ANTI MICROBIAL DRUG RESISTANCE (AMDR)
Self-Study Materials

April 24, 2012
Antimicrobial Drug Resistance (AMDR)

A Continuing Medical Education Activity

Joint Sponsorship Statement:
This activity is jointly sponsored by the Center for the Study of International Medical Policies and Practices (CSIMPP), School of Public Policy, George Mason University and MedEDirect, LTD., in collaboration with the World Medical Association (WMA) and the International Society for Microbial Resistance (ISMR).

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Updates

First update issued in April 24, 2012. Please refer to the updates list on page 5.

Disclosure of Conflicts of Interest:

This activity was not supported by a commercial source. All individuals participating in the development and implementation of activities sponsored by MedEDirect have disclosed real or perceived conflicts of interest related to this activity:

- Drs. Nicogossian, Kloiber, Zimmerman, Habayeb, Koizumi and Thomas have no conflicts of interest.
- Dr. Edward Septimus is a speaker for Sage, Merck and Cubicin pharmaceutical companies, and a clinical professor at the Medical College, Texas A&M.
- Dr. Morrison is a speaker for the Pfizer, Cubist, Merck, Ortho-McNeil, Glaxo-Smith-Kline, and Care Fusion.
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Needs Statement:
The rising global spread of antibiotic drugs resistance and associated incidence of morbidity and mortality from hospital- and community-acquired infections dictates that all healthcare providers understand the principles of antimicrobial drugs stewardship.

Learning Objectives:
At the conclusion of this activity, participants will:
1. Understand the global threats presented by the antimicrobial drug resistance (AMDR),
2. Explore the mechanisms responsible for the global spread of AMDR, and
3. Recognize and apply the principles of antibiotic drug stewardship and infection control.

Target Audience:
This educational activity is intended for all healthcare professionals and managers involved in the prevention and management of infectious diseases.

Estimated Time for Completion of Self-Study Materials:
This activity should take approximately 2.0 hours to complete.

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“Antimicrobial resistance: no action today, no cure tomorrow.”

Statement by the Director-General
WHO World Day – 7 April 2011
Overview

In 2011, the World Health Organization (WHO) reported that 63,000 patients die each year in US hospitals and 25,000 patients lose their lives annually in the European Union due to anti-biotic-resistant infections. The annual estimated economic burden is US $2.1 billion in the European Union, US $34 billion in the United States, and US $2.453 billion globally.

Antimicrobial drug resistance (AMR or AMDR) is a multidimensional and systemic failure of the health, education, societal behavior, and medical policies and practices.

Four major challenges should be recognized and addressed by the world medical community.

1. AMDR is extending beyond national boundaries, presenting a significant threat to health and increasing the costs of medical care.

2. Collaboration among healthcare, pharmaceutical, agricultural, and consumer communities is a prerequisite to ward off this evolving pandemic.

3. Adequate funding for proactive surveillance and development of new antimicrobial drugs and vaccines should be made available.

4. Antibiotic drug stewardship, including responsible use and dispensing, education of stakeholders, surveillance, infection control, and hygiene practices are necessary steps in the fight against AMDR.
GENERAL INFORMATION

Activity Highlights

Microorganisms resistant to antibiotic drugs, disinfectants and contributing to increased global morbidity and mortality are reviewed. The following pathogens are not addressed, except as indicated in parentheses:

1. Viruses (influenza and HIV/AIDS, which increase the risk of secondary opportunistic infections)
2. Protozoa (malaria is addressed)
3. Protista
4. Helminthes and fungi resistant to specific drug preparations
5. Prions

Consistent definitions of different AMDR terms is helpful in improving communications among healthcare providers. Terminology used in this activity reflects, as much as possible, the International Classification of Diseases 9th Revision (ICD-9), and as applicable the ICD-10, which is to take effect in 2013. For example, the ICD-10 classification for “Bacterial Agents Resistant to Antibiotics” can be found in Codes U80 to U89.

The authors selected up-to-date AMDR clinical and other epidemiological data. As with any new educational material, some errors, omissions, and inconsistencies could have been inadvertently introduced. A critical review by subject matter experts was completed before the release of these materials. We intend to update the scientific and clinical information at least quarterly and the self-assessment questions as appropriate.

The proposed best practices and policies rely primarily on evidence-based information. Common sense and experience from clinical practice were used when sufficient scientific and/or research data were lacking.

A glossary of select terms used in the text is included after the Appendices. Images of microorganisms cited in this monograph, courtesy of the U.S. Centers for Disease Control and Prevention, are exhibited at the end and called plate.

Limitations
Caution should be exercised when adapting the information presented in this self-study to a specific geographical or regional practice and/or prevailing socioeconomic situation.
SECTION ONE: Introduction

Specific Learning Objective: Understand the global threats presented by the antimicrobial drug resistance (AMDR),

Defining the Problem

Humans coexist with many microorganisms, of which only a small subset presents a threat to health. Bacteria have evolved diverse protective mechanisms to cope with and survive in the ever-changing environment (Russell 1997). In the course of evolution, bacteria have had ample time to recognize harmful substances, developing and sharing defense mechanisms to ensure their own survival. As a result, antibiotics, naturally produced by bacteria, existed long before humans discovered their properties and used them on an unprecedented scale. Resistance to modern antibiotics can be demonstrated in bacteria from ecosystems that have been isolated for over 4 million years (Bhullar 2012).

The 2008 global antibiotic market was estimated at US $24 billion and is projected to reach US $40.3 billion by 2015 (PRWeb 2011). Antibiotic drugs, including antiviral, anthelminthic, and antifungal preparations, are sold for both therapeutic and industrial (agricultural) uses. The rate of antibiotic prescriptions is on the rise in Greece, Croatia, Denmark, and Ireland for both outpatient and inpatient services. A modest downward trend (1998-2005) was reported for Belgium, the Czech Republic, France, Slovakia, Slovenia, Sweden, and the United Kingdom (Monnet and Kristinsson 2008; Meropol et al. 2009), whereas in the United States and Japan, the overall rate for antibiotic use remains high (Higashi and Furuhara 2009). Some experts are concerned that we are entering a critical “post-antibiotic era” with a decreasing pipeline of new and effective antibiotics and rising trends in mortality from AMDR (Alanis 2005).

The importance of the AMDR threat has been recently highlighted by the WHO (World Health Organization “Combat antibiotic resistance” 2011):

- Infections caused by resistant microorganisms often fail to respond to conventional treatment, often leading to prolonged illness and greater mortality risk
- About 440,000 new cases of multidrug-resistant tuberculosis (MDR-TB) emerge annually, causing at least 150,000 deaths
- Resistance to earlier generations of antimalarial preparations such as chloroquine and sulfadoxine-pyrimethamine is widespread in most malaria-endemic countries
- Inappropriate and irrational use of antimicrobial drugs does provide a fertile environment for resistant microorganisms to emerge, spread, and persist

The economic burden of AMDR is estimated to exceed US $38 billion (Tucker 2010). Nearly 7 out of every 1000 hospitalized patients (in market economy countries) are either infected with or carriers of microorganisms resistant to common antibiotic drugs. In US hospitals, annually 96,000 patients contract nosocomial infection (s), are making it one of the 10 leading
causes of death, claiming between 16,000 and 19,000 lives each year. The 2000 EU hospital estimates (Kaier et al. 2008) of AMDR infection incidence found that:

- Thirty percent to 40% of cases are linked to cross-infection by the hands of healthcare workers (HCW)
- Twenty percent to 25% of cases are due to selective antimicrobial pressure
- Twenty percent to 25% of patients suffer from new pathogen introduction

The remaining 20% of nosocomial infections are caused by the lack of proper control and oversight of antibiotic prescriptions (Weinstein 2001; Woodward et al. 1987).

Inappropriate and sometimes careless use of antibiotic drugs in healthcare and agriculture is a major contributing factor to the rise of AMDR. In 2005, the WHO reported that more than 50% of all medicines (including antibiotic drugs) are prescribed, dispensed, or sold inappropriately, with 50% of patients failing to take them correctly (World Health Organization 2010). Although a 17% decline in counterfeit antibiotics was reported between 2009 and 2010, this class of medications still remains the second largest counterfeit therapeutic category (Pharmaceutical Security Institute 2011).

Countries that implemented policies on the appropriate use of antibiotics observed a positive impact on infections caused by AMDR (Awad et al. 2007; Isturiz and Carbon 2000; Berild et al. 2008; Tünger et al. 2000). However, between 2003 and 2005, only 26% of all countries adopted a national strategy and less than half implemented public awareness and education programs (Khor 2005). This lack of action is of concern since many medical and surgical procedures might be at risk for AMDR complications, including death.

In the fall of 2008 the World Medical Association (WMA) updated its 1996 resolution on microbial resistance, in response to the risk of an emerging AMDR pandemic (World Medical Association 2011). This action was sponsored by the American Medical Association. The School of Public Policy at George Mason University contributed to the peer review and update of the proposed resolution. World Health Day 2011 was marked on April 7, 2011, by focusing on antimicrobial resistance, including drug resistance issues related to HIV/AIDS (World Health Organization “World Health Day 2011” 2011). Professional societies continue to update guidelines on the prevention and treatment of infections caused by AMDR pathogens.

Plasmid provides a mechanism for gene transfer and produces a selective survival advantage for microorganisms in many hostile environments. Plasmids may carry genes that provide resistance to antibiotics.

Factors contributing to AMDR include:
1. Compromised immune system
2. Drugs administered for chronic and/or debilitating diseases
3. Age
4. Nutritional deficiencies
5. Increased gastric pH
6. Bronchopulmonary disorders interfering with sputum clearance
7. Invasive procedures or devices (such as orthopedic prostheses, indwelling catheters, or heart valves)
8. Intensive interventions such as hemodialysis, surgery, or catheterization

Patients receiving antibiotic treatments, especially those who are immunocompromised, can act as foci for emergence and spread of AMDR microorganisms.
SECTION TWO: Understanding AMDR

Learning Objective: Explore the mechanisms responsible for the global spread of AMDR.

