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## INTRODUCTION

*“To avoid taking action to resolve antimicrobial resistance is to commit Canadians to the perils of living in the pre-antibiotic era.”*

Canadian Committee on Antibiotic Resistance<sup>1</sup>

Antibiotics have given modern medicine an incomparable boost. Many bacterial infections that used to jeopardize health, or even life itself, are now routinely treated with antibiotics.

There’s just one problem: the bacteria that antibiotics are meant to kill are smarter than we suspected. They have the genetic capability to mutate and adapt to antibiotics – in other words, to develop resistance against the drugs.

A growing problem since antibiotics became widely available in the 20th Century, antibiotic resistance has in some cases, led to an increase in death and illness from common infections. Antibiotic resistance poses a particular threat for people with underlying medical conditions or weakened immune systems.

Worldwide, virtually all significant bacterial infections are becoming resistant to commonly used antibiotics. In trying to contain the problem, scientists, health practitioners and policymakers face an enormous challenge.

Fortunately, the creation of powerful new antibiotics has become a major contributor to enabling modern medicine to offer help to patients with antibiotic-resistant infections. However, the solution to antibiotic resistance encompasses far more than new drugs alone. Both doctors and patients need to unlearn old prescribing habits that contribute to the problem of resistance and acquire new attitudes and practices that help keep it in check.

This booklet outlines key developments in antibiotic usage, provides up-to-date information about antibiotic resistance in Canada, and discusses the steps needed to contain the problem.



## A. HISTORY AND NATURE OF ANTIBIOTICS

### THE MAGIC DISCOVERY

In the late 1800s, the growing acceptance of the germ theory of disease led scientists to search for drugs that would kill disease-causing bacteria. In 1877, Louis Pasteur showed that the injection of soil bacteria could neutralize the bacterial disease anthrax in animals. Just over a decade later, the German scientist E. de Freudenreich demonstrated that a pigment released by a certain bacterium arrested the growth of other bacteria in a cell culture. And in the early 1920s, the British scientist Alexander Fleming discovered that a product in human tears could destroy bacterial cells.

It was Fleming's second major discovery that changed the course of medicine and earned him lasting fame. Returning from a weekend vacation in 1928, Fleming looked through an old glass plate and observed that the bacterial cells he had smeared on it had broken down in an area adjacent to some *Penicillium* mould growing on the plate. He named the active ingredient in the mould penicillin.

Just over a decade later, a trio of British researchers purified penicillin and tested it on animals and humans, with spectacular results. Throughout the 1940s, Great Britain and the United States cooperated to mass-produce penicillin, which they used primarily to treat soldiers injured during World War II. By 1946, the drug was ready for universal public use.

### THE WONDER YEARS

Penicillin was not the only drug to offer near-miraculous healing during this era. Even before Fleming's discovery, a German biochemist's experiments with various antibacterial chemicals led to the development of a family of drugs called the sulfonamides, also known as sulfa drugs. The year 1936 saw the first use of sulfanilamide, the grandparent of this drug class.

That same year, an outbreak of meningitis in the French Foreign Legion in Nigeria yielded dramatic proof of the drug's effectiveness: while sulfanilamide was available, the mortality rate during the outbreak stood at 11%; when the supply ran out, the mortality climbed to 75%. The wonder drugs of their time, sulfa antibiotics carried the main therapeutic burden in both military and civilian medicine during World War II and showed particular effectiveness against bacterial pneumonia.

As early as the 1940s, bacteria began resisting penicillin, leading researchers to fight back with such chemical cousins as methicillin and oxacillin. By the mid-1950s, the antibiotic arsenal included such drugs as neomycin, chloramphenicol, tetracycline, and erythromycin. The solution to antibiotic resistance seemed simple at the time: just create more drugs. Today, researchers fear the well may be drying up.



## Important Dates in Infectious Diseases and the History of Antibiotics<sup>1</sup>

- 500 B.C. Hippocratic Oath is written
- 1000 Chinese practice early immunization by inhaling powdered smallpox lesions
- 1798 Edward Jenner inoculates a boy with matter obtained from a cowpox lesion
- 1875 Ferdinand Cohn publishes early classification of bacteria
- 1880s Louis Pasteur modifies a virulent pathogen to play an immunizing role
- 1928 Alexander Fleming discovers that mould can destroy virulent bacteria
- 1939 Researchers use penicillin to save patients
- 1944 Researchers discover streptomycin
- 1952 Researchers link antibiotic resistance to bacterial mutation
- 1967 World Health Organization (WHO) launches program to eradicate smallpox
- 1979 Smallpox is declared defeated
- 1981 Canada reports first case of methicillin-resistant *Staphylococcus aureus* (MRSA)
- 1993 Ontario reports first case of vancomycin-resistant enterococcus (VRE)
- 1995 A dramatic increase in MRSA is reported across Canada
- 2000 WHO describes antibiotic resistance peril in its "Report on Infectious Diseases"
- 2004 Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) describes patterns of antibiotic prescribing and use in Canada
- 2006 Canadian National Intensive Care Unit (CAN-ICU) study documents a higher-than-expected prevalence of resistant bacteria in hospitals across Canada



## CHARACTERISTICS OF ANTIBIOTICS

The most important property of an antibiotic is its selective toxicity, or the ability to kill or inhibit bacteria without toxicity to the user. Antibiotics may have either a cidal (killing) or static (inhibitory) effect on a range of bacteria. They do not have any effect against viruses.

Bacteria divide into Gram-positive or Gram-negative sub-

types, depending on how they retain dye during the Gram staining process. Gram-positive bacteria have a thicker cell wall, while Gram-negative ones have a thinner cell wall. Broad-spectrum antibiotics act against a wide range of Gram-positive and Gram-negative bacteria, narrow-spectrum antibiotics act mainly against either Gram-positive or Gram-negative bacteria.

