2009). The Central province has about twice the number of facilities per population compared with the Nyanza and Western provinces. The Central province also has the best health indicators, according to the 2003 Demographic and Health Survey, with higher life expectancies, better immunisation coverage and a higher proportion of attended deliveries than other provinces except for Nairobi. It also has the lowest infant mortality rate—nearly three times lower than the Nyanza province.

Human resources. Kenya faces many challenges in the area of human resources, including a lack of qualified professionals due to inadequate training, poor recruitment and low retention rates. In 2004, there were 63,277 registered medical personnel (198 per 100,000 population), including about 5,000 doctors (16 per 100,000 population) and 10,210 registered nurses (32 per 100,000 population) (Ministry of Health 2004). About 60 percent work in the public sector, and of them, about 70 percent are concentrated in hospitals (Ministry of Health 2005; Muga, Kizito et al. 2005).

Table A-1. Health Facilities by Province, 2006

Province	Hospitals	Health centres	Dispensaries	Mission and private facilities	Total hospital beds and cots, 2002	Beds and cots per 100,000 pop.	Total health facilities
Nairobi	23	76	101	239	4,891	190	368
Central	33	59	328	534	8,191	209	941
Nyanza	35	127	240	146	11,922	248	536
N/eastern	4	8	64	64	1,707	144	146
Rift	55	183	757	343	12,390	157	1,243
Eastern	35	83	435	349	7,412	145	894
Western	21	81	111	205	6,457	168	405
Coast	21	35	216	337	7,687	274	596

Note: 'Hospitals' includes mission and private facilities, and 'mission and private facilities' includes nursing homes and clinics not numbered elsewhere. Thus, the totals column does not add up across the rows.

Sources: NHSSP-II 2005 (Ministry of Health 2005), The Kenyan Health System (Wamai 2009)

References

Abbett, S. K., D. S. Yokoe, et al. 2009. Proposed checklist of hospital interventions to decrease the incidence of healthcare-associated Clostridium difficile infection. *Infection Control and Hospital Epidemiology* 30(11): 1062-1069.

Adegbola, R. A. and D. Saha. 2010. Vaccines: A Cost-Effective Strategy to Contain Antimicrobial Resistance. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

African Population and Health Research Center. 2002. Health and Livelihood Needs of Residents of Informal Settlements in Nairobi City. Nairobi, African Population and Health Research Center.

Akumu, A. O., M. English, et al. 2007. Economic evaluation of delivering Haemophilus influenzae type b vaccine in routine immunication services in Kenya. *Bulletin of the World Health Organization* 85: 511-518.

Aiken, A. 2010. Surveillance of Hospital Infections. Presentation. Kenya Medical Research-Wellcome Trust. Nairobi, Kenya.

Allegranzi, B., S. Bagheri Nejad, et al. 2011. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *The Lancet* 377(9761): 228-241.

Alphonse, E. 2005. Accredited Drug Dispensing Outlets (ADDO) Program in Tanzania. Presentation. Forum on Engaging the Private Sector in Child Health, November 30–December 2, 2005. Munyonyo, Uganda.

Amabile-Cuevas, C. F. 2010. Global Perspectives of Antibiotic Resistance. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Andhoga, J., A. G. Macharia, et al. 2002. Aerobic Pathogenic Bacteria in Post-Operative Wounds at Moi Teaching and Referral Hospital. *East African Medical Journal* 79(12): 640-644.

Arimi, S. M., E. Koroti, et al. 2005. Risk of infection with *Brucella abortus* and *Escherichia coli* O157:H7 associated with marketing of unpasteurized milk in Kenya. *Acta Tropica* 96: 1-8.

Aronovich, D. G. and S. Kinzett. 2001. Kenya: Assessment of the Health Commodity Supply Chains and the Role of KEMSA. Arlington, VA, DELIVER/John Snow, Inc., for the U.S. Agency for International Development (USAID).

Bartoloni, A. and E. Gotuzzo. 2010. Bacterial-Resistant Infections in Resource-Limited Countries. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Bejon, P., S. Mohammed, et al. 2008. Fraction of all hospital admissions and deaths attributable to malnutrition among children in rural Kenya. *The American Journal of Clinical Nutrition* 88: 1626-1631.

Bejon, P., I. Mwangi, et al. 2005. Invasive Gram-negative bacilli are frequently resistant to standard antibiotics for children admitted to hospital in Kilifi, Kenya. *Journal of Antimicrobial Chemotherapy* 2005 DOI: 10.1093/jac/dki145.