According to the US Centers for Disease Control and Prevention (CDC), the number of antibiotic-resistant pathogens is on the rise, creating a major public health problem. AMDR is the ability of a specific microorganism to withstand a drug or a biocide preparation that interferes with its growth and functions (Meyers 1987; Russell 1999). Resistance is a complex phenomenon involving the microorganism, the drug, the environment, and the patient. It is important to note that resistance and virulence are not related; a resistant pathogen may be no more virulent than its antibiotic-sensitive parent strain (Holmberg et al. 1987; Berkowitz 1995).

The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), both hospital and community strains, as well as metallo-β-lactamase–resistant Gram-negative pathogens, are two recent examples of how microbial resistance emerges and spreads worldwide (Liu et al. 2011; Walsh and Toleman 2011). Central to the emergence and proliferation of antimicrobial resistance in developed countries is the inappropriate use of antibiotics and patient contact with AMDR pathogens, whereas in emerging and developing countries, poor hygiene and crowded living conditions are important additional drivers (Walsh and Toleman 2011). Global mobility and socioeconomic problems such as overcrowding, sanitation, war, health disparities, poor public health literacy, and poor public health systems are intertwined with the spread of resistant infections.

In the United States, spending on antibiotic prescriptions increased 22% from 1980 to 1996, with a steep increase in resistance rates during the same period (Howard 2004). Studies in European countries also demonstrate a relationship between antimicrobial use and antimicrobial resistance rates (Livermore and Pearson 2007; Naber 2009). Infections caused by AMDR pathogens are associated with increased healthcare resource utilization. MRSA infections increase hospital length of stay (LOS), resource utilization, and cost, and are still associated with higher mortality (Cosgrove 2006). A similar pattern is noted for recently emergent Gram-negative antimicrobial-resistant strains (Walsh and Toleman 2011). Extended-spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae* are associated with increased hospital LOS and costs, whereas bloodstream infections caused by ESBL-producing *Enterobacteriaceae* are associated with increased rates of mortality. Multidrug-resistant (MDR) *Pseudomonas aeruginosa* (resistant to 4 or more antibiotic drugs) is also associated with increased mortality and hospital length of stay (Giske et al 2008). Overall, such AMDR trends have prompted governments and professional associations to draft stronger guidelines on the use of antimicrobial therapies (US Government Accountability Office 2011; World Health Organization 2011).

1. Etiology and Epidemiology

   Microorganisms naturally produce antibiotics as a defense mechanism against other microbes, and antibiotic-resistance genes originally evolved as a mechanism for microbes to withstand chemical attacks from other microorganisms (Cohen and Tartasky 1997). Resistance genes can appear through spontaneous mutation of existing genes or through
transmission of plasmids (small pieces of mobile genetic material) between bacterial species or as recently suggested by the formation of *persisters* enhancing transcription of indoles (Vega 2012)\(^1\). The incorporation of resistance genes allows antibiotic resistance to become a stable feature of a bacterial strain, resulting in loss of clinical efficacy for that antibiotic or class of antibiotics. Patients receiving antibiotic therapy can become an important source of resistant pathogens in hospitals and the community (Weinstein 1991; Long et al. 2009; Naber 2009; Schentag 1995; Hota et al. 2009; Choi et al. 2008; Riley 1988; Small et al. 1993).

Multiple epidemiologic studies confirm that infections potentially caused by AMDR pathogens should be suspected:

- Following contact with individuals infected or colonized with resistant pathogens
- During and/or following a course of antibiotic treatment
- When the prevalence of resistant pathogen strains within a population is high

Additional factors that contribute to the emergence of AMDR pathogens (Cohen and Tartasky 1997; Smith and Coast 2002; Gulbinovic et al. 2001) include failures to:

- Perform drug susceptibility testing
- Select appropriate antibiotics
- Complete the treatment course

The spread of AMDR in community settings is also the result of the dissemination of resistant microorganisms (from hospitals or outpatient settings), transfer of resistant genes, or both (Pallecchi et al. 2007). In the United States, more than 58% of community-acquired infections were found to be caused by strains traceable to a hospital or long-term care facility (Charlebois et al. 2004). Interestingly, recent evidence demonstrates that MRSA strains known to have their origin in community settings have become prominent pathogen strains in hospital settings (D’Agata et al. 2009). The latter emphasizes the high mobility of AMDR pathogens associated with the flow patterns of individuals.

Beyond molecular (genetic) resistance, several host factors can increase the risk for an individual to an infection caused by an AMDR organism, including (Fridkin et al. 2005; H. L. Chang et al. 2009; O’Fallon et al. 2009):

1. Patient’s age
2. Compromised immune system
3. Prior antibiotic use
4. Recent hospitalization
5. Poor hand hygiene
6. Bronchopulmonary disorders that interfere with clearance of pathogens from the airway
7. Intensive interventions such as hemodialysis or complex surgical procedures
8. Nutritional deficiency

\(^{1}\)Indoles are secreted by bacteria, such as *E. coli*, to protect colonies against the onslaught of antibiotics and confer multi-drug resistance
9. Crowded living conditions
10. Increased gastric pH (increased alkalinity facilitating microorganisms survival)

Some of these host factors can be improved through public and healthcare policy initiatives that improve overall health and well-being, whereas others are intrinsic features of the patients themselves.

A notable patient risk factor for development of certain AMDR infections is the individual’s colonization status. Patient colonization can occur through contact with other infected or colonized individuals or from contact with contaminated surfaces and objects (Tenover and McGowan 1996; Lei et al. 2010). Major colonization sites are skin folds, especially groin and antecubital areas, which are extensively used for indwelling lines. Proper skin cleaning, physical hygiene and regular culturing is required to detect and handle the multidrug-resistant organism (MDRO) colonization (Barraclough et al. 2009). In a 2009 prospective surveillance study of patient and environmental colonization with MRSA, 50% of hospitalized subjects had nasal colonization with MRSA, while the remainder had either a history of MRSA or an ongoing infection (S. Chang et al. 2009). Skin and environmental contamination with MRSA was equivalent between the 2 groups, indicating that colonized patients can be transmitters of resistant organisms. Environmental contamination has been implicated in the transmission of vancomycin-resistant Enterococcus, Clostridium difficile and Acinetobacter baumannii (especially among injured US soldiers returning from the Middle East war theater) (Weintrob et al. 2010). In some regions, more than 61% of patients carry at least 2 resistant organisms, whereas 14% are colonized by 3 or more (O'Fallon et al. 2009).

The emergence of AMDR pathogens is accelerated by the misuse of antimicrobial drugs. France, Australia, the United States, Canada, Italy, and the United Kingdom have high rates of oral antimicrobial drug prescriptions, with a corresponding high rate of infections caused by AMDR pathogens (Baird 1997; Livermore and Pearson 2007; Naber 2009). Additional factors include: over-the-counter dispensing of antimicrobial drugs without professional controls; the use of low-potency drugs attributable to poor manufacture or counterfeiting; the availability of drugs from roadside stalls and hawkers who have little or no knowledge of dosage regimens; and, finally, through purchases over the Internet (Smith and Coast 2002, Mainous et al. 2009). A 2009 report draws attention to the availability of antibiotics “over the counter” in some countries, despite regulations requiring a physician prescription (Llor and Cots 2009).
Patient attitudes and expectations play an important role in the use of antimicrobial drugs (Holmberg et al. 1987; Levy 1993). Demand for and use of antibiotic drugs is second only to that of analgesics (Standing Medical Advisory Committee Sub-group on Antimicrobial Resistance 1998). Worldwide, 20% of prescribed antibiotics are used in hospitals, whereas 80% are used in the community. In the primary care (community) setting, patients receiving antibiotic drugs for respiratory or urinary tract infections can develop resistance to the antibiotic prescribed. This resistance can persist up to 12 months after treatment, thereby increasing carriage of resistant organisms in community settings (Costelloe et al. 2010).

Believing that an antibiotic will provide a quicker recovery, patients and families expect and frequently demand a prescription from their physician (Mangione-Smith et al. 2001). There is a limited awareness by patients and their families that inappropriate use of antibiotics increases patients’ risk for developing a resistant infection. Some physicians, in order to preserve a comfortable relationship with their patients, may not wish to challenge these expectations and may prescribe an antimicrobial drug without identifying the pathogen or its susceptibility to the drug (Laxminarayan 2001; Powers 2009).

The global market of counterfeit drugs also contributes to the rise and spread of AMDR (Targett 1991; Schlagenhauf-Lawlor 2008). Specifically, if the counterfeit drug has sub-potent levels of the active ingredient, resistance may be significant (Shakoor et al. 1997). A WHO survey of 20 countries found that 78% of counterfeit drug sales occurred in developing countries (Wondemagegnehu 1999). As much as of half of the antimalarial medications in Southeast Asia may be counterfeit (Dondorp et al. 2004), with antibiotics being from 8 to 10 times and antiparasite drugs 2 to 3 times more frequently adulterated than any other medications (Kelesidis et al. 2007; ten Ham 2003).

Travel and the use of antibiotic drugs in agriculture, such as in animal feed for growth promotion purposes, continues to contribute to the development of resistance (Tenover and McGowan 1996; Lei et al. 2010). The amount of non-therapeutic use of antibiotics in swine production can select for antibiotic resistance in commensal and pathogenic bacteria in swine (Rosengren et al. 2008). Retail pork products, as well as surface and groundwater contaminated with swine waste, have been shown to be sources of human exposure to antibiotic-resistant bacteria (Chapin et al. 2005; Akwar et al. 2008). High-level MDR Enterococcus, coagulase-negative staphylococci, and Viridans streptococci strains were detected in the air of a concentrated swine-feeding operation (Chapin et al. 2005). These findings suggest that the inhalation of air...
from these facilities could serve as a pathway for the transfer of MDR bacterial pathogens from swine to humans.