Examples of Gram-positive bacteria	Examples of Gram-negative bacteria
Staphylococcus epidermidis	Escherichia coli
Staphylococcus aureus	Bordetella pertussis
Streptococcus pyogenes	Salmonella typhi
Streptococcus pneumoniae	Vibrio cholerae
Clostridium tetani	

## CLASSES OF ANTIBIOTICS

Antibiotics fall into various classes based on their mode of action against bacterial cells. Today's antibiotic classes include the following:

- **Beta-lactams:** This class of drugs, which includes the penicillins and cephalosporins work only on actively growing bacterial cells. While harmless to most people, penicillins may cause life-threatening reactions in allergic individuals. Often used as penicillin substitutes, cephalosporins have a somewhat broader spectrum than natural penicillins.
- **Macrolides:** These drugs commonly serve as penicillin substitutes.
- **Tetracyclines:** These broad-spectrum antibiotics have a remarkably low toxicity and minimal side effects.
- **Glycopeptides:** These drugs prevent bacterial cells from proliferating. Vancomycin has assumed an important role in the treatment of *Staphylococcus aureus* infections that resist all other antibiotics.
- **Aminoglycosides:** These antibiotics have been used against a wide variety of bacterial infections, though prolonged use can impair kidney function and damage auditory nerves.



- **Rifamycins:** This class of antibiotics has proven useful against tuberculosis and preventing bacterial meningitis.
- **Sulfonamides:** While differing widely in their pharmacological activity, these drugs have broadly similar effects. They work especially well against *Escherichia coli* and are frequently used for urinary infections.
- **Quinolones/fluoroquinolones:** These drugs enter cells easily, giving them the ability to combat such intracellular invaders as *Legionella pneumophila* and *Bacillus anthracis*.
- **Novel antibiotics:** This broad and continually evolving family includes drugs that belong to some of the other classes. The most recent addition to this group, tigecycline, targets complicated skin, skin structure, and intra-abdominal infections, including a high proportion of bacteria that are resistant to other antibiotics. Another new drug is linezolid, which combats several antibiotic-resistant nosocomial (hospital-acquired) infections. Another novel approach for enhancing antibiotic effectiveness is to combine two or more drugs that have complementary effects (e.g., Tazocin®, a combination of piperacillin and tazobactam).

Antibiotic class	Representative drugs
Beta-lactams	Amoxicillin, ampicillin, ceftriaxone
Glycopeptides	Vancomycin
Aminoglycosides	Streptomycin, gentamicin
Tetracyclines	Tetracycline, doxycycline
Macrolides	Erythromycin, clarithromycin
Rifamycins	Rifampin
Sulfonamides	Trimethoprim/Sulfamethoxazole
Quinolones	ciprofloxacin, levofloxacin
Novel antibiotics	Tigecycline, linezolid



## B. THE RISE OF ANTIBIOTIC RESISTANCE

### HOW ANTIBIOTIC RESISTANCE DEVELOPS

A natural outcome of evolution, bacterial resistance to antibiotics has a genetic basis. Any population of organisms includes variants, arising from genetic processes, with unusual traits. In the case of bacteria, some members of a population will have a better ability to withstand an antibiotic's attack than their defenseless neighbours. When a person takes an antibiotic, the drug destroys the defenseless bacteria, leaving the resistant ones to multiply freely. Through this process of natural selection, these renegade bacteria can soon become the dominant strain.

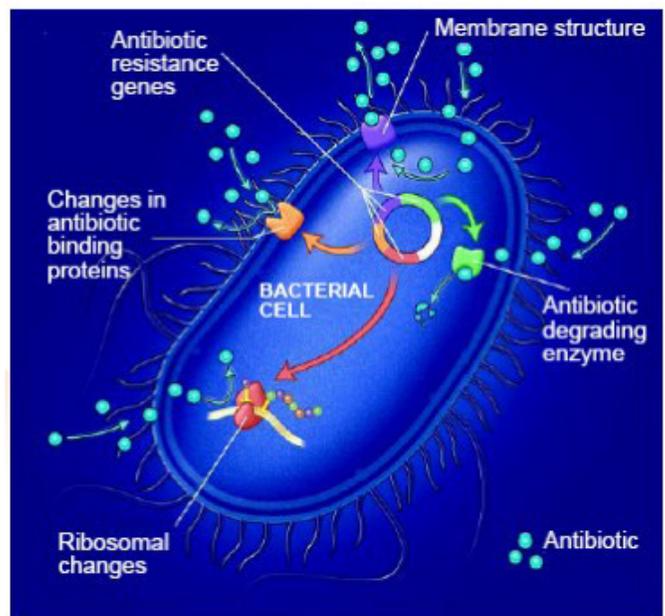
In other words, the antibiotic doesn't actually cause the resistance. It allows resistance to happen by creating an environment in which tiny groups of naturally resistant bacteria can flourish.

Bacteria have two ways of acquiring genes that confer resistance to antibiotics. Through happenstance, natural mutations may create gene alterations that produce structural or biochemical changes that lead to resistance. Genetic material favouring resistance can also enter bacteria from other sources, such as viruses. Some types of bacteria are able to transfer these resistant genes from one bacterium to another, spreading resistance through a bacterial population.

Several biological mechanisms share responsibility for bacterial resistance. Some bacteria have developed efflux pumps, which help flush antibiotics out of bacterial cells. Others have devised ribosomal protection mechanisms that

prevent antibiotics from interfering with bacterial protein synthesis. A further strategy is to chemically modify the antibiotic so it no longer binds to the bacterium's cell wall. Still other bacteria have enzymes that degrade antibiotics before they can do any damage.

### Mechanisms of antibiotic resistance



Conly J. Can Med Assoc J 2002;167:885.