Bennish, M. L. and W. A. Khan. 2010. What the Future Holds for Resistance in Developing Countries. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Berkley, J. A., B. Lowe, et al. 2005. Bacteremia among Children Admitted to a Rural Hospital in Kenya. *New England Journal of Medicine* 352(1): 39-47.

Berkley, J. A., K. Maitland, et al. 2008. Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study. *BMJ* DOI: 10.1136/bmj.38408.471991.8F.

Bigogo, G., A. Audi, et al. 2010. Health-seeking patterns among participants of population-based morbidity surveillance in rural western Kenya: implications for calculating disease rates. *International Journal of Infectious Diseases* 14(11): e967-973.

Bii, C. C., H. Taguchi, et al. 2005. Detection of virulence-related genes by multiplex PCR

in multidrug-resistant diarrhoeagenic *Escherichia coli* isolates from Kenya and Japan. *Epidemiology and Infection* 133(4): 627-633.

Blum, L. S. 2008. Formative Research on Avian Influenza, Kenya, Centers for Disease Control and Prevention (CDC).

Breiman, R. F. 2009. Opportunities for Reducing Antimicrobial Use Through New Vaccines, Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Brent, A. J., I. Ahmed, et al. 2006. Incidence of clinically significant bacteraemia in children who present to hospital in Kenya: community-based observational study. *The Lancet* 367: 482-488.

Brooks, J., J. Ochieng, et al. 2006. Surveillance for Bacterial Diarrhea and Antimicrobial Resistance in Rural Western Kenya, 1997-2003. *Clinical Infectious Diseases* 43(15 August): 393-401.

Burton, D., B. Flannery, et al. 2011. Healthcare-seeking behaviour for common infectious disease-related illnesses in rural Kenya: a community-based house-to-house survey. *Journal of Health, Population and Nutrition* 29(1): 61-70.

Center for Pharmaceutical Management. 2008. Accredited Drug Dispensing Outlets in Tanzania: Strategies for Enhancing Access To Medicines Program. Prepared for the Strategies for Enhancing Access to Medicines Program. Accessed on 29 July 2011 from http://www.msh.org/seam/reports/TANZANIA_Final_ADDO.pdf.

Cheng, Allen C. et al. 2008. Strategies to reduce mortality from bacterial sepsis in adults in developing countries. *PLoS Medicine* 5(8):e175.

Cherian, T. 2009. Hib and Spn Burden of Disease in Kenya. Geneva, World Health Organization.

Cooper, B. S., S. P. Stone, et al. 2004. Isolation measures in the hospital management of methicillin resistant Staphylococcus aureus (MRSA): systematic review of the literature. *BMJ* **329**(7465): 533.

Cooper, B. S., S. P. Stone, et al. 2003. Systematic review of isolation policies in the hospital management of methicillin-resistant Staphylococcus aureus: a review of the literature with epidemiological and economic modelling. *Health Technology Assessment* **7**(39): 1-194.

du Prey, B., B. D. Ford, et al. 2004. Antimicrobial recommendation by health care providers in Kenya. *American Journal of Health-System Pharmacy* **61**(Feb 1): 302-303.

Ecumenical Pharmaceutical Network. 2008. Workshop on Local and Regional Actions to Address Antimicrobial Resistance. Saint Luke Foundation Moshi, Tanzania. Ecumenical Pharmaceutical Network (EPN).

Ecumenical Pharmaceutical Network. 2009. Fight AMR! Call to Action. Ecumenical Pharmaceutical Network. Nairobi.

Ecumenical Pharmaceutical Network. 2010. An exploratory pilot study on knowledge, attitudes, and perceptions concerning antimicrobial resistance and antibiotic use practices among hospital staff in Kenya. Ecumenical Pharmaceutical Network. Nairobi, Kenya

Edgeworth, R. 2001. Assessment of Infection Prevention Practices at Coast Provincial General Hospital, Kenya. *Kenya: APHIA Financing and Sustainability Project*. Boston, Management Sciences for Health.

English, M., F. Esamai, et al. 2004. Assessment of inpatient paediatric care in first referral level hospitals in 13 districts in Kenya. *The Lancet* **363**: 1948-1953.

English, M. and A. G. Scott. 2008. What Is the Future for Global Case Management Guidelines for Common Childhood Diseases? *PLoS Medicine* **5**, e241 DOI: 10.1371/journal.pmed.0050241.