2. Incidence and Prevalence of Microbial Resistance

In 2008, the US National Institute of Allergy and Infectious Diseases published a list of pathogens resistant to antibiotics and antivirals:

- Staphylococci, *Enterococcus faecium*, *Escherichia coli*
- *Klebsiella pneumoniae*, tuberculosis
- Several influenza strains
- Food-borne pathogens such as *Salmonella*, *Shigella*, and *Campylobacter jejuni*
- Sexually transmitted organisms such as *Neisseria gonorrhea*, HIV/AIDS, *Candida albicans*, and other fungal infections
- Parasites such as *Plasmodium falciparum*
- *P aeruginosa* and *A baumannii* (in returning wounded US servicemen from the Middle East and Afghanistan; probably acquired in Europe-based health-care facilities)
- *C difficile*

3. Major AMDR Pathogens

a. *Acinetobacter baumannii* (Plate 1)

*Acinetobacter baumannii* (*A. baumannii*) is an aerobic encapsulated, non-fermenting gram-negative bacterium resistant to most antibiotics. It can be found in the soil and water. There are more than 29 species of *Acinetobacter* and *A baumannii* is responsible for more than 80% of infections. Recently *A baumannii* became a nosocomial infection and the organism has been reported to survive for months on high-touch surfaces such as patients’ beds, clothing, room doorknobs, call buttons, and bathrooms. It has also been implicated in nosocomial outbreaks of septicemia, ventilator-acquired pneumonia (VAP), urinary tract and wound infections. About 20% to 40% of cases are attributed to cross infections by the hands of HCWs (Weber et al. 2010). *A baumannii* is an opportunistic infection. There have been many reports of *A baumannii* infections among American soldiers wounded in Iraq, earning it the nickname "Iraqibacter." Multidrug-resistant *Acinetobacter* is not a new phenomenon; it has always been inherently resistant to multiple antibiotics. The illness can cause severe pneumonia and infections of the urinary tract, bloodstream, and other body organs (Aquirre-Avalos et al. 2010). Decreased susceptibility to tigecycline, following treatment, has been recently reported.

b. *Clostridium difficile* (Plate 2)

*Clostridium difficile* (*C. diff.*) is a commensal human intestine organism in about 2 to 3 % of the population. It is a major cause of hospital-acquired infectious diarrhea and is associated with increased healthcare costs, prolonged hospitalizations, and higher patient morbidity. Both *C. diff.* toxins A and B play a role in the pathogenesis of the infection (Ananthankrishnan 2011). *C. diff.* antibiotic therapy has been implicated in the development
of enterocolitis, which can be fulminant and result in death. It is an anaerobic spore-forming bacillus which can produce a pseudomembranous colitis. Previous antimicrobial use, especially clindamycin or ciprofloxacin, is a risk factor for development of C. diff-associated diarrhea (CDAD) by disrupting normal bowel flora and promoting C. diff. overgrowth (Centers for Disease Control and Prevention 2008). Historically, CDAD has been associated with hospitalized elderly patients or long-term care facility (LTCF) residents. Since 2000, a strain of C diff has been identified as a North American pulsed-field type 1 (NAP1). This strain produces an extra toxin (binary toxin), and is the cause of increased morbidity and mortality among hospitalized patients (Centers for Disease Control and Prevention 2008). In the United States, C diff infections among hospitalized children are also on the rise (Nylund et al. 2011). Patients with vancomycin-resistant C diff infections, especially with diarrhea, have been found to have significant levels of environmental contamination (Sethi et al. 2009). Rifampin-resistant C. diff. has been found in a US hospital with 37% of recovered isolates and 82% of clone isolates resistant (Curry et al. 2009). Relapse following treatment with metronidazole or vancomycin occurs in 20% of first-time cases, increasing to 40% to 60% in subsequent recurrences (Kelly and LaMont 2008). MDR C diff strains have also been identified in hospital and chronic care facility settings. Guidelines for handling outbreaks of C diff in a healthcare setting include:

- Visitors and HCWs should be instructed to wash their hands with soap (or antimicrobial soap) and water after being in contact with or caring for patients with C diff infection (CDI).
- For contact with all body substances, gloves are recommended.
- Disposable thermometers are preferable to electronic thermometers. In areas of increased CDI transmission, chlorine-containing cleaning agents or other sporocidal agents (such as paracetic acid) should be used to disinfect surfaces (Oie et al. 2011).
- Antimicrobial usage should be monitored, and stewardship efforts should especially focus on antimicrobial drugs associated with a high risk for CDI, especially clindamycin, cephalosporins, and fluoroquinolones.
- Treatment of asymptomatic carriers is not recommend.

Use of probiotics to treat C. diff. carriers and CDI patients remains controversial (Hsu et al. 2010).

c. Escherichia coli (Plate 3)

Escherichia coli (E. coli) is a diverse group of bacteria and only a few strains cause disease by making a toxin called Shiga toxin. The toxin-producing bacteria are known as “Shiga toxin-producing” E coli or STEC. The most commonly identified STEC in North America is E coli O157:H7. Other serogroups can also produce infections.

Fewer than half of all pediatric urinary tract infections are susceptible to commonly prescribed antibiotics (Gaspari et al. 2006). The prevalence of E coli resistant to amoxicillin with ESBLs responsible for the community-acquired urinary tract infections (CA-UTIs) in Phnom-Penh, Cambodia, was reported to be in excess of 82.3% (Ruppé et al. 2009). CA-UTIs were also resistant to cotrimoxazole (75.3%), ciprofloxacin (67.7%), gentamic(42.5%),
and third-generation cephalosporins (37.7%). MDR strains resistant to fluoroquinolones and aminoglycosides have emerged recently (DuPont et al. 2009). In the United States, resistance is also on the rise. A large study of children treated for UTIs found that long-term use of antibiotics appeared to reduce the risk of relapse, but the benefit was small and must be weighed against the development of resistance (Williams and Craig 2011). More than 48% of self-serve beverage and soft drink dispensing fountains have been found to be contaminated by coliform bacteria, including E coli (White et al. 2010). NDM-1, a gene responsible for AMDR, has been isolated from the E coli residing in drinking fountains and soil water in India. This gene can spread to other bacteria and confer resistance to the last-resort antibiotics called carbapenems. NADM-1 has been already found in France and in some UK hospitals, as well as among patients undergoing treatment in India and those suffering from “traveler’s diarrhea” (Diene et al. 2011; Walsh et al. 2011).

In May 2011, STEC O104:H4 was reported among several travelers returning to the United States from Germany. The Germany-based Robert Koch Institute reported several hundred cases of hemolytic uremic syndrome and deaths due to the STEC O104:H4, presumed to originate from the ingestion of raw vegetables (Robert Koch Institute 2011; Centers for Disease Control and Prevention 2011).

d. HIV/AIDS (Plate 9) and Sexually Transmitted Infection (STI)

HIV/AIDS, commonly referred to as the “silent epidemic,” has reached pandemic proportions. In 2009, 33.3 million people were estimated to be living with HIV/AIDS (World Health Organization and UNAIDS 2010). Sub-Saharan Africa remains the most affected region. More than two-thirds (68%) of all HIV-positive patients live in this region, making up more than three-quarters (76%) of all related deaths. HIV/AIDS alone or in combination with other STIs contributes to the emergence of AMDR (Savona 2010) and are more likely to seek treatments and use antibiotic preparations.

<table>
<thead>
<tr>
<th>Region</th>
<th>Adults &amp; children living with HIV/AIDS</th>
<th>Adults &amp; children newly infected</th>
<th>Adult prevalence*</th>
<th>AIDS-related deaths in adults &amp; children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>22.5 million</td>
<td>1.8 million</td>
<td>5.0%</td>
<td>1.3 million</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>460,000</td>
<td>75,000</td>
<td>0.2%</td>
<td>24,000</td>
</tr>
<tr>
<td>South and South-East Asia</td>
<td>4.1 million</td>
<td>270,000</td>
<td>0.3%</td>
<td>260,000</td>
</tr>
<tr>
<td>East Asia</td>
<td>770,000</td>
<td>82,000</td>
<td>&lt;0.1%</td>
<td>36,000</td>
</tr>
<tr>
<td>Oceania</td>
<td>57,000</td>
<td>4500</td>
<td>0.3%</td>
<td>1400</td>
</tr>
<tr>
<td>Central &amp; South America</td>
<td>1.4 million</td>
<td>92,000</td>
<td>0.5%</td>
<td>58,000</td>
</tr>
<tr>
<td>Caribbean</td>
<td>240,000</td>
<td>17,000</td>
<td>1.0%</td>
<td>12,000</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>1.4 million</td>
<td>130,000</td>
<td>0.8%</td>
<td>76,000</td>
</tr>
<tr>
<td>North America</td>
<td>1.5 million</td>
<td>70,000</td>
<td>0.5%</td>
<td>26,000</td>
</tr>
<tr>
<td>Western &amp; Central Europe</td>
<td>820,000</td>
<td>31,000</td>
<td>0.2%</td>
<td>8500</td>
</tr>
<tr>
<td>Global Total</td>
<td>33.3 million</td>
<td>2.6 million</td>
<td>0.8%</td>
<td>1.8 million</td>
</tr>
</tbody>
</table>

*Proportion of adults aged 15 to 49 years who are living with HIV/AIDS. (Source UNAIDS 2010)
Southern Africa accounts for 35% of all people living with HIV, with almost one-third (32%) of all new HIV infections and AIDS deaths. In contrast with other regions, the majority of people living with HIV in sub-Saharan Africa (61%) are women. Infections with HIV in Ugandan infants despite nevirapine prophylaxis correlated with the length of the treatment regimen (Church et al. 2008). In Cameroon, more than 90% of patients with HIV resistance had strains that were also resistant to nevirapine-efavirenz and lamivudine-emtricitabine (Kouanfack et al. 2009). The association of HIV/AIDS and extensive drug resistance results in high mortality (Gandhi et al. 2006).

In North America, the prevalence of transmitted resistance to antiretroviral drugs has been estimated to be between 1% and 11% among newly infected patients (Little et al. 2002). Overall prevalence of HIV strains resistant to 1 or more drugs is on the rise (Scott et al. 2004), especially in smaller clinical centers.

In Europe, 1 in 10 antiretroviral-naive patients carried viruses with more than 1 drug-resistance mutation. Newly infected patients harbored resistant variants more often than did chronically infected patients (13.5% vs. 8.7%, respectively). Non–subtype B viruses (30%) carried resistance mutations less frequently than did subtype B viruses (4.8% vs. 12.9%, respectively). Baseline resistance increased over time in newly diagnosed cases of non–subtype B infection—from 2.0% in 1996–1998 to 8.2% in 2000–2001 (Wensing et al. 2005).