A person can develop an antibiotic-resistant infection either by contracting a resistant bug to begin with, or by taking antibiotics that allow a resistant bacterial strain to emerge inside the body.



## A GROWING CONCERN

Although antibiotic resistance occurs spontaneously, societal behaviours add considerable fuel to the fire. Over-prescribing, insufficient doses, insufficient duration of treatment, and misdiagnosis all contribute to antibiotic resistance.<sup>2</sup> The practice of adding antibiotics to agricultural feed may also promote resistance.

Antibiotic resistance poses a particular problem in hospitals harbouring critically ill patients who rely on antibiotics to fight off routine infections. In such patients, heavy use of antibiotics can lead to drug-resistant strains that can fend off even the strongest antibiotics in our armamentarium. Patterns of antibiotic resistance may vary from hospital to hospital, putting the onus on hospitals to keep accurate records of antibiotic use and outcomes.

Although antibiotic resistance develops most commonly in nosocomial infections, the spectre of antibiotic resistance also looms large outside the hospital environment. Among patients admitted to hospitals, a growing number harbour antibiotic-resistant bacteria acquired in the community.<sup>3</sup> Resistant strains may spread to communities from hospitals or emerge right in the community.

## SUPERBUGS

Most worrisome among antibiotic-resistant bacteria are those with resistance to several antibiotics, also known as superbugs. These scourges of hospital wards have led to quarantines, temporary hospital closures, and patient deaths. The fight to fend off these superbugs with newer and more powerful antibiotics has been likened to an arms race.



## TEN COMMON SUPERBUGS<sup>4</sup>

Bacterium	Diseases caused	Drugs resisted
<i>Staphylococcus aureus</i>	Bacteremia (blood infection), pneumonia, surgical-wound infections	Chloramphenicol, rifampin, ciprofloxacin, clindamycin, erythromycin, beta-lactams, tetracycline, trimethoprim
<i>Streptococcus pneumoniae</i>	Meningitis, pneumonia, otitis media (ear infection)	Penicillin, erythromycin, chloramphenicol, trimethoprim-sulfamethoxazole, fluoroquinolones
<i>Mycobacterium tuberculosis</i>	Tuberculosis	Aminoglycosides, ethambutol, isoniazid, pyrazinamide, rifampin
<i>Haemophilus influenzae</i>	Epiglottitis, meningitis, otitis media, pneumonia, sinusitis	Beta-lactams, chloramphenicol, tetracycline, trimethoprim
<i>Enterobacteriaceae</i> (e.g. <i>Escherichia coli</i> , <i>Klebsiella spp.</i> )	Bacteremia, pneumonia, urinary tract or surgical-wound infections, diarrhea	Aminoglycosides, beta-lactams, fluoroquinolones, chloramphenicol, trimethoprim
<i>Enterococcus</i>	Bacteremia, urinary tract or surgical-wound infections	Aminoglycosides, beta-lactams, vancomycin
<i>Neisseria gonorrhoeae</i>	Gonorrhoeae	Beta-lactams, spectinomycin, fluoroquinolones, tetracycline
<i>Pseudomonas aeruginosa</i>	Bacteremia, pneumonia, urinary tract infections	Aminoglycosides, beta-lactams, ciprofloxacin, carbapenems
<i>Bacteroides</i>	Septicemia, anaerobic infections	Clindamycin, ceftiofloxacin, fluoroquinolones
<i>Shigella dysenteriae</i>	Severe diarrhea	Ampicillin, tetracycline, chloramphenicol, trimethoprim-sulfamethoxazole



## REAL-WORLD SCENARIOS

### A RACE AGAINST TIME

A 75-year-old man with insulin-dependent diabetes is admitted to a general hospital with a suspected blood infection (sepsis). He had been discharged from hospital just 12 days earlier, following treatment for pneumonia with the antibiotics ceftazidime and ciprofloxacin. Over the past few years, the patient has taken several courses of fluoroquinolone antibiotics for recurrent urinary tract infections.

Suspecting a recurrence of pneumonia, the attending doctor decides to administer ciprofloxacin, the same antibiotic that proved successful in the previous pneumonia episode. Unfortunately, the drug doesn't work this time: not only does the patient's fever continue to spike, but he begins to show signs of moderate respiratory failure. A blood and urine culture exposes the culprit: a ciprofloxacin-resistant strain of *Klebsiella pneumoniae*. Hoping for the best, the physician starts the patient on a course of a carbapenem antibiotic. Within two weeks, the pneumonia resolves. But will the antibiotic win the fight the next time?

Adapted from [www.infectionacademy.org](http://www.infectionacademy.org), case identifier ICU\_c1 (Accessed August 29, 2006)

### SICK CHILD, TIRED PARENT: WILL PROFESSIONAL REASON PREVAIL?

A woman brings her two-year-old child to a pediatric walk-in clinic. After a fairly busy evening, the attending doctor has been hurrying to get everybody seen before the 8 p.m. closing time. The child has had a mild fever since the previous evening and a nasal discharge for the past two days. The mother, a laboratory technician, says she spent most of the previous night lying awake with the child. Upon examination, the doctor concludes the child has a simple viral upper respiratory infection, with no sign of infected ears or sinuses, and suggests acetaminophen for the fever and saline nose drops for the nasal congestion.

"I have nose drops and tried Tylenol last night and it didn't help one bit," the mother protests. She looks tired, and a note of fear creeps into her voice. "Can't you give him an antibiotic?" The doctor explains that antibiotics have no effect on viral infections, but the mother insists on a prescription. Closing time is approaching. What's a busy doctor to do?

Adapted from Virtual Health Care Team case 899: [www.vhct.org/case899/antibiotic\\_case\\_2.htm](http://www.vhct.org/case899/antibiotic_case_2.htm) (Accessed August 29, 2006)



**THIS COULD HAPPEN...**

*Doctor:* Mrs. C., I'm afraid the samples we sent off to the laboratory for your son have confirmed that he has a bloodstream infection for which no medication can help. We'll keep trying, but you should know there's a good chance he won't make it.