Enserink, M. 2010. A Dow Jones for Drug Resistance. *ScienceNOW.* Accessed 1 August 2011, from http://news.sciencemag.org/sciencenow/2010/11/a-dow-jones-for-drug-resistance.html?ref=hp.

Export Processing Zones Authority. 2005. Kenya's Pharmaceutical Industry 2005. Nairobi, Export Processing Zones Authority (Government of Kenya).

Feikin, D., B. Olack, et al. 2011. The Burden of Common Infectious Disease Syndromes at the Clinic and Household Level from Population-Based Surveillance in Rural and Urban Kenya. *PLoS ONE* **6**(1): e16085.

Foster, S. D. 2010. The Economic Burden of Antimicrobial Resistance in the Developing World. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Franco-Paredes, C. and J. I. Santos-Preciado. 2010. The Introduction of Antimicrobial Agents in Resource-Contrained Countries: Impact on the Emergence of Resistance. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amábile-Cuevaset al, Springer.

Fresle DA and Wolfheim C. 1997. Public education in rational drug use: a global survey. Geneva, World Health Organization, (WHO/DAP/97.5).

Gichia, M. G. 2009. Residue Monitoring Plans for Livestock Products. Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Goel, P. K., D. Ross-Degnan, et al. 1996. Influence of Location and Staff Knowledge on Quality of Retail Pharmacy Prescribing for Childhood Diarrhea in Kenya. *International Journal for Quality in Health Care* **8**(6): 519-526.

Government of Kenya. 2000. Interim Poverty Reduction Strategy Paper 2000-2003. Nairobi, Government of Kenya, International Monetary Fund (IMF).

Government of Kenya. 2005. Kenya: Poverty Reduction Strategy Paper. Nairobi, Government of Kenya, International Monetary Fund (IMF).

Government of Kenya. 2008. Millennium Development Goals: Status Report for Kenya - 2007, Ministry of State for Planning, National Development and Vision 2030.

Haak, H. and A. Radyowijati. 2010. Determinants of Antimicrobial Use: Poorly Understood-Poorly Researched. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

HARP. 2009. Challenges for Global Health: Focus Area—Acute Respiratory Infection (ARI). December 2009, from http://www.harpnet.org/focus/ari.html.

HARP. 2009. Challenges for Global Health: Focus Area - Diarrheal Diseases. December 2009, from http://www.harpnet.org/focus/diarrheal.html.

Haynes, A. B., T. G. Weiser, et al. 2009. A surgical safety checklist to reduce morbidity and mortality in a global population. *The New England Journal of Medicine* **360**(5): 491-499.

Irungu, P., B. Bett, et al. 2007. Evidence of improper usage of veterinary drugs in cattle in Maasailand, Kenya. *Bulletin of Animal Health and Production in Africa* **55**(4): 210-225.

Kakai, R. 2009. Antibiotic Resistance in Western Kenya, Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Kakai, R. and I. A. Wamola. 2002. Minimising Antibiotic Resistance to *Staphylococcus Aureus* in Developing Countries. *East African Medical Journal* **79**(11): 574-579.

Karambu, I. 2011. Abuse of 'prescription only' drugs on the rise. Corporate News. Accessed 29 July 2011 from http://www.businessdailyafrica.com/Corporate+News/-/539550/1116580/-/rlfi4x/-/index.html.

Kariuki, S. 2009. Antimicrobial Resistance in Kenya: What Surveillance Tells Us, Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Kariuki, S. 2010. Antimicrobial Resistance in Enteric Pathogens in Developing Countries. *Antimicrobial Resistance in Developing Countries*. A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Kariuki, S., C. Gilks, et al. 1996. Multi-drug resistant non-typhi salmonellae in Kenya. *Journal of Antimicrobial Chemotherapy* **38**: 425-434.

Kariuki, S., C. Gilks, et al. 1997. Plasmid diversity of multidrug resistant Escherichia coli isolated from children with diarrhoea in a poultry-farming area in Kenya. *Annals of Tropical Medicine and Parasitology* **91**: 87-94.

Kariuki, S., C. Gilks, et al. 1999. Genotype Analysis of Escherichia coli Strains Isolated from Children and Chickens Living in Close Contact. *Applied and Environmental Microbiology* **65**(2): 472-476.

Kariuki, S., J. Muyodi, et al. 2003. Antimicrobial Susceptibility in Community-Acquired Bacterial Pneumonia in Adults. *East African Medical Journal* **80**(4): 213-217.