Also, 76% of all viremic patients are resistant to 1 or more antiviral drugs, with the odds of resistance increasing in the presence of a history of antiretroviral drug use, advanced HIV disease, higher plasma HIV viral load, and lowest CD4 cell counts (Richman et al. 2004). Between 1987 and 2003, 10.3% of seroconverting patients carried a drug-resistant primary human immunodeficiency type 1 (HIV-1) variant (Masquelier et al. 2005). Of those, 9.1% showed resistance mutations to only 1 class of antiretroviral drugs, 0.5% to 2 classes, and 0.7% to 3 classes of antiretroviral therapy.

e. **Influenza virus (Plate 10)**

Influenza A viruses—including the 2 subtypes 2009 (H1N1) and A (H3N2)—and influenza B viruses are currently circulating worldwide. The pandemic H1N1 is becoming the predominant strain in both hemispheres with an increased activity in the Southeast Asia (Nicogossian et al. 2010).

It is estimated that annually influenza viruses are responsible for infecting 1 billion individuals worldwide, accounting for 300,000 to 500,000 deaths. The economic burden in the US alone is a staggering US $1 to 3 billion, annually attributed to related absenteeism, secondary respiratory bacterial infections, hospitalizations, and use of scarce and costly medical resources.

Primary protective measures consist of a combination of vaccinations, environmental and physical hygiene practices, and, in appropriate settings, the use of antiviral drugs to either prevent or shorten the course of the infection. Recently, however, resistance to antiviral drugs
was reported (Glickman et al. 2010; Memoli et al. 2010; Bright et al. 2006; Gooskens et al. 2009).

In the United States, the CDC has issued interim recommendations and updates for the prevention of the development of resistance to antiviral medications (Centers for Disease Control and Prevention 2009; Centers for Disease Control and Prevention 2010). Recently, influenza has been implicated as a contributing factor in the development of AMDR and fatal MRSA pneumonia (Creel et al. 2009; Pedal and Nolte 2010).

f. Malaria (Plate 8)

In tropical regions, malaria coexists with tuberculosis and HIV/AIDS infections. The dual infection of HIV and malaria contributes to the spread of both diseases in sub-Saharan African (Abu-Raddad et al. 2006) and could result in nosocomial infections and AMDR. A decade ago, the US National Intelligence Council reported that first-line drug treatment for malaria was no longer effective in 80 of the 92 countries where the disease is a major health problem (Gordon and Gannon 2000). The resistance to chloroquine is so widespread that it is currently not recommended as a therapeutic intervention (Adjuik et al. 2004).

Malaria is a threat to half of the world's population and the cause of death of more than 1 million people annually. Malaria is caused by 4 different protozoan intracellular parasite species transmitted primarily by the bite of the female Anopheles mosquito.

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*

An increase in human infections with *Plasmodium knowlesi* is being observed in Southeast Asia, probably due to human activities and encroachment into the primate habitat (Lee et al. 2011). Malaria is endemic in parts of Asia, Africa, Central and South America, Oceania, and some Caribbean islands. Malaria infections coexist with HIV/AIDS and tuberculosis in several equatorial countries in the African continent and contribute to the excess burden of morbidity and mortality in the area.

According to the WHO, resistance of *P falciparum* to chloroquine, the cheapest and the most prescribed antimalarial drug, is spreading throughout the endemic countries. Resistance to the combination of sulfadoxine-pyrimethamine that is present in South America and in Southeast Asia is now emerging in East Africa (World Health Organization 2011).

Resistance develops most rapidly with sub-therapeutic concentrations of antimalarial drugs. Emergence of resistance to antimalarial drugs is associated with:

- Greater exposure
- Use of single, shorter-action conventional drugs first
• Use of primary antimalarial drugs for non-malarial indications in high-risk areas (e.g., chloroquine for rheumatoid arthritis in a malarial endemic area)
• Poor compliance with therapy and other preventive measures, such as bed netting at night
• Failure of monitoring for resistance to prevent spread
• Lack of clear policy and protocols for use of newer antimalarial drugs

WHO recommends treating resistant malaria using a combination regimen which includes azithromycin, an antibiotic with weak antimalarial properties. No significant benefit for this practice was identified using the Cochrane Database (van Eijk and Terlouw 2011). Isolated cases of resistance to artemisinin were recently reported and a research into antimalarial vaccines is in progress (Breman 2009; Pongtavornpinyo et al. 2008).

g. Methicillin-Resistant Staphylococcus aureus (MRSA Plate 4)

The first cases of hospital-acquired infections were reported in the U.K. in 1961 and in the U.S.A. in 1968 (HA-MRSA). The first community acquired case (CA-MRSA) was reported in 1990 in U.S.A. (Huang et al. 2006). Approximately 32% (89.4 million persons) and 0.8% (2.3 million persons) of the US population are colonized with Staphylococcus aureus (S. aureus) and MRSA respectively (Kuehnert et al. 2006). The number of healthcare-associated staphylococcal infections due to MRSA is on the rise—from 2% of S. aureus infections in US intensive care units (ICUs) in 1974 to 22% in 1995 and 64% in 2004 (Klevens et al. 2006). The rate of MRSA has been found to be as high as 59.2% in some hospital wards (Naber 2009). There are an estimated 292,000 hospitalizations due to S. aureus infections annually in US (Kuehnert et al. 2005). Of these, approximately 126,000 hospitalizations are related to MRSA. Nosocomial MRSA infections with reduced susceptibility to vancomycin are found to be more virulent than other strains and are a major contributor to in-hospital morbidity and mortality (The Medical Letter 2009; Peleg et al. 2009; Xiong et al. 2009). Presentation with soft tissue infections (cSSTI) is common and usually responds to vancomycin therapy. Linezolid is more effective in achieving microbial eradication, however it carries the risks of thrombocytopenia, nausea and diarrhea (Bounthavong and Hsu 2010).

In 2007, rates of MRSA bacteremia ranged from 0.8% in Denmark to 52.4% in Malta (Naber 2009). In Belgium, the MRSA bacteremia–associated mortality among critically ill patients was 23.4% compared with 1.3% for methicillin-susceptible S aureus (MSSA) strains (Blot et al. 2002). The estimated risk of mortality associated with MRSA bacteremia compared with MSSA bacteremia is 1.93 (Cosgrove et al. 2003) with a relative risk of 2.12 (Whitby et al. 2001).

In Europe, S. aureus, including MRSA, are the leading isolates in skin and soft tissue infections (SSTI), with a range of 10% to 51% (Kollef et al. 2008). A study of 9 European country hospitals revealed that 28% of patients with bacteremia received less than optimal therapy, resulting in higher morbidity and mortality rates (Ammerlaan et al. 2009). A study of MRSA and MSSA from 450 European hospitals in 26 different countries showed that strains of MRSA tend to cluster in individual healthcare facilities and also within regional borders. This suggests the spread of MRSA through multiple admissions to different care facilities by
infected patients (Grundmann et al. 2010). Spatial mapping and geographic information could help identify the patterns of spread and help in the control of the MRSA transmission (Lowy 2010).

**Figure 1. Prevalence (%) of MRSA Among EU Patients Presenting with Bacteremia (2009)**

![Prevalence (%) of MRSA Among EU Patients Presenting with Bacteremia (2009)](image)


It is estimated that more than 20% of all HCWs are carriers of MRSA (Chan et al. 2009). Of these, 88% are nasal carriers with the remainder being throat carriers. Colonization with MRSA can persist for to 2 years or longer (Robicsek et al. 2009). Aerosols containing MRSA are commonly found in many residential homes (Gandara et al. 2006). In 2011 the Infectious Diseases Society of America (IDSA) issued guidelines for prevention and treatment of MRSA (Liu et al. 2011).

MRSA is a significant cause of skin and soft tissue infections (SSTI) outside of the hospital, too (Johnson et al. 2009). Community-acquired MRSA (CA-MRSA) strains have increased dramatically during the last 2 decades (Klevens et al. 2007). It is estimated that 13.7% of invasive MRSA infections are community acquired (Klevens et al. 2007). Between 6% and 21.7% of end-stage renal disease patients are colonized with MRSA (Wang et al. 2009; Johnson et al. 2009), and the prevalence of CA-MRSA colonization increases with the number of years that a patient is on dialysis (Lin et al. 2009). Available evidence suggests that CA-MRSA pneumonia continues to be associated with seasonal influenza virus, including the 2009 A (H1N1) pandemic (Murray et al. 2010). An increased cross colonization with MRSA has been reported between mothers and newborns, peaking at 20.9% in 2 months old infants (Jimenez-Truque 2012). The virulent MRSA (USA300-0114) has now reached international epidemic proportions in- and outside –health care facilities, causing life-threatening diseases such as necrotizing pneumonia, osteomyelitis and arthritis (Nimmo 2012). Risk factors for CA-MRSA include:
• Group living and activities that increase the frequency of personal physical contact
• Poor personal hygiene practices and inadequate hand washing.
• Scarce resources or inappropriate hygiene practices among group living (such as dormitories, military barracks, prisons, and locker rooms) and activity settings (such as physical impact sports)
• Insufficient local surveillance system and laboratory diagnostic capacity
• Inappropriate use of antibiotics

MRSA ventilator acquired pneumonia (VAP) has spread globally and is associated with poorer treatment outcomes (Sandiumenge 2012, Uhlemann et al 2012). Beyond the conventional designation of nosocomial and community strains, novel MRSA strains have now been identified worldwide in domesticated animals (particularly swine), which are also capable of transmitting infections to humans (Smith 2011, ). A MRSA mecA (LGA251) was recently isolated in United Kingdom and Denmark laboratories that require special diagnostic testing for detection (García-Álvarez et al. 2011).

h. *Streptococcus pneumoniae* (Plate 5)