*Mother:* Is there really nothing you can do?

*Doctor:* I'm afraid not.

*Mother:* But how is this possible? When I was growing up, antibiotics cured all infections.

Adapted from the University of Western Ontario Ecosystem Health website: [www.schulich.uwo.ca/ecosystemhealth/education/casestudies/antibioticresistance.htm](http://www.schulich.uwo.ca/ecosystemhealth/education/casestudies/antibioticresistance.htm) (Accessed August 29, 2006)



## C. ANTIBIOTIC RESISTANCE IN CANADA TODAY

### THE FACTS

While Canada still boasts lower antibiotic resistance rates than most other countries, data collected from various surveillance programs raise some concern and argue strongly against complacency.

The CAN-ICU (Canadian Intensive Care Unit) Surveillance Study is currently surveying the prevalence of antibiotic-resistant bacteria in intensive care units (ICUs) in 19 hospitals across the country. The study has revealed that antibiotic-resistant bacteria are much more common than previously thought. Overall, about 10% of sampled bacteria showed resistance to the commonly used antibiotic offensive of piperacillin/tazobactam and meropenem, and about 20% of bacterial samples resisted third-generation cephalosporins, fluoroquinolones, and gentamicin.<sup>5</sup> These surprisingly high levels of resistance to common antibiotics underscore the need for a broad-based prevention strategy, one aspect of which is new, effective antibiotics that can be used empirically (i.e., as a broad-spectrum therapy before the particular infecting bacterial species has been identified).

The U.S. faces an even bleaker picture. According to data from the Centers for Disease Control and Prevention, more than 70% of bacterial infections acquired in U.S. hospitals can resist at least one of the antibiotics commonly used to treat them.<sup>6</sup> Worldwide, one in seven new tuberculosis patients is resistant to the two drugs most commonly used to

treat it, and 5% of these patients die.<sup>7</sup>

### THE CULPRITS

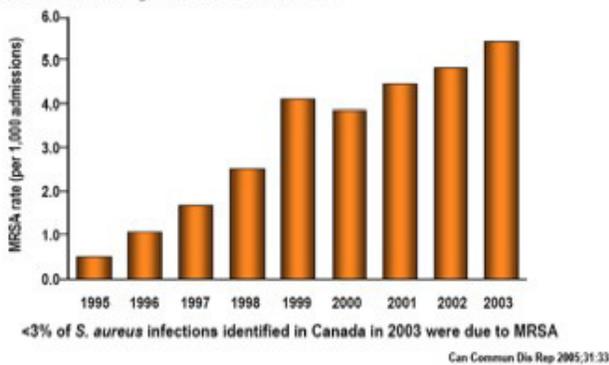
- *Methicillin-resistant Staphylococcus aureus (MRSA):* *Staphylococcus aureus* (staph) is a common cause of hospital infections that enter the body through the skin and in serious cases can spread to the heart, bones, lungs, and bloodstream. In the past, staph infections responded very well to the antibiotic methicillin, but methicillin-resistant staph strains began to proliferate in the 1990s. A five-year Canadian surveillance program found that the proportion of staph strains with methicillin resistance surged from just 1% in 1995 to 6.1% in 1999.<sup>1</sup> In 2002, an estimated 57.1% of staph strains found in U.S. hospitals were methicillin-resistant.<sup>8</sup> In the CAN-ICU study, the prevalence of MRSA ranged from 4.2 to 50.0% across Canadian ICUs with an average of 22.3%.<sup>5</sup> Two types of MRSA exist: healthcare associated – HA-MRSA and community-associated – CA-MRSA. The CAN-ICU study found that 91.9% of MRSA in Canada were HA-MRSA and 8.1% were CA-MRSA. CA-MRSA may be even more able than HA-MRSA to cause infections in both hospital as well as in healthy individuals living in the community. Patients with MRSA have longer hospital stays, more severe disease, and more costly treatment than those with methicillin-sensitive *Staphylococcus aureus* strains.



[chart copied & pasted from Antibacterial Resistance in Canada – Past, Present, and Future” presentation – for positioning only, to be re-designed]

**MRSA rates in Canadian hospitals, 1995-2003**

Includes isolates causing infection and colonization



MRSA typically thrives in healthcare settings such as hospitals, where people have open wounds and tubes. However, recently it has become increasingly common in the broader community. At greatest risk are elderly or very ill people, IV drug users, and those with a history of extensive or intensive antibiotic use.

- *Vancomycin-resistant enterococci (VRE)*: Although normally present in the intestines of healthy humans and farm animals, various species of enterococci (especially *Enterococcus faecalis*) can also lead to urinary tract, bloodstream, cardiovascular and other infections. The appearance of enterococcus strains resistant to vancomycin, the drug of last resort for many infections, has caused great concern in the healthcare community.

In 2003, an estimated 28.5% of enterococci identified from patients in U.S. ICUs were resistant to vancomycin,<sup>9</sup> while the CAN-ICU study turned up vancomycin-resistant enterococci in 6.7% of Canadian ICUs.<sup>5</sup>

- *Extended-spectrum beta-lactamase (ESBL) bacteria*: Extended-spectrum beta-lactamase (ESBL) bacteria produce enzymes that can break down common antibiotics. The bacteria *Escherichia coli* and *Klebsiella pneumoniae* take centre stage in the ESBL family. Present in Europe and the U.S. for close to two decades, ESBL bacteria have recently made significant inroads into Canada. In the CAN-ICU study, ESBL *Escherichia coli* turned up in 4.7% of Canadian ICUs and *Klebsiella pneumoniae* in 1.8%.<sup>5</sup> Only a very limited group of oral and intravenous antibiotics remain effective against the most resistant ESBL strains.
- *Clostridium difficile*: Typically found in the stool and most frequently associated with watery diarrhea, *Clostridium difficile* may also cause colitis in hospitalized patients taking antibiotics. About 80% of *Clostridium difficile*-induced diarrhea occurs in people still taking antibiotics, though the increased risk can persist for months after antibiotic exposure. Most patients treated for *Clostridium difficile* infection improve, but about 20%



relapse. In Quebec, a new and highly virulent strain of the bacterium resulted in 1,270 deaths from nosocomial infections in 2004.<sup>10</sup> Resistant to most antibiotics, *Clostridium difficile* responds only to metronidazole and vancomycin.