Kariuki, S., G. Revathi, et al. 2006. Characterisation of community acquired non-typhoidal Salmonella from bacteraemia and diarrhoeal infections in children admitted to hospital in Nairobi, Kenya. *BMC Microbiology* **6**, 101 DOI: 10.1186/1471-2180-6-101.

Kariuki, S., G. Revathi, et al. 2006. Invasive multidrug-resistant non-typhoidal *Salmonella* infections in Africa: zoonotic or anthroponotic transmission? *Journal of Medical Microbiology* **55**: 585-591.

Kariuki, S., G. Revathi, et al. 2005. Increasing prevalence of multidrug-resistant non-typhoidal salmonellae, Kenya, 1994-2003. *International Journal of Antimicrobial Agents* **25**(2005): 38-43.

Kariuki, S., G. Revathi, et al. 2006. Decreasing prevalence of antimicrobial resistance in non-typhoidal Salmonella isolated from children with bacteraemia in a rural district hospital, Kenya. *International Journal of Antimicrobial Agents* **28**(2006): 166-171.

Kariuki, S., G. Revathi, et al. 2004. Characterization of Multidrug-Resistant Typhoid Outbreaks in Kenya. *Journal of Clinical Microbiology* **42**(4): 1477-1482.

Katz, M. 2009. Overview of Influenza Surveillance and Antiviral Resistance in Kenya. Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Kelly, J., B. Osamba, et al. 2001. Community Health Worker Performance in the Management of Multiple Childhood Illnesses: Siaya District, Kenya 1997-2001. *American Journal of Public Health* **91**(10): 1617-1624.

KEMSA Task Force. 2008. KEMSA Task Force Report to the Minister for Medical Services. Nairobi, KEMSA Task Force, chaired by Dr. Richard Muga.

Kenya National Bureau of Statistics (KNBS) and ICF Macro. 2010. Kenya Demographic and Health Survey 2008-09. Calverton, MD, KNBS and ICF Macro.

Kenya Veterinary Association. 2009. Policy Position Paper on Regulation of Veterinary Medicines in Kenya. Nairobi, Kenya Veterinary Association (KVA).

Kesah, C., S. Ben Redjeb, et al. 2003. Prevalence of methicillin-resistant Staphylococcus aureus in eight African hospitals and Malta. *Clinical Microbiology and Infection* **9**(2): 153-156.

Kiiru, J. (Ongoing study 2007-2011). Overview of the Antibiotic Resistance Project. Nairobi, Unpublished data.

Kiiru, J., S. Saidi, et al. 2009. Molecular characterisation of Vibrio cholerae O1 strains carrying an SXT/R391-like element from cholera outbreaks in Kenya: 1994-2007. *BioMed Central Microbiology* **9**, 275 DOI: 10.1186/1471-2180-9-275.

Kikuvi, G. M., S. Schwarz, et al. 2007. Streptomycin and Chloramphenicol Resistance Genes in *Escherichia coli* Isolates from Cattle, Pigs and Chicken in Kenya. *Microbial Drug Resistance* **13** DOI: 10.1089/mdr.2006.9998.

Kingsley, R., C. L. Msefula, et al. 2009. Epidemic multiple drug resistant Salmonella Typhimurium causing invasive disease in sub-Saharan Africa have a distinct genotype. *Genome Research* DOI: 10.1101/gr.091017.109.

Kiulia, N., R. Kamenwa, et al. 2008. The Epidemiology of Human Rotavirus Associated with Diarrhoea in Kenyan Children: A Review. *Journal of Tropical Pediatrics* **54**(6): 401-405.

Klugman, K. P. (2009). Drivers of Antibiotic Resistance. Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Kwena, Z., A. Sharma, et al. 2008. Provider Characteristics Among Staff Providing Care to Sexually Transmitted Infection Self-Medicating Patients in Retail Pharmacies in Kibera Slum, Nairobi, Kenya. *Sexually Transmitted Diseases* **35**(5): 480-483.

Kyobutungi, C., A. Ziraba, et al. 2008. The burden of disease profile of residents of Nairobi's slums: Results from a Demographic Surveillance System. *Population Health Metrics* **6**(1).

Lennell, A., S. Kuhlmann-Berenzon, et al. 2008. Alcohol-based hand-disinfection reduced children's absence from Swedish day care centers. *Acta Paediatrica* **97**(12): 1672-1680.

Lin, Y. and P. Tavrow. 2000. Assessing Health Worker Performance of IMCI in Kenya. *Quality Assurance Project Case Study*. Bethesda, Maryland, U.S.A.