This organism causes more than 800,000 deaths among children younger than 5 years (Saha et al. 2009). Although availability of effective pneumococcal vaccines reduces the prevalence of invasive disease in vaccinated children and those they contact in the home (Hicks et al. 2007; Hicks et al. 2011), recent evidence suggests an upward trend in invasive infections by serotypes that are not covered by available vaccines (Rosen et al. 2011). From 2001 to 2004, 824 consecutive *S pneumoniae* isolates from all Kuwait teaching hospitals and primary-care centers showed 63% resistance to penicillin (55% were of intermediate resistance and 8% were of full resistance) (Mokaddas et al. 2007). *S pneumoniae* isolates collected during 2000 to 2004 in the United States showed 29.3%, 21.2%, 0.9%, and 0.02% of isolates to be resistant to erythromycin, penicillin, levofloxacin, and telithromycin, respectively. The proportion of isolates exhibiting multidrug resistance remained stable at ~30% during the 4-year study period (Jenkins et al. 2008). The antimicrobial susceptibility of *S pneumoniae* isolates from hospitalized children in Bangladesh revealed complete resistance to chloramphenicol and cotrimoxazole in 6% and 32% of patients, respectively (Saha et al. 2009).

i. *Mycobacterium tuberculosis*, MDR- and XMDR-TB (Plate 6)

Globally MDR-TB and extensively-drug resistant (XDR-TB) tuberculosis are becoming a critical problem (LoBue 2009). The global proportion of resistance among all tuberculosis cases was estimated at 4.8% in 2009. WHO 2010 global estimates for MDR-TB was 0.65 million out of a total of 12 million prevalent cases or 5, 4% of all TB cases, ranging from 3% incidence in newly diagnosed cases and up to 20% previously treated patients. China, India, and the Russian Federation combined have the highest number of MDR-TB cases: China and India account for approximately 50% of the global burden and the Russian Federation accounts for an additional 7% (Wright and Zignol 2008). The population-weighted mean of MDR-TB among all TB cases is 5.3%, but ranges from 0% in some western European countries to more than 35% in some countries of the former Soviet Union (Wright and Zignol
2008). The highest proportions of TB cases are resistant to isoniazid and streptomycin, followed by rifampicin and ethambutol (Wright and Zignol 2008). Isolated resistance to fluoroquinolones has also been documented (Long et al. 2009). Increased incidence of pulmonary cavities is associated with MDR-TB (Aguiar et al. 2009). Drug-resistant TB disproportionately affects young adults (Palacios 2009); previously failed treatment, recent relapse, and homelessness are all associated with MDR- and XDR-TB. Recently clusters of MDR-TB patients were found in the Russian Federation and the Republic of Moldova. Lack of well documented prevalence and incidence data from India and some African countries precludes reliable estimates of overall global trends (Zignol et al. 2012). WHO treatment guidelines published in 2011 recommend drug sensitivity testing (DST) in all TB MDR- and XMDR-TB patients before initiating treatments. In some areas of the Russian Federation and Spain, the number of MDR-TB cases did stabilize and even dropped, indicating the possibility of successful treatment of such cases (Ramirez Lapausa et al. 2012).

j. **Vancomycin-Resistant Enterococcus** (Plate 7)

Enterococci have been identified as the third most frequent cause of nosocomial bacteremia (Boucher et al. 2009). *E. faecium* is now the major contributor to AMDR in surgical wounds and urinary tract infections. Penicillin, ampicillin, piperacillin, imipenem, and vancomycin are among the few antibiotics that show consistent inhibitory, but not bactericidal, activity against *Enterococcus faecalis* (Huycke et al. 1998). The spread of antibiotic resistance among enterococci, with some microorganisms becoming resistant to all standard therapies, highlights both the vulnerability of available antibiotics as well as the looming prospect of a "postantibiotic era" with no effective drugs to fight the infections (Huycke et al. 1998). Vancomycin resistance is independently associated with increased mortality among patients with enterococcal bloodstream infection (Diaz-Granados et al. 2005).
SECTION THREE: Control and Prevention of AMDR

Specific learning objective: Recognize and apply the principles of antibiotic drug stewardship and infection control

1. Implications of Microbial Resistance

Quantifying the burden of AMDR is a challenge. Deaths from acute respiratory infections, diarrheal diseases, measles, AIDS, malaria, and tuberculosis account for more than 85% of the mortality from infections worldwide. Rising resistance to first-line drugs in most of the pathogens that cause these diseases ranges from zero to almost 100% (Cassell and Mekalanos 2001). It has been suggested that the use of quinine versus chloroquine as first-line therapy in 150 million patients with malaria would increase spending by as much as US $100 million (Phillips and Phillips-Howard 1996). Costs associated with patient fear of infection and behavior change in populations living in high-prevalence areas also contribute to the overall morbidity, mortality, and cost associated with AMDR pathogens (Philipson and Posner 1993).

Prolonged illness and hospitalization are costly, and the use of expensive first-line antibiotics can further increase cost, making newer antibiotics unaffordable for many governments and patients, especially in developing countries (World Health Organization 2005; Naber 2009). In 1995, the US Congressional Office of Technology Assessment (COTA) estimated that antibiotic resistance costs the United States US $1.3 billion annually (US Congress, Office of Technology Assessment 1995). An Institute of Medicine report estimated that the total cost to society of antimicrobial resistance in the United States was at least US $4 to 5 billion annually (Harrison and Lederberg 1998). Reliable estimates worldwide are not available.

2. Infections and Chronic Diseases

The belief that many chronic diseases are infectious in origin goes back to the mid-19th century, when cancer was studied as a possible infectious disease (Institute of Medicine 2002). In the last 15 years, several chronic disorders have been linked to a virus or microorganism, such as peptic ulcer disease with *Helicobacter pylori*, human papilloma viruses and cervical cancer, Whipple's disease with *Tropheryma whippeli*, Lyme ar-
thritis and neuroborreliosis with *Borrelia burgdorferi*, hepatitis viruses with liver cancer, colon cancer with *Streptococcus bovis*, and HIV with Kaposi sarcoma (see Appendix C). It has been suggested that the incidence of infection-related cancers is underestimated (de Martel and Franceschi 2009; Yeung et al. 2011). Thus, microorganisms that develop resistance to antibiotic or antiviral drugs might contribute to the burden of increasing incidence of chronic and debilitating diseases.

3. **Policy and Best Practices** (also refer to AMDR Guidelines, Standards and Policy Reports on page 37)

It is essential that governments, professional organizations, and individual practitioners seriously contemplate policies to contain the advance of resistant pathogens (Garrett 2001; Small and Fujiwara 2001; Podolsky 2005). Historical examples of successful approaches to the eradication or control of infectious diseases include improved basic hygiene, vaccination, and environmental practices combined with sustained effective educational and outreach campaigns. Today, strategies to lower microbial resistance are also linked to guiding the appropriate use of antibiotics and minimizing environmental contamination with AMDR pathogens (Dellit et al. 2007; Guidos 2011; Rybak et al. 2009; Schlaes et al. 1997; Siegel et al. 2006). Strategies can target either the prevention of the emergence of new resistance, or interruption of the transmission of existing resistance. Pursuing both approaches usually provides the best results.

The core elements of all major national, regional, and global strategies consist of (Smith and Coast 2002):

- Surveillance programs to monitor pathogen prevalence and susceptibility to antibiotics
- Tracking of antimicrobial drug consumption
- Incentives to encourage research and development of new antimicrobial preparations
- Application of appropriate alternative treatments
- Adoption of policies promoting antibiotic drug stewardship

Successful implementation of public health policies and practices is driven through the combined influences of formal legislation, practice regulations, professional standards and guidelines, and informal procedures and customs. Data from evidence-based literature serve as a starting point for developing healthcare policy, further molded by social (cultural or religious) beliefs, applicable models for delivering healthcare, and political perspectives.

a. **Antimicrobial Drug Stewardship**

The physician’s role and responsibility for the management of antimicrobial drug resources is substantial (Arnold and Straus 2005). The goal of any clinical intervention with an antimicrobial agent is concisely expressed by Tenover as “the prudent use of the appropriate drug at the appropriate dose and for the appropriate duration” (Tenover 2006). Thus, the primary objective is the “eradication of the infection while minimizing side effects” (Paskovaty et al. 2005).
The Society for Health Care Epidemiology of America together with the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society issued a policy statement on antimicrobial stewardship (Fishman et al. 2012). The policy emphasis is on optimization of antimicrobial use to achieve the best clinical outcomes, minimizing adverse events and limit selective pressures that drive the emergence of AMDR. The impact will result in decreased morbidity, mortality, better surveillance, treatment and cost reduction.

According to a survey of hospital practitioners, barriers to establishing an antimicrobial stewardship program include (Pope et al. 2009):

1. Personnel shortages
2. Financial considerations
3. Other higher-priority initiatives
4. Opposition from physicians and prescribers
5. Resistance from the health care administration

From a resource perspective, critical barriers to achieving optimal infection management include; lack of timely laboratory diagnostic information and the availability of community or regional AMDR sensitivity information. In developing nations, access to effective agents may be limited. Community, regional, and global surveillance networks are also lacking.

The CDC Get Smart (launched in 2002) and WHO campaigns to prevent antimicrobial resistance provide evidence-based principles for judicious use of antimicrobial preparations and tools for implementation. The program emphasizes effective antimicrobial treatment of infections through:
- Use of narrow-spectrum agents
- Avoidance of excessive durations of therapy
- Restricting use of broad-spectrum or more potent antimicrobial preparations to treatment of serious infections when the pathogen is not known or when other effective agents are unavailable

Strategies for influencing antimicrobial prescribing patterns within healthcare facilities include education; formulary restriction; prior-approval programs, including preapproved indications; automatic stop orders; academic interventions to counteract pharmaceutical influences on prescribing patterns; antimicrobial cycling; computer-assisted management programs; and active efforts to remove redundant antimicrobial combinations. In a recent follow-up report from one region of Canada, implementation of a multipronged education strategy was associated with a significant reduction in antibiotic use and associated costs (Weiss et al. 2011).

A systematic review of controlled studies identified several successful practices. These include social marketing (e.g. consumer education), practice guidelines, authorization systems,
formulary restriction, and mandatory consultation, as well as peer review and feedback. It is also recommended that online systems providing clinical information, structured order entry, and decision support are promising strategies. These practice changes are best accomplished through an organizational, multidisciplinary, antimicrobial management program. These programs should also include the periodic feedback reviews of the effectiveness of the therapy and monitoring for possible development of AMDR (Behta et al. 2008).