- *Multi-drug resistant (MDR) Pseudomonas aeruginosa:* An increasing percentage of *Pseudomonas aeruginosa* bacteria, the culprits behind many urinary tract infections, lung infections, and infected wounds, have acquired resistance to a variety of antibiotic groups including penicillins, cephalosporins, aminoglycosides, fluoroquinolones and carbapenems. Quinolone-resistant strains now account for 15% of *Pseudomonas aeruginosa* infections.<sup>11</sup>
- *Antibiotic-resistant Streptococcus pneumoniae:* *S. pneumoniae* holds the lion's share of responsibility for respiratory infections including bronchitis, sinusitis, middle ear infections, and pneumonia. When the bacterium was first identified, all *Streptococcus pneumoniae* bacteria succumbed reliably to penicillin, and beta-lactams served as the antibiotic class of choice for these infections. Today, antibiotic-resistant strains of *Streptococcus pneumoniae* exist throughout the world.

The Canadian Respiratory Organism Susceptibility Study (CROSS), conducted between 1997 and 2002, collected and analyzed 6,991 isolates of *Streptococcus pneumoniae*. Despite decreases in the rates of

antibiotic consumption over that time period, some resistant strains of *Streptococcus pneumoniae* gained considerable ground in Canada, a phenomenon that study investigators attribute to the proliferation of a small number of particularly resistant bacteria.<sup>12</sup>

The Canadian Bacterial Surveillance Network (CBSN) has been evaluating antibiotic resistance in *Streptococcus pneumoniae* for over a decade. Most alarming among the CBSN's findings is the steady increase in erythromycin-resistant *Streptococcus pneumoniae* between 1993 (less than 2% of samples) and 2005 (close to 20% of samples), though the 2005 rate still falls well below those in most other countries.<sup>13</sup> On a more encouraging note, *Streptococcus pneumoniae* resistance to penicillin has hovered at about 15% over the past five years, suggesting that rates may have stabilized.

## THE CHALLENGE IN HOSPITALS

In hospitals, bacterial pathogens live and breed on every surface, from cabinets to bedside tables. Research has shown that MRSA, for instance, can live on such surfaces for weeks.<sup>10</sup> Killing these bugs requires drenching surfaces in cleaning solution for several minutes, not just giving them



a quick spray or wipe, so the bacteria often thrive despite cursory attempts to destroy them. Constrained hospital budgets, which may preclude thorough cleansing programs, compound the problem.<sup>10</sup> When patients, caregivers, or visitors touch bacteria-laden surfaces, their hands can spread the bacteria within the hospital, placing vulnerable patients at risk of infection. Other risk factors include a patient's length of hospital stay, severity of underlying illness, use of invasive devices, surgery, and intensity and duration of antibiotic exposure.<sup>14</sup>

All told, between 5 and 10% of hospitalized patients acquire an infection during their stay.<sup>15</sup> These infections cover a wide spectrum, ranging from respiratory tract infections to urinary tract infections to blood poisoning. Surgical-wound infections occur in up to 10% of patients undergoing clean surgery.<sup>15</sup> Catheters, which facilitate the entry of microbes into the body, account for many other hospital acquired infections.

Antibiotics are a fact of life in hospitals, with more than half of patients in acute-care hospitals receiving antibiotics as treatment or prophylaxis.<sup>14</sup> Excessive or inappropriate use of antibiotics drives the development and spread of antibiotic-resistant infections in hospitals, making nosocomial infections a serious public health threat.

In the U.S., nosocomial infections alone afflict about 2 million people and kill nearly 90,000 every year.<sup>16</sup> In Canada, 220,000 to 250,000 annual nosocomial infections result in 8,000 to 12,000 deaths.<sup>10</sup> As multi-drug-resistant infections often require longer hospital stays and more complex treatment, drug resistance incurs estimated annual costs of between 4 and 5 billion dollars in the U.S.<sup>17</sup> If a similar per-capita cost is assumed, the economic toll of antibiotic resistance in Canada could be as high as \$500 million per year.

#### **HOSPITAL FORMULA**

Heavy antibiotic use + high-density patient population  
+ frequent contact with healthcare staff = development  
and spread of antibiotic-resistant infections



## D. A FUTURE AT RISK

### COMING TO A COMMUNITY NEAR YOU

Having stepped outside hospital doors and infiltrated the community, antibiotic-resistant bacteria now pose a much greater public health threat than they did even a few short years ago. While antibiotic-resistant bacterial infections spare no demographic or socio-economic group, the risk of contracting such infections tends to increase with increasing frequency of antibiotic use, susceptibility to infections, and exposure to other infected people. Communities at highest risk for the spread of antibiotic-resistant infections include sports teams, nursing home residents, children attending daycare, homeless or inadequately housed people, chronic intravenous (IV) drug users, and isolated populations such as those found in First Nations reservations. In fact, the CAN-ICU study has unearthed at least sixteen cases of community-associated MRSA. These types of CA-MRSA were first identified in Canada in IV drug users and First Nations people.<sup>5</sup>