Madhi, S., K. Petersen, et al. 2000. Impact of human immunodeficiency virus type 1 on the disease spectrum of Streptococcus pneumoniae in South African children. *Journal of Pediatric Infections Diseases* **19**(12): 1141-1147.

Makau, M. 2009. AMR Surveillance: Aga Khan University Hospital (AKUH) Experience. Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Matata, L., C. Ondieki, et al. 2008. Hospital Burden and Incidence of Invasive Pneumococcal Disease among Adults at Kilifi District Hospital, Kenya. Kenya Medical Research Institute - Wellcome Trust.

Ministry of Finance. 2009. The Medium Term Budget Strategy Paper 2009/10-2011/12. Nairobi, Ministry of Finance (Government of Kenya).

Ministry of Health. 1994. The Kenya National Drug Policy. Nairobi, Ministry of Health (Government of Kenya).

Ministry of Health. 2003. Assessment of the Pharmaceutical Situation in Kenya: A Baseline Survey. Nairobi, Ministry of Health (Government of Kenya) with Health Action International and the World Health Organization.

Ministry of Health. 2004. Kenya Demographic and Health Survey. Calverton, Maryland, Central Bureau of Statistics (CBS) [Kenya], Ministry of Health (Government of Kenya), and ORC Macro.

Ministry of Health. 2004. Kenya Demographic and Health Survey 2003: Key Findings. Calverton, Maryland, Central Bureau of Statistics (CBS) [Kenya], Ministry of Health (Government of Kenya), and ORC Macro.

Ministry of Health. 2004. A Survey of Medicine Prices in Kenya - 2004. Nairobi, Ministry of Health (Government of Kenya), Health Action International (HAI), World Health Organization.

Ministry of Health. 2005. The Second National Health Sector Strategic Plan - Reversing the Trends, NHSSP II - 2005-2010. Nairobi, Ministry of Health (Government of Kenya).

Ministry of Health. 2007. Antimalarial Medicines in Kenya: Availability, Quality and Registration Status. Nairobi, Ministry of Health (Government of Kenya), Health Action International (HAI), World Health Organization.

Ministry of Health. 2007. Health and Health Related Indicators 2006: Facts and Figures at a Glance. Nairobi, Ministry of Health (Government of Kenya).

Ministry of Health. 2007. Reversing the trends: NHSSP-II of Kenya - Annual Operational Plan (AOP) 3 2007/08. Nairobi, Ministry of Health (Government of Kenya) with the Sector Planning and Monitoring Department.

Ministry of Health. 2010. National Infection Prevention and Control Policy for Healthcare Services in Kenya. Nairobi, Ministry of Public Health and Sanitation and Ministry of Medical Services (Government of Kenya).

Ministry of Medical Services 2009. Report on 2007/08 Medicines and Medical Supplies Price Survey in the Public Health Sector. Nairobi, Ministry of Medical Services (Government of Kenya), United States Agency of International Development (USAID).

Ministry of Medical Services and Ministry of Public Health and Sanitation. 2010. Clinical

Guidelines for Management and Referral of Common Conditions in Kenya at Levels 2-3: Primary Care. Nairobi, Government of Kenya with the World Health Organization.

Ministry of Medical Services and Ministry of Public Health and Sanitation. 2010. Kenya Essential Medicines List Nairobi, Government of Kenya with the World Health Organization.

Miralles, M. A. 2010. Strengthening Health Systems to Improve Access to Antimicrobials and the Containment of Resistance. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Mitema, E. S. 2009. Antimicrobial Usage and Resistance Development in Food Animals in Kenya: An Emerging Global Problem. Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Mitema, E. S. 2010. The Role of Unregulated Sale and Dispensing of Antimicrobial Agents on the Development of Antimicrobial Resistance in Developing Countries. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amábile-Cuevaset al, Springer.

Mitema, E. S. and G. M. Kikuvi. 2004. Surveillance of the overall use of antimicrobial drugs in humans over a 5 year period (1997-2001) in Kenya. *Journal of Antimicrobial Chemotherapy* DOI: 10.1093/jac/dkh433.

Mitema, E. S., G. M. Kikuvi, et al. 2001. An assessment of antimicrobial consumption in food producing animals in Kenya. *Journal of Veterinary Pharmacology and Therapeutics* **24**: 385-390.