Antimicrobial guidelines and treatment algorithms for infectious diseases may further aid rational use of antimicrobial preparations. When reliable data are available, local AMDR trends for infectious diseases should be considered when deciding upon inclusion of each antimicrobial (World Health Organization 2005; Liu et al. 2011). Use of biomarkers, such as procalcitonin and C-reactive protein (CRP), are currently being evaluated to guide the antibiotic therapy in intensive care sepsis patients to minimize the development of microbial resistance (Kibe et al. 2011).

b. Surveillance

Surveillance is a critically important component of any infection control program, allowing detection of newly emerging pathogens, monitoring epidemiologic trends, and measuring the effectiveness of interventions. Multiple MDRO surveillance strategies have been employed, ranging from surveillance of clinical microbiology laboratory results obtained as part of routine clinical care to use of active surveillance cultures (ASC) to detect asymptomatic colonization. In the United States, legislative mandates for the use of surveillance systems for infection control have started to be implemented at the state level (Weber et al. 2007), while several European countries have imposed aggressive national surveillance programs that have contributed to low MDR rates (Monnet and Kristinsson 2008).

The simplest form of MDRO surveillance is the monitoring of clinical microbiology isolates resulting from tests ordered as part of routine clinical care. This method is particularly useful to detect emergence of new MDROs within either individual healthcare or community-wide facilities. Some investigators have used clinical microbiology results to calculate the incidence of MDROs in specific populations or patient care locations (eg, new MDRO isolates/1000 patient days, new MDRO isolates/month). Such measures may be useful for monitoring MDRO trends and assessing the impact of prevention programs. Clinical cultures can also be used to identify targeted MDRO infections in certain patient populations or units. This strategy requires the monitoring of clinical circumstances surrounding a positive culture to
guish colonization from infection, but it can be particularly helpful in defining the clinical impact of MDROs within a facility. Many investigators have used molecular typing of selected isolates to confirm clonal transmission, enhancing understanding of MDRO transmission and the effect of interventions within their facility.

Another form of MDRO surveillance is the use of ASC to identify patients who are colonized with a targeted MDRO. This approach is based on the observation that, for some MDROs, detection of colonization may be delayed or missed completely if culture results obtained in the course of routine clinical care are the primary means of identifying colonized patients.

Use of geographic information combined with the genotyping of the microorganism(s) can help with the identification of the sequence of the source and transmission pathways of AMDR within and outside the healthcare setting (Harris et al. 2010).

c. Environmental Decontamination

The role of environmental reservoirs, such as surfaces and medical equipment, in the transmission of MDROs has been the subject of several reports. Monitoring for adherence to recommended environmental cleaning practices is an important determinant for success in controlling transmission of MDROs and other pathogens in the environment. The interior design of healthcare facilities is receiving increased attention in the prevention of transmission of AMDR microorganisms, especially MRSA. High-touch surfaces covered with copper alloys are being tested as potential countermeasures for AMDR, along with control of interior temperatures and humidity (Michels et al. 2009).

Increased pollution of effluent potable water (Lateef 2004; Naddeo et al. 2009) and antibiotic uses in agriculture (Marshall and Levy 2011) also contribute to AMDR spread. Extensive use of antibiotics in the food chain can contribute to the development of AMDR.

d. Infection Control

Prevention and control of infections caused by MDRO pathogens require knowledge of known critical infection pathways (Livermore 2003), elucidated by surveillance and coupled with application of appropriate contact and environmental controls, as well as antimicrobial stewardship principles for appropriate antibiotic use.

Since 1996, the CDC has recommended the use of standard and contact precautions for MDROs. Hand hygiene is an important component of this. There is a demonstrated temporal relationship between improved adherence to recommended hand hygiene practices and control of MDROs. In a recent article, Goldman emphasized that infections such as MRSA are transmitted primarily by the contaminated hands of healthcare providers who have touched a colonized patient or something in the patient's environment (Goldmann 2006). It is estimated that 30% to 40% of endemic institutional antibiotic resistance is caused by ineffective or absent hand washing (Jarvis 1994).
In the absence of antibiotic sensitivity data, a patient’s MDRO colonization status is frequently unknown. Therefore, standard precautions must be used in order to prevent transmission from potentially colonized patients. In situations where an MDRO outbreak has been detected, or for patients at high risk for MDRO colonization, more aggressive contact precautions should be implemented (Smith et al. 2008). Even in facilities that use contact precautions for patients with an identified MDRO, standard precautions play an important role in infection control (Cooper et al. 2004). Patients may remain colonized with MDROs for prolonged periods. Shedding of these organisms may be intermittent and surveillance cultures may fail to detect their presence. The duration of contact precautions following successful treatment of MDRO pathogen infections for patients who remain colonized at one or more body sites remains an unresolved issue.

e. Patient Education

Individuals need knowledge to make informed decisions about how to prevent infection and reduce transmission of infectious diseases through simple, cheap and effective measures. Such measures include prevention of:

- Diarrheal disease through hand washing, using safe water sources and containers, boiling unsafe water and using latrines
- Malaria through the use of bed nets impregnated with insecticide
- Sexually transmitted infections through the use of condoms
- HIV/AIDS and hepatitis B and C through the avoidance of injections (unless oral medicines cannot be used, in which case a sterile needle and syringe must be used)
- Benefits of vaccines to reduce morbidity and mortality

Information on preventive measures can be successfully introduced into school and adult health educational curriculum (World Health Organization 2005). Specifically, the fundamentals of AMDR can be included into biology classes and become part of regular occupational health information awareness programs. Educating prospective parents is an effective mode of communicating and teaching AMDR facts. Properly managed media campaigns targeting patient behavior can contribute to reducing the rate of inappropriate antibiotic use (Gonzales et al. 2008; Hemo et al. 2009)
4. Antibiotic Development Pipeline

Investment in drug research and production has reached a staggering US $1.2 billion over a 10- to 15-year period (Knowles 2010). The IDSA has as one of its policy foci the drying up of the pipeline of new antibiotics (Spellberg et al. 2004; Boucher et al. 2009). Pharmaceutical companies have found the antibiotics market to be more difficult than and not as profitable as that for drugs to treat chronic illness and lifestyle issues. Approximately 2 million people acquire bacterial infections in the United States and 90,000 die as a result. The IDSA notes that about 70% of those infections are resistant to at least 1 drug.

The FDA review and approval of new antibiotics has declined 56% during the last 20 years according to a 2004 IDSA assessment. In 2000, 1 in every 10,000 compounds that entered drug discovery was estimated to make it to market, with an average cost for development in excess of US $800 million. Given the high risks associated with new drug development, new financial incentives are needed to encourage the exploration for new therapeutic agents. Government and professional organizations can develop policies and allocated resources to maintain an adequate pipeline of antibiotics and vaccines targeting AMDR. The rate of the arrival to the US market of different antimicrobial drugs is shown in Figure 2. Some of the newer antibiotics, such as tigecycline, have been found to be no better than treatment with standard antimicrobial agents, carry a higher risk of clinical failure and patient mortality, and should not be used as a monotherapy regimen (Yahav et al. 2011; Tasina et al. 2011). Oritavancin, a potent semisynthetic lipoglycopeptide, might be available in 2013 for the treatment of serious skin and soft tissue infections caused by Gram positive pathogens. (Moellering and Ferraro 2012).

Please refer to Appendices A and B at the end of the Syllabus to view the classification of the antibiotic drugs and the top 8 most prescribed drugs, currently at risk of becoming ineffective due to AMDR.
5. Travel, Trade, Mass Gatherings and AMDR Global Spread

AMDR can “travel” with passengers. Increasing travel for business and pleasure facilitates this intra- and intercontinental transmission mechanism. For example, there has been a remarkable increase in the prevalence of penicillin-resistant *Streptococcus pneumoniae* (PRSP) isolates in Kuwait during the last 20 years (Mokaddas et al. 2007). Policies promoting concentration of human beings in dense living conditions are likely to exacerbate resistance and are socially and politically difficult to change (Livermore 2003).

Historical spread of infections such as plague, SARS, influenza and sexually transmitted diseases is well documented. The spread of AMDR pathogens is a more recent human made technological disaster (Moellering 2012, MacPhernson et al. 2009, Peirano et al. 2011). Each year tens of millions of individuals move by ground, air and maritime transports within countries and across international borders for vacation, business, migrations, religious or sporting events. The World Tourism Organization estimated over 980 million international arrivals in 2011, with over 300 million of religious pilgrimages. The *International Organization for Migration* estimates that the number of migrants has reached 3.1% of the world population. The migrant groups also include refugees, internally displaced individuals, trafficked illegal workers and adoptions (Hagleitner 2012). Mass religious events have raised health and medical concerns among the public health professionals (Tam 2012). Many of the AMDR pathogens were spread globally by patients and silent carriers. Major concerns are raised by the spread of XDTR tuberculosis totally resistant to all antibiotic drugs and malaria strains resistant to artemisinin (Zumla et al. 2012, Khamsiriwatchara et al. 2011). Medical tourism, travel and consumption of food products in high risk areas also contribute to the spread of AMDR pathogens, especially *E. coli* and *Salmonella species*. 
The International Health Regulations (IHR) of 1969, revised in 2005, is a legally binding international agreement designed to prevent the spread of infections. The 2005 regulations entered into effect in 2007. Implementation of the regulations, backed by an effective international infectious diseases surveillance network, availability and administration of vaccines for preventable infections and institution of physical health measures requires strict enforcement to protect the world from future pandemics threats. Health care providers should be cognizant of the IHR and their implications to tourism, trade and migration. Education of prospective travelers and consumers of processed foods should be actively pursued.
SECTION FOUR: Conclusions

Antimicrobial resistance recognizes no national boundaries. Unless antibiotic resistance is detected and contained, the world could be faced with diseases that once more will become untreatable (U.S. Centers for Disease Control and Prevention 2010). Development of resistant microorganisms is a concern whenever antimicrobial agents are used. Careless use of antibiotics, lack of adherence to prescribed treatment regimens, poor environmental hygiene, antibiotic use in agriculture, and contamination of the food supply chain further exacerbate the situation and accelerate the spread of resistance to antibiotics. The increase in high-risk populations, including immune-compromised patients, those undergoing invasive medical interventions, those with implanted medical devices, and patients with chronic debilitating diseases, has increased the problem. Food-producing animals are frequently given antibiotic drugs for therapeutic, disease prevention, or production reasons. However, these drugs can cause microbes to become resistant to antibiotic drugs used to treat human illness, ultimately making some human sicknesses harder to treat.