#### ONE FOR THE TEAM

The Centers for Disease Control and Prevention in the U.S. have reported outbreaks of MRSA among such athletic groups as college football players in Pennsylvania, wrestlers in Indiana, and a fencing club in Colorado. The issue garnered national attention in 2003 when MRSA broke out in Florida among the Miami Dolphins, driving

With 80% of antibiotics being prescribed for outpatients in the community rather than hospital inpatients,<sup>18</sup> prescribing practices can make or break a community's capacity to withstand antibiotic resistance. Unfortunately, patients and parents continue to pressure doctors for antibiotics, and doctors often cave in. A recent study of pediatric care showed that doctors prescribe antibiotics 65% of the time if they sense that parents expect them and only 12% of the time if they don't.<sup>19</sup>

In Canada, a new consumer survey commissioned by the National Information Program on Antibiotics and conducted by Léger Marketing has found that Canadians still harbour serious misconceptions about the use of antibiotics.<sup>20</sup> While 85% of those surveyed agree that antibiotics are useful for treating bacterial infections, 53% mistakenly believe they also play a role in the treatment of viral infections and almost half (47%) incorrectly agree that "antibiotics will be a part of the defense against a global flu pandemic." Most tellingly, 63% of Canadians believe they can avoid contracting antibiotic-resistant infections by using antibiotics judiciously, suggesting a failure to understand that bacteria, not people, become resistant to antibiotics.

### COMMUNITY-ASSOCIATED MRSA IN CANADA

While MRSA does most of its damage in hospitals, community-associated (CA) strains of MRSA have been



appearing with increasing frequency in Canada. With a 20-year history in northern aboriginal prairie communities, CA-MRSA is hardly new to the country. However, recent years have seen CA-MRSA infections move into other marginalized populations, such as prison populations or drug users, and even to the wider community to a limited extent.<sup>21</sup> Experts speculate that MRSA will come to dominate over methicillin-sensitive strains within the next decade or two, paralleling the displacement of penicillin-susceptible *Staphylococcus aureus* with penicillin-resistant strains in the 1960s.<sup>21</sup> To date, CA-MRSA strains have shown milder resistance profiles than the hospital varieties, though this profile may change.

### THE DRYING WELL

In the 1970s and 1980s, research and development of new antibiotics began to stall, possibly because the optimistic notion that medicine had conquered infectious diseases had seeped into the drug-development industry. Likewise, today's economic and prescribing climate has led many pharmaceutical companies to sidestep the antibiotics market in favour of drugs that target chronic conditions and lifestyle concerns.<sup>22</sup>

Out of the 89 new drugs approved in the U.S. in 2002, not one was an antibiotic.<sup>22</sup>

Without innovative public health policies and adequate financial support, the options for antibiotics to treat the increasing number of resistant infections will continue to dwindle. To use the arms race analogy, the stockpile of bacterial bombs threatens to outstrip the arsenal of antibacterial missiles.



## E. THE WAY FORWARD

### ANTIBIOTIC STEWARDSHIP

People often talk of stewardship in an environmental context. To preserve and protect our planet, the thinking goes, we must be responsible stewards rather than indiscriminate users of the earth’s resources. The same principle applies to our microenvironment – the milieu of bacteria and the drugs we’ve developed to combat them. To protect ourselves from antibiotic-resistant diseases, we must adopt attitudes and practices that mitigate the spread of antibiotic resistance.

antibiotics to patients undergoing surgery.

These include:

- *Judicious use*: Having demonstrated that previous antibiotic use increases the risk of antibiotic resistance,<sup>18</sup> experts agree that antibiotics should be given only to patients who stand to benefit from these drugs. Viral illnesses such as colds, flus, and sore throats (unless caused by streptococcus) do not require antibiotics,<sup>23</sup> and not all bacterial infections automatically warrant their use. For example, the great majority of children with conjunctivitis get better without any medical intervention. Leading thinkers and institutions are also re-evaluating the practice of administering prophylactic

### CENTERS FOR DISEASE CONTROL PARENTAL GUIDELINES FOR ANTIBIOTIC USE<sup>19</sup>

Condition	Role of antibiotics
Ear infections	There are several types; some may need antibiotics, while others do not.
Sinus infections	Thick or green mucus does not indicate a sinus infection. Antibiotics are needed for some long-lasting (> 7 days) or severe sinus infections.
Bronchitis	Children rarely need antibiotics for bronchitis.
Sore throat	Caused by viruses in most cases. Only the bacterially induced strep throat (diagnosed by a doctor) requires antibiotics.
Colds	Caused by viruses, colds may last two weeks or even longer and do not respond to antibiotics.



Of some concern, 2005 saw a slight increase in the rate of penicillin prescriptions (22.7 per 100 Canadians) from the previous year (22.1 per 100).<sup>13</sup> This represents a departure from the steady downward trend observed since 1994. On a more encouraging note, the 2004 Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) report has noted a modest decrease in the total number of antibiotic prescriptions per 1,000 inhabitants, from 730 in 2000 to 661 in 2004.<sup>24</sup>

*“The increase in penicillin prescriptions should serve as a reminder that physicians, pharmacists and patients need to be more prudent about the use of antibiotics.”*

2006 National Report Card on Antibiotic Resistance<sup>13</sup>

Judicious use also means administering narrow-spectrum antibiotics, which target fewer bacteria and thus allow fewer resistant strains to emerge, whenever possible. That said, broad-spectrum antibiotics will continue to play an important role in treating infections that require prompt intervention before the bacterial offender has been identified.

- *Education:* To combat antibiotic resistance, people need to know about the problem in the first place. Studies show that when people get the information they need, their behaviour changes. As the following table illustrates, arming people with appropriate knowledge can substantially reduce antibiotic prescription rates.