MSH. 2008. TANZANIA: Accredited Drug Dispensing Outlets—Duka la Dawa Muhimu. Strategies for Enhancing Access to Medicines Program. Accessed 29 July 2011 from www.msh.org/.../SEAM_Final_Report_Summary-Tanzania_ADDOs.pdf

MSH. 2009. GHANA: Creating a Franchise System for Drug Sellers—CAREshops®. Strategies for Enhancing Access to Medicines Program. Accessed 29 July 2011 from http://www.msh.org/seam/reports/seam_ghana_careshops.pdf

Mudhune, S. and M. Wamae. (2009). The Network Surveillance for Pneumococcal Disease in the East African Region: Report on Invasive Disease and Meningitis due to *Haemophilus influenzae* and *Streptococcus pneumonia* from the Network for Surveillance of Pneumococcal Disease in the East African Region. *Clinical Infectious Diseases* **48**(Suppl 2): 147-152.

Muga, R., P. Kizito, et al. 2005. Chapter 2: Overview of the Health System in Kenya. Kenya: HIV/MCH SPA, 2004 - Final Report. National Coordinating Agency for Population and Development (NCAPD), Ministry of Health and Central Bureau of Statistics.

Mugoya, I., S. Kariuki, et al. 2008. Rapid Spread of *Vibrio cholerae* O1 Throughout Kenya, 2005. *American Journal of Tropical Medicine and Hygiene* **78**(3): 527-533.

Musoke, R. N. and G. Revathi. 2000. Emergence of Multidrug-resistant Gram-negative Organisms in a Neonatal Unit and the Therapeutic Implications. *Journal of Tropical Pediatrics* **46**: 86-91.

Mwabu, G. 2009. Do Economic Incentives (or Disincentives) Affect Antibiotic Use? Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Mwangi, I., J. A. Berkley, et al. 2002. Acute bacterial meningitis in children admitted to a rural Kenyan hospital: increasing antibiotic resistance and outcome. *Journal of Pediatric Infections Diseases* **21**(11): 1042-1048.

Mwangi, M. 2008. Opportunities in Fish Farming for Employment and Sustainable Livelihoods in Kenya. Nairobi, Ministry of Fisheries Development.

NAS. 1999. The Use of Drugs in Food Animals: Benefits and Risks. Washington, DC: *National Academies Press*.

National Aids Control Council. 2010. Kenya 2007 Estimates report with revised HIV prevalence and incidence trends. 2010. Accessed 29 July 2011 from http://www.nacc.or.ke/2007/default2.php?active_page_id=281.

Ndegwa, L. 2009. Hospital infection control efforts. Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi,

Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Ndegwa, L., K. Ellingson, et al. Surveillance for Healthcare-associated Respiratory Illness in Kenya. Unpublished protocol.

Newton, O. and M. English. 2007. Young infant sepsis: aetiology, antibiotic susceptibility and clinical signs. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **101**(10): 959-966.

Newton, P. N., F. M. Fernández, et al. 2010. Counterfeit and Substandard Anti-infectives in Developing Countries. *Antimicrobial Resistance in Developing Countries*. A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Ngigi, A. and D. Macharia, IT Power East Africa. 2006. Health Sector Policy Overview Paper. Nairobi, ENABLE.

Ngumi, Z. W. W. 2006. Nosocomial Infections of Kenyatta National Hospital Intensive-Care Unit in Nairobi, Kenya. *Dermatology* **212**(suppl 1): 4-7.

Norris, P. 2007. Interventions to improve antimicrobial use: evidence from ICIUM 2004. *WHO.* Dunedin, New Zealand.

Nugent, R., R., Back, et al. 2010. The Race against drug resistance. A report for the Center for Global Development's drug resistance working group. 2010. Accessed 29 July 2011 from http://www.cgdev.org/files/1424207_file_CGD_DRWG_FINAL.pdf

Nys, S., I. N. Okeke, et al. 2004. Antibiotic resistance of faecal *Escherichia coli* from health volunteers from eight developing countries. *Journal of Antimicrobial Chemotherapy* **54**(5): 952-955.

Okeke, I. N. 2010. Poverty and Root Causes of Resistance in Developing Countries. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Okeke, I. N., O. Aboderin, et al. 2007. Growing Problem of Multidrug-Resistant Enteric Pathogens in Africa. *Emerging Infectious Diseases* **13**(11): 1640-1646.

Okeke, I. N., R. Laxminarayan, et al. 2005. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infectious Diseases* **5**: 481-493.

Okeke, I. N., R. Laxminarayan, et al. 2005. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infectious Diseases* **5**(8): 481-493.