Increasing prevalence of multi-drug resistant bacterial pathogens specifically methicillin-resistant staphylococci (MRS), Staphylococcus aureus (MRSA) and Staphylococcus pseudintermedius (MRSP) as well as extended-spectrum beta-lactamases)-producing Enterobacteriaceae (ESBL) has been reported in companion animals (pets). This finding is also associated with a steady increase of nosocomial infection rates in veterinary clinics. These microorganisms exhibit the sequence types (ST), included ST254, ST8 and ST22 for MRSA and ST131, ST398, ST405, and ST648 for ESBL-producing E. coli. Such findings suggest additional pathways for the spread of antibacterial drugs resistance and infections (Wieler 2011).

The global increase in resistance to antimicrobial drugs, including the emergence of bacterial strains resistant to all available antibacterial agents, has created a public health problem of crisis proportions with significant economic and human implications. Increasing antimicrobial resistance presents a major threat to public health by reducing the effectiveness of antimicrobial agents, leading to increased morbidity, mortality, and healthcare expenditures. Salmonella species and other food-borne pathogens resistant to antimicrobial drugs continue to spread globally (Teuber 1999; Smith and Coast 2002). In 1995, the cost of containing an outbreak of infection caused by MRSA in a district general hospital in the United Kingdom was estimated to exceed US $560,000, while the annual healthcare cost associated with the treatment of resistant infections in the United States was estimated at more than US $4 billion in 2002, an amount recently revised to more than US $7 billion (Smith and Coast 2002). Antimicrobial resistance is a cause of professional, governmental, and public concern and has been classified as a national security risk in the United States (Smith and Coast 2002).

Globalization increases the vulnerability of all nations to imported diseases, and today infectious diseases travel faster and farther than ever before. During the 1990s, a resistant Pneumococcus spp first identified in Spain rapidly spread to Argentina, Brazil, Chile, Taiwan, Colombia, Malaysia, Mexico, the Philippines, Republic of Korea, South Africa, Thailand, United States, and Uruguay. No country acting on its own can adequately protect the health of its population against AMDR.
A potentially significant disparity between the problems and solutions associated with AMDR, healthcare institutions, and the regulatory and funding systems available to deal with them (U.S. Centers for Disease Control and Prevention 2010). Morbidity and mortality increases with delayed diagnosis and initiation of effective treatment (World Health Organization 2005).

Physicians in developing countries may have to use older antimicrobial drugs that are becoming increasingly ineffective, resulting in higher rates of treatment failure (Howard et al. 2003). Most developing countries lack drug susceptibility testing, a key tool to guide the delivery of an effective antimicrobial therapy. Countries of market economy should consider political and policy solutions such as redefining AMDR as a complex humanitarian crisis and provide appropriate tools and knowledge management to developing countries to handle this emerging global security threat.

Development of vaccines is essential to protect against infections and transmission of resistant organisms (Interagency Task Force on Antimicrobial Resistance 2001, Tranatlantic Task Force Report 2011). Further, vaccines are needed to prevent common bacterial infections, thus reducing antibacterial use. The development of novel vaccines occurs over a continuum, beginning with basic research, extensive clinical research, and trials and moving to product education, marketing, and distribution. An understanding at the molecular level of the mechanisms of resistance, policy, and political support for extensive evaluation of intervention strategies, as well as capital investment and product development capability, are required to successfully bring new vaccines into mass availability.

In 2009, the United States and the European Union signed a collaborative agreement to address the global AMDR health crisis. Although microbial resistance is a serious concern in countries of market economy, it is potentially devastating in developing countries. The global cost of AMDR morbidity and mortality now outstrips the total antibiotic market. All healthcare providers should have access to tools such as patient testing for AMDR, timely training to enhance knowledge, modification of attitudes, and improvement in the standards of clinical practices. Proactive polices and public education to fight AMDR should be implemented by all national Ministries of Health and Agriculture including restrictions for non-therapeutic uses and growth promoting antibiotic drugs.

In conclusion, preventing transmission of infections should be priority in all healthcare settings and include as a minimum:

- **Hand washing or alcohol-based rinses by staff between patients and before undertaking invasive procedures such as injections**
- **Use of barrier precautions, e.g., wearing gloves and gowns for procedures that might result in transmission of pathogens**
- **Adequate sterilization and disinfection of all supplies and equipment**
• Use of sterile techniques, together with protocols, for medical and nursing procedures capable of bridging skin or mucosal membrane integrity such as: bladder catheterization, administration of injections, insertion of intravenous cannulas, use of respirators, sterilization of equipment, and other surgical interventions

• Maintenance of appropriate disinfection and sanitary control of the hospital environment, including:
  – Adequate ventilation
  – Cleaning of wards, operating theater, laundry, and other objects used by patients
  – Provision of adequate water supply and sanitation
  – Safe food handling Safe disposal of infectious equipment, e.g., dirty needles, body fluids, and other suspected contaminated materials

• Isolation of infected patients from non-infected patients, e.g., separation of suspected and proven sputum-positive TB cases (particularly from HIV-positive patients)

• Visiting policies, such as preventing visitors with infections from visiting patients who may be immune-compromised (for example, patients with AIDS or leukemia or premature babies)

• Training of healthcare staff in appropriate sterile techniques and infection control procedures
Useful Web-based Resources (Pagani et al. 2009; U.S. Centers for Disease Control and Prevention 2010):

5. Ovid Medlines® — http://www.ovid.com/site/catalog/DataBase

AMDR Guidelines, Standards and Policy Reports


SECTION FIVE: Reference Materials

Bibliography

SECTION ONE: Introduction


SECTION TWO. Understanding AMDR: The Knowledge Base


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SECTION THREE: Control and Prevention of AMDR Best Practices


SECTION FOUR: Conclusions


APPENDICES
## Appendix A: Antibiotics and Anti-infective Agents by Category and Mechanism of Action

<table>
<thead>
<tr>
<th>Categories</th>
<th>Subcategories</th>
<th>Mode of Action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Bacteriostatic</td>
<td></td>
<td>Broad-spectrum activity against both gram-negative and gram-positive bacteria</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Bactericidal</td>
<td></td>
<td>Effective against many gram-negative and some gram-positive bacteria</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Bactericidal</td>
<td></td>
<td>Grouped in four broad classes: First generation: More gram-positive than gram-negative activity, Second generation: Enhanced gram-negative activity vs first-generation, Third generation: more gram-negative than gram-positive activity, Fourth generation: gram-positive and gram-negative activity</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Bacteriostatic</td>
<td></td>
<td>Broad-spectrum drugs effective against intracellular bacteria</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Bacteriostatic</td>
<td></td>
<td>Effective against aerobic gram-negative and select aerobic gram-positive bacteria</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Bactericidal</td>
<td></td>
<td>Effective against both gram-positive and gram-negative bacteria</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Bacteriostatic</td>
<td></td>
<td>Also called “erythromycins”; mostly active against gram-positive bacteria</td>
</tr>
<tr>
<td><strong>Antiviral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferes with life cycles</td>
<td>Prereceptor</td>
<td></td>
<td>Neutralizes virus before reaching receptor</td>
</tr>
<tr>
<td>Receptor</td>
<td></td>
<td></td>
<td>Inhibits viral attachment to target cell receptors. Primarily used for HIV infections</td>
</tr>
<tr>
<td>Transcription/reverse transcription</td>
<td></td>
<td></td>
<td>Inhibits viral replication in host cells. Divided in 2 groups: nucleoside and non-nucleoside analogs</td>
</tr>
<tr>
<td>Integrase</td>
<td></td>
<td></td>
<td>Inhibits integrase, a vital enzyme that integrates viral genome into host genome. Mainly used against retroviruses</td>
</tr>
<tr>
<td>Class</td>
<td>Example</td>
<td>Function</td>
<td>Action</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Protease</strong></td>
<td></td>
<td></td>
<td>Inhibits protease. Used in HIV infection</td>
</tr>
<tr>
<td><strong>Assembly</strong></td>
<td></td>
<td></td>
<td>Principally used as anti-influenza drug</td>
</tr>
<tr>
<td><strong>Release</strong></td>
<td></td>
<td></td>
<td>Principally used as anti-influenza drug</td>
</tr>
<tr>
<td><strong>Antifungal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td></td>
<td>Damages fungal cell membrane</td>
<td>Changes the fluidity of fungal cell membrane</td>
</tr>
<tr>
<td>Azoles</td>
<td>Impair fungal cell membrane</td>
<td></td>
<td>Inhibit enzyme cytochrome P450 14α-demethylase</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Inhibit cell wall synthesis</td>
<td></td>
<td>Their target has no mammalian counterpart</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Nucleic acid analog</td>
<td></td>
<td>Administered in combination with amphotericin B</td>
</tr>
</tbody>
</table>
## Appendix A (cont)

<table>
<thead>
<tr>
<th>CATEGORIES</th>
<th>SUBCATEGORIES</th>
<th>MODE of ACTION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiparasite</td>
<td>Aminoquinoline</td>
<td>Suppression or chemoprophylaxis of malaria</td>
<td>Treatment of uncomplicated or mild-to-moderate malaria</td>
</tr>
<tr>
<td></td>
<td>(Chloroquine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aminoquinoline</td>
<td>Generates reactive oxygen species or interferes with the electron transport chain in the parasite.</td>
<td>Treatment and prevention of malaria</td>
</tr>
<tr>
<td></td>
<td>(Primaquine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aminoquinoline</td>
<td>Form toxic complexes with free heme that damage membranes and interact with other plasmodia components</td>
<td>Treatment of acute malarial infections and prevention of malaria</td>
</tr>
<tr>
<td></td>
<td>(Melfoquine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abamectin</td>
<td>Stunning or killing worms</td>
<td>Nematocide</td>
</tr>
<tr>
<td></td>
<td>Benzimidazole</td>
<td>Stunning or killing worms</td>
<td>Effective against threadworms, roundworms, tapeworms, hookworms</td>
</tr>
<tr>
<td></td>
<td>(Albendazole)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meglumine antimoniate</td>
<td>Disrupts energy production/metabolism of microorganism</td>
<td></td>
</tr>
</tbody>
</table>
Appendix B

### Top 8 Most Prescribed Antibiotics (2008)

<table>
<thead>
<tr>
<th>Antibiotic Name (generic)</th>
<th>Select Target Pathogen(s)</th>
<th>Indications</th>
<th>Manufacturer</th>
<th>2008 Global Sales (USD Billion) (estimated)</th>
<th>USD Billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (erythromycin derivative)</td>
<td><em>Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Chlamydia pneumoniae, Mycoplasma pneumoniae</em></td>
<td>Upper and lower respiratory, urinary tract, middle ear, and soft tissue infections</td>
<td>Pfizer</td>
<td>1,280</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td><em>S pneumoniae, Streptococcus pyogenes, or Streptococcus agalactiae, Staphylococcus aureus, vancomycin-resistant enterococci, methicillin-resistant S aureus</em></td>
<td>Pneumonia (hospital acquired), soft tissue infections resistant to antibiotics</td>
<td>Pfizer</td>
<td>1,100</td>
<td>NA</td>
</tr>
<tr>
<td>Amoxicillin-clavulinate</td>
<td><em>H influenzae, M (Branhamella) catarrhalis,</em></td>
<td>Bacterial infections of the middle ear and upper respiratory tract</td>
<td>GlaxoSmithKline Pfizer (veterinary) NeoMedD Mascot</td>
<td>1,100</td>
<td>0.8</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td><em>H influenzae, Neisseria gonorrhoeae, Escherichia coli, pneumococci, streptococci, and certain strains of staphylococci</em></td>
<td>Upper and lower respiratory tract infections, middle ear infections in children, urinary tract and skin (cystic acne) infections, and gonorrhea</td>
<td>Multiple international manufacturers for nonproprietary preparations</td>
<td>1,100 (estimated)</td>
<td>0.5</td>
</tr>
<tr>
<td>Oseltamivir phosphate</td>
<td>Seasonal and pandemic influenza A virus</td>
<td>Uncomplicated influenza infections and prophylaxis in children &lt;1 year</td>
<td>Hoffman-La Roche/Gilead Chugai Pharma. Co</td>
<td>&gt;1.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Cephalexin</td>
<td><em>S pneumoniae, H influenzae, S aureus, S pyogenes, M catarrhalis</em></td>
<td>Urinary tract, skin, and soft tissue infections</td>
<td>Eli Lilly Ranbaxy</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td><em>E coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter species, coagulase-negative Staphylococcus species</em></td>
<td>Urinary tract, upper and lower respiratory tract infections</td>
<td>Multiple international pharmaceutical companies</td>
<td>0.5 (estimated)</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Appendix C

Pathogens Suspected in the Genesis of Chronic Disorders²-⁵

1. Chronic Disorders and Cancers

- **Hepatitis viruses (B and C)**
  - Hepatocellular carcinoma
- **Epstein-Barr Virus**
  - Lymphomas, nasopharyngeal carcinoma
- **Human papilloma virus 16, 18, 33, 39**
  - Cervical, anal, vulvar carcinoma; laryngeal papillomatosis
- **Human herpetic virus-8**
  - Kaposi's sarcoma, Castleman's disease
- **Human T-cell leukemia/lymphoma virus-I**
  - Adult T-cell leukemia
- **Helicobacter pylori**
  - Gastric carcinoma, lymphoma
- **Mycobacterium paratuberculosis**
  - Crohn’s disease
- **Troherima whippelii**
  - Whipple’s disease
- **Enterovirus**
  - Type 1 diabetes

2. Neurological Disorders

- **Treponema pallidum**
  - Tertiary syphilis (neurosyphilis)
- **Borellia burgdorferi**
  - Lyme disease complications
- **Prions**
  - Creutzfeldt-Jakob disease variants
- **HHV-6**
  - Multiple sclerosis
- **HTLV-I**
  - Myelopathy, tropical spastic paraparesis
- **Chlamydia pneumoniae**
  - Alzheimer's disease, multiple sclerosis
- **Bornavirus**
  - Autism
- **JC virus**
  - Progressive multifocal leukoencephalopathy
- **Herpes simplex virus, cytomegalovirus**
  - Mental impairment
- **Rubella**
  - Mental impairment
- **Toxoplasmosis**
  - Mental impairment, retinal lesions
- **Campylobacter jejuni**
  - Guillain-Barré syndrome
Glossary, Definitions and Abbreviations

1. **Antibiotics** are medications used to treat infections caused by a microorganism(s). They are either extracted from specific microorganisms to selectively inhibit the growth of another microorganism(s) or produced through synthetic manufacturing. Antibiotics specifically target microbes. Based on their mode of action, the antibiotics are divided into two major categories:
   - *Bactericidal*: kills bacteria
   - *Bacteriostatic*: impedes bacterial growth

2. **Antibiotic stewardship** refers to improved treatment outcomes and cost savings through appropriate use of antimicrobial agents. Major outcomes in patient care are lower iatrogenic side effects and AMDR incidence. To be effective, the stewardship program should include multicultural changes in healthcare practice, with contributions and participation by the veterinary, agriculture, and industry communities.

3. **Bacteria** are categorized as gram-positive and gram-negative based on their ability to retain the crystal violet dye. Many Gram-negative bacteria are pathogens and cause infections. Gram-positive bacteria are responsible for both nosocomial and community-acquired infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA).

4. **ESKAPE** refers to a group of microorganisms (*E. coli, Staph. aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa* and *Enterobacter* species) responsible for the spread of ventilator associated pneumonia (VAP).

5. **cSSTI** refers to a complicated skin and soft tissue infection.

6. **ESBL**, or extended spectrum β-lactamase, is an enzyme produced by some bacteria; it is capable of breaking down the cephalosporin class of antibiotics and increases AMDR.

7. **Iatrogenic events** are medical side effects (complications) resulting from a treatment and/or a surgical procedure.

8. **Immunocompromise** denotes illness- or treatment-induced loss of effective response by the host’s immune system.

9. **Invasiveness** is the ability of an infective agent to penetrate and spread in the body tissues and/or organs.

10. **Infectivity** can be described as the attack rate, usually estimated by the ratio of the number of individuals contracting the illness over the number of individual exposed.

11. **Isolates** are patients’ tissue or secretion samples collected for the laboratory identification and confirmation of a suspected microorganism(s) or other infective agent(s).

12. **MDRAB** refers to the multidrug-resistant *Acinetobacter baumanii* microorganism.
13. **Microorganisms** are microscopic life forms ubiquitous in the environment and on the human body. Most are harmless to humans and actually benefit many life processes. Occasionally and due to alterations in the host immunity system, they become invasive and cause infections (example: *Staphylococcus aureus*). Microorganisms include bacteria, protista, viruses, prions, fungi, and parasites.

14. **Microbe** is a nonspecific term used to describe a microorganism(s). Specific species are identified by their proper names in the Syllabus.

15. **Microbial resistance (MR)** is a generic term describing antimicrobial, antibiotic, antiviral, antifungal, antihelminthic, or antiparasitic drug resistance. MR defines the ability of a microorganism to withstand a drug that interferes with its life functions. This ability describes a diminished or failed response of an organism to the intended effectiveness of a chemical or biological agent. Resistance can involve only one drug or multiple antimicrobial drugs.

16. **MDR** is multidrug resistance or mega-drug resistance; it was recently documented in infections caused by HIV/AIDS, *Mycobacterium tuberculosis*, and *Acinetobacter* species.

17. **Nosocomial** refers to a hospital-acquired infection.

18. **Pantone-Valentine leukocidin** (PVL) and **gAMMA-hemolysin** (Hlg) are synergohymenotropic toxins produced by the *pvl* and *hlg* genes of *Staphylococcus aureus*.

19. **Pathogen** is a nonspecific term used to describe an infection-causing microorganism.

20. **Selective pressure** is the influence exerted by many factors, such as antibiotic drugs, resulting in the elimination of susceptible species and promoting the natural survival of another group of microorganisms.

21. **STI** describes a group of sexually transmitted infections caused by different microbes and viruses, such as *Neisseria gonorrhoea*, *Treponema pallidum* (syphilis), HIV/AIDS, *Chlamydia trachomatis*, human papillomavirus (HPV with types 16 and 18 implicated in the genesis of cancer), *Trichomonas vaginalis*, herpes simplex, and others, including hepatitis.

22. **Sentinel event** is an unexpected event in a healthcare setting involving death or serious physical or psychological injury, or the risk thereof, and not related to the patient’s illness (adapted from the *Joint Commission for Accreditation of Healthcare Organizations USA*).

23. **Spp.** Species

24. **Virulence** defines the ability of an infective agent to cause disease. The number of microorganisms required to trigger the infection is inversely correlated with the virulence level of the infective agent. Sometimes referred to as “extremely infective pathogen” capable of a rapid course and high morbidity and mortality.
Microbiology Plates

The images of pathogens used in this continuing professional education are from the Public Health Image Library (PHIL: www.phil.cdc.gov), Centers for Disease Control and Prevention (CDC) site. The image are in the public domain and are provided only for academic and educational purposes and should not be reproduced for any other uses without prior permission of the CDC (PHIL). All U.S. governments’ publication policies and restrictions apply to the images below.

Plate 1 Acinetobacter baumannii (ID#: 10095)

Plate 2 Clostridium difficile (ID#: 3876)
Plate 3 *Eschereshia coli* (ID#: 2156)

Plate 4 *Methicillin-Resistant Staphylococcus aureus* (ID#: 10047)
Plate 5 *Streptococcus pneumonia* (ID#: 2170)

Plate 6 Acid-fast Ziehl-Neelsen stain of the *Mycobacterium tuberculosis* (ID#: 4427)
Plate 7 Vancomycin-Resistant Enterococcus (ID#: 209)
Plate 8 *Plasmodium falciparum* ring-form in red cell, a Giemsa stained micrograph (ID# : 5939)

Plate 9 HIV-1 spherical appearance and human lymphocyte (scanning electron micrograph) (ID#: 11279)
Plate 10  Russian Influenza-A H1N1 virus (ID#: 7813)