Okeke, I. N. and K. K. Ojo. 2010. Antimicrobial Use and Resistance in Africa. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Okwemba, A. 2010. Doctors alarmed about HIV drug. *Daily Nation.* Nairobi.

Omuse, G. 2009. Methicilin Resistant Staphylococcus Aureus (MRSA): The Aga Khan Experience. Global Antibiotic Resistance Partnership Inaugural Meeting, Nairobi, Kenya, Unpublished conference proceedings. Resources for the Future, Washington DC, 2009. Powerpoint.

Onyango, D., F. Machoni, et al. 2008. Multidrug resistance of *Salmonella enterica* serovars *Typhi* and *Typhimurium* isolated from clinical samples at two rural hospitals in Western Kenya. *Journal of Infection in Developing Countries* **2**(2): 106-111.

Oxfam. 2011. Stop Stock-Outs. 2011. Accessed 29 July 2011 from http://www.oxfam.org/en/campaigns/health-education/stop-stock-outs.

Paul, J., J. Bates, et al. 1996. Serotypes and Antibiotic Susceptibilities of *Streptococcus pneumoniae* in Nairobi, Kenya. *Journal of Infection* **32**: 139-142.

Peacock, J. E., Jr., F. J. Marsik, et al. 1980. Methicillin-resistant Staphylococcus aureus: introduction and spread within a hospital. *Annals of Internal Medicine* **93**(4): 526-532.

Pemba, L., S. Charalambous, et al. 2008. Impact of cotrimoxazole on non-susceptibility to antibiotics in *Streptococcus pneumoniae* carriage isolates among HIV-infected mineworkers in South Africa. *Journal of Infection* **56**: 171-178.

Pharmaceutical Society of Kenya. 2008. *The Pharmaceutical Journal of Kenya*. Hurlingham, Nairobi, Pharmaceutical Society of Kenya. **18**.

PharmaSupport Services. 2006. *The Greenbook*. Nairobi, Sketchpad Studioz.

Phillips-Howard, P. A., K. Wannemuehler, et al. 2003. Diagnostic and Prescribing Practices in Peripheral Health Facilities in Rural Western Kenya. *American Journal of Tropical Medicine and Hygiene* **68**(Suppl 4): 44-49.

Pittet, D., B. Allegranzi, et al. 2006. Evidence-based model for hand transmission during patient care and the role of improved practices. *The Lancet infectious diseases* **6**(10): 641-652.

Pittet, D., S. Hugonnet, et al. 2000. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. *Lancet* **356**(9238): 1307-1312.

Ram, P. K. 2008. Community case management of childhood diarrhoea in Asembo and Kibera, Kenya, 2007. University at Buffalo, Centers for Disease Control and Prevention, the Ministry of Health of the Republic of Kenya, and U.S. Agency for International Development.

Rosenthal, Victor D. (2008) International Nosocomial Infection Control Consortium report, data summary for 2002-2007, Issues January 2008. *American Journal of Infection Control*. **36**(9).

Ross-Degnan, D., S. B. Soumerai, et al. 1996. The impact of face-to-face educational outreach on diarrhoea treatment in pharmacies. *Health Policy and Planning* **11**(3): 308-318.

Shankar, P. Ravi et al. 2003. Investigation of antimicrobial use pattern in the intensive treatment unit of a teaching hospital in western Nepal. *American Journal of Infection Control* **31**(7): 410-414.

Scott, A. G., S. Mwarumba, et al. 2005. Progressive Increase in Antimicrobial Resistance among Invasive Isolates of *Haemophilus influenzae* Obtained from Children Admitted to a Hospital in Kilifi, Kenya, from 1994 to 2002. *Antimicrobial Agents and Chemotherapy* **49**(7): 3021-3024.

Scott, J. A. G., S. Mwarumba, et al. 2005. Progressive Increase in Antimicrobial Resistance among Invasive Isolates of *Haemophilus influenzae* Obtained from Children Admitted to a Hospital in Kilifi, Kenya from 1994 to 2002. *Antimicrobial Agents and Chemotherapy* **49**(7): 3021-3024.

Scrascia, M., M. Forcillo, et al. 2003. Susceptibility to rifaximin of *Vibrio cholerae* strains from different geographical areas. *Journal of Antimicrobial Chemotherapy* DOI: 10.1093/jac/dkg318.

Shapiro, R. L., L. Kumar, et al. 2001. Antimicrobial-Resistant Bacterial Diarrhea in Rural Western Kenya. *Journal of Infectious Diseases* **183**(1 June): 1701-1704.

Shitandi, A. and A. Sternesjö. 2004. Prevalence of Multidrug Resistant Staphylococcus aureus in Milk from Large- and Small-Scale Producers in Kenya. *Journal of Dairy Science* **87**: 4145-4149.

Sinha, A., O. S. Levine, et al. 2007. Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: an international economic analysis. *The Lancet* **369**: 389-396.

Hu, S., et al. 2002 Assessment of Antibiotic Prescription in Hospitalized Patients at a Chinese University Hospital. *Journal of Infection* **46**(3): 161-163

Tate, J., R. Rheingans, et al. 2009. Rotavirus disease burden and impact and cost-effectiveness of a rotavirus vaccination program in Kenya. *Journal of Infectious Diseases* **200 Suppl 1:S76-84**.

Taylor, P. 2010. Kenya will pilot mPedigree medicine validation system. SecuringPharma. Accessed 29 July 2011 from http://www.securingpharma.com/40/articles/723.php

The World Bank. 2008. Kenya at a glance, The World Bank.

The World Bank. 2010. Zambia Study Shows Stronger Supply Chains for Key Drugs can Reduce Child Mortality. Accessed 29 July 2010 from http://web.worldbank.org/WBSITE/EXTERNAL/COUNTRIES/AFRICAEXT/ZAMBIAEXTN/0,,contentMDK:22549748~menuPK:50003484~pagePK:2865066~piPK:2865079~theSitePK:375589,00.html

Thoithi, G. and K. Abuga. 2008. Drug Quality Control in Kenya: Observation in the Drug Analysis and Research Unit During the Period 2001-2005. *East and Central African Journal of Pharmaceutical Sciences* **11**(3).

Thoithi, G. N. and F. A. Okalebo. 2009. Country case study: Kenya. 2009 FIP Global Pharmacy Workforce Report, International Pharmaceutical Federation.

Thompson, R. L., I. Cabezudo, et al. 1982. Epidemiology of nosocomial infections caused by methicillin-resistant Staphylococcus aureus. *Annals of Internal Medicine* **97**(3): 309-317.

Tornheim, J., A. Manya, et al. 2007. The epidemiology of hospitalized pneumonia in rural Kenya: the potential of surveillance data in setting public health priorities. *International Journal of Infectious Diseases* **11**: 536-543.

Tornheim, J., A. Manya, et al. 2009. The epidemiology of hospitalization with diarrhea in rural Kenya: the utility of existing health facility data in developing countries. *International Journal of Infectious Diseases* DOI: 10.1016/j.ijid.2009.07.021.

Vlieghe, E., A. M. Bal, et al. 2010. Surveillance of Antibiotic Resistance in Developing Countries: Needs, Constraints and Realities. *Antimicrobial Resistance in Developing Countries.* A. Sosa, D. K. Byarugaba, C. F. Amabile-Cuevaset al, Springer.

Wamai, R. G. 2009. The Kenya Health System - Analysis of the situation and enduring challenges. *Japan Medical Association Journal* **52**(2): 134-140.

World Bank. 2009. Public Sector Healthcare Supply Chain Strategic Network Design for KEMSA. Improving Health Systems: Driving Service Improvements through Supply Chain Excellence. International Bank for Reconstruction and Development/World Bank.

World Health Organization. 2004. Mission for Essential Drugs and Supplies, Kenya. Perspectives and Practice in Antiretroviral Treatment. Geneva, World Health Organization.

World Health Organization. 2006. Kenya: Country Health System Fact Sheet 2006, World Health Organization.

World Health Organization. 2008. Cholera Country Profile: Kenya, Global Task Force on Cholera Control for the World Health Organization.

World Summit for Children. 2003. World Summit for Children Indicators, Kenya, 2003, UNICEF.

World Trade Organization. 2006. TRIPS and pharmaceutical patents: fact sheet. Accessed December 2009 from http://www.wto.org/english/tratop_E/TRIPS_e/factsheet_pharm00_e.htm.

Ye, Y., E. Zulu, et al. 2009. Seasonal Pattern of Pneumonia Mortality among Under-Five Children in Nairobi's Informal Settlements. *American Journal of Tropical Medicine and Hygiene* **81**(5): 770-775.

Zaman, K., E. Roy, et al. 2008. Effectiveness of maternal influenza immunization in mothers and infants. *The New England Journal of Medicine* **359**(15): 1555-1564.

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, Kenya, and the United States, and relies on a distinguished team of academics and policy analysts around the world.

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