### RECENT STUDIES PROMOTING THE JUDICIOUS USE OF ANTIBIOTICS (1999–2003)<sup>25</sup>

Study	Intervention	Outcomes
Wisconsin; 1,136 patients and 151 pediatricians	Educational materials to staff and parents in clinics	19% drop in antibiotic prescriptions (vs. 8% drop in control group)
Denver; four primary care practices	Home- and office-based patient education; clinician education	Substantial decline in antibiotic prescriptions
Alaska; 13 rural villages	Education of providers and villagers	35% decrease in antibiotic courses
Tennessee; Medicaid patients in four counties	Year-long education program for providers, parents, and public	Significant decline in prescription rates



- *Well-targeted therapy:* In general terms, well-targeted antibiotic therapy (which depends on an accurate diagnosis) reduces the need for sequential, hit-and-miss courses of antibiotics and the consequent risk of antibiotic resistance. In some groups of patients, early and aggressive antibiotic therapy can dramatically improve survival. In a five-year Canadian study that concluded in 2004, an hour's delay in beginning antibiotic therapy led to a 7.6% decrease in survival in patients with septic shock.<sup>26</sup>
- *Combination therapy:* Combining two or more antibiotics can increase the odds of defeating a bacterial infection, since a bacterium that becomes resistant to one antibiotic does not necessarily achieve resistance to a second or third one. Two antibiotics can also work synergistically to speed up healing and possibly short-circuit the development of resistance. Belgian scientists have demonstrated that, in patients with neutropenic fever, a one-two antibiotic punch of ceftazidime and a glycopeptide mitigates the development of resistance in the bacterial organism responsible for the disease.<sup>27</sup> Combination therapy with beta-lactam and aminoglycoside antibiotics has proven effective against *Pseudomonas aeruginosa*.

Thanks to a growing body of clinical evidence, combination antibiotic formulations such as piperacillin/tazobactam are becoming recognized as empiric first-choice treatments for serious infections. The efficacy of the synthetic beta-lactam antibiotic piperacillin is enhanced by tazobactam, which stops bacterially produced beta-lactamase enzymes from inactivating the drug. This gives piperacillin/tazobactam a wide spectrum of antibiotic activity against a broad range of Gram-positive and Gram-negative bacteria.

In a similar vein, combining antibiotics with other types of drugs can enhance their efficacy, thereby reducing the need for prolonged antibiotic exposure. Several drugs combining antibiotics with topical retinoids, for example, have mounted successful assaults against mild to moderate acne.

- *Preventive hygiene:* The news could hardly be less glamorous: hand-washing still offers the best protection against bacterial infections, antibiotic-resistant or otherwise. Antibacterial soap, on the other hand, does more damage than good as it destroys the "good" bacteria that keep virulent bacteria in check. Experts also caution against sharing towels or sports equipment.



### HEALTH CANADA'S SUGGESTED PRACTICES TO MINIMIZE ANTIBIOTIC RE- SISTANCE<sup>28</sup>

- Avoid the use of antibacterial soap and cleaning products.
- Wash hands regularly with soap and water for at least 20 seconds.
- When preparing food, wash cutting boards and knives with detergent and water; use bleach on all surfaces in contact with raw poultry and thoroughly wash all fruits and vegetables that will be served raw.
- Keep vaccinations up to date.
- Take antibiotics as directed, and do not stop a prescription partway through the course of treatment unless you have a serious adverse reaction.
- Do not share prescriptions with anyone else.
- Do not flush antibiotics or any other drugs down the toilet, as the introduction of antibiotics into the water table could compound the drug-resistance problem.

- *Vaccines:* By reducing the frequency of infections and resulting antibiotic use, vaccines play a key role in preventing the emergence and spread of resistance in the community. Efforts to develop pneumococcal vaccines began as early as 1911, dwindled in the golden era of penicillin, then began anew in the late 1960s. The year 2000 saw the introduction of a pneumococcal vaccine suitable for children. Use of this vaccine has dramatically reduced the incidence of invasive pneumococcal disease and led to a reduction in drug-resistant *Streptococcus pneumoniae*.<sup>18</sup>
- *New drug development:* New antibiotics play an important role in the ongoing fight against antibiotic resistance. Recognizing the barriers to new drug development, governments are creating or considering incentives such as tax breaks and liability protections to jump-start the process.

### OLD-TIMERS AND NEWCOMERS

Canadians continue to use established antibiotics. The CIPARS report flagged extended-spectrum penicillins (25%), macrolides (20%), tetracyclines (14%), fluoroquinolones (12%), and second-generation cephalosporins (5%) as the most frequently dispensed antibiotic classes supplied by retail pharmacies in Canada.<sup>24</sup>

At the same time, several promising new antibiotics have entered the market in recent years. Some of these new

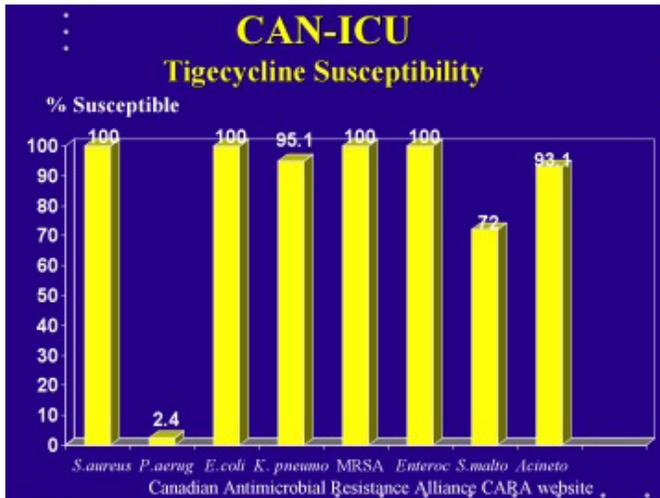


drugs closely resemble drugs already on the market, others may occupy a new treatment niche, while still others may offer new ammunition for infections resistant to established antibiotics. Along with their official indications, many of these drugs have off-label, investigational uses. The following list covers some of the important antibiotics to reach the market in recent years:

- *Ertapenem (Invanz®)*: A member of the carbapenem class, ertapenem works well against a variety of bacteria and conditions and has particularly strong activity against intestinal organisms.<sup>29</sup> Some experts have likened ertapenem to a combination of ceftriaxone and metronidazole.
- *Gemifloxacin (Factive®)*: Indicated for the treatment of acute bacterial exacerbation of chronic bronchitis and for mild to moderate pneumonia, this drug can bring down multi-drug-resistant strains of *Streptococcus pneumoniae*.<sup>29</sup>
- *Linezolid (Zyvoxam®)*: This member of the oxazolidinone class targets VRE, MRSA, some skin and skin structure infections, and some forms of nosocomial and community-acquired pneumonia. The weight of evidence from large clinical studies comparing linezolid with vancomycin suggests that the two agents have similar efficacy, although linezolid seems to have an edge in combating hospital-acquired pneumonia caused by MRSA.<sup>29</sup>
- *Telithromycin (Ketek®)*: A derivative of erythromycin, this antibiotic was developed to manage the problem of macrolide resistance in pneumococci and other Gram-positive bacteria.
- *Tigecycline (Tygacil®)*: Approved in 2005 by the Food and Drug Administration in the U.S. and in Canada in 2006, tigecycline is the world's first and only glycylcycline. Indicated for the treatment of intra-abdominal infections as well as complicated skin and skin structure infections in adults, tigecycline meets the growing need to circumvent resistance mechanisms in common bacteria such as *Staphylococcus aureus* and enterococci. A powerful broad-spectrum antibiotic with activity against several drug-resistant bacteria including MRSA, tigecycline can be administered before the bacterial culprit has been identified. It can be used alone to treat a wide variety of skin and abdominal infections, and is conveniently dosed every 12 hours.

A study that pitted tigecycline, both alone and in combination with other drugs, against two strains of VRE and several antibiotic-resistant *Staphylococcus aureus* strains found these strains to be susceptible to tigecycline.<sup>30</sup> The combination of tigecycline and gentamicin showed good promise as a treatment strategy for VRE and *Staphylococcus aureus* infections. In the CAN-ICU study, tigecycline was active against the majority of antibiotic-resistant bacteria found in the hospitals surveyed.<sup>5</sup>





## NOVEL STRATEGIES FOR COMBATING RESISTANCE

A growing understanding of the mechanisms responsible for bacterial resistance to antibiotics is leading research in promising new directions.

- *Beta-lactamase inhibitors*: Beta-lactamase is a bacterial enzyme that degrades penicillin-type antibiotics and renders them inactive. Thus, drugs that inhibit this enzyme could help restore antibiotic potency.
- *Anti-infection drugs*: New technologies can detect bacterial genes that switch on at critical times during infection and ensure the “success” of that infection. For example, scientists have discovered that the genes responsible for the virulence of *Staphylococcus aureus* don't switch on immediately upon infection, when the

host's immune system could overwhelm low numbers of bacteria. Instead, the bacteria monitor their own number and density, waiting until they reach a critical mass before switching on their virulence genes.<sup>6</sup>

The products (i.e., proteins) of such virulence genes are ideal targets for new anti-infection drugs. Since these drugs would simply disarm bacteria, rather than killing them, resistant strains would be much slower to emerge. And since they would only affect infection-causing bacteria, they wouldn't prompt other bacteria to develop resistance and possibly transfer their resistant genes to virulent bacteria.

- *Antimicrobial peptides*: Found in a wide variety of organisms including humans, antimicrobial peptides physically disrupt the cellular structure of invading germs, much like a needle popping a balloon. Scientists are now working on creating more potent synthetic molecules that mimic the activity of the natural peptides.
- *Plasmid expulsion*: Bacteria frequently acquire antibiotic resistance by ingesting circular pieces of DNA called plasmids, which encode proteins that thwart antibiotic potency. Researchers are developing mechanisms to expel the resistance-carrying plasmids from bacteria, thereby re-sensitizing the bacteria to an antibiotic.



- *Antibiotics from new sources:* Hoping to create entirely new classes of antibiotics, researchers at the University of California in San Diego are assessing the antibiotic potential of cyanobacteria (blue-green algae).<sup>31</sup>

### A COORDINATED VISION

Today's healthcare practitioners face the challenge of containing antibiotic resistance in a complex medical environment. To limit the impact of antibiotic resistance on the Canadian public, scientists, health practitioners, and policymakers must join forces to spur research, prioritize development, and fine-tune the use of antibiotics. Public education will play an important role in this regard.



## GLOSSARY

**Antibiotic:** A chemical substance, either from natural sources or synthetic, that treats infections by destroying or inhibiting the bacteria that cause them.

**Antibiotic resistance:** The genetically acquired capacity for a bacterium to withstand antibiotic treatment.

**Broad-spectrum antibiotics:** Antibiotics that work against a wide range of Gram-positive and Gram-negative bacteria.

**Cidal activity:** An antibiotic's ability to kill bacteria.

**Combination therapy:** Treatment involving more than one drug.

**Community-acquired infection (CAI):** An infection acquired in the community by someone who has not recently been hospitalized or had a medical procedure.

**Efflux pump:** Resistance mechanism that allows bacteria to pump out any antibiotics that penetrate them.

**Escherichia coli (E. coli):** A bacterial species that populates the human intestinal tract and has the potential to cause infection.

**Extended-spectrum beta-lactamase (ESBL):** A bacterial enzyme that inactivates some antibiotics.

**Gram stain:** A laboratory staining technique used to distinguish between two groups of bacteria (Gram-positive and Gram-negative) that differ in their cell wall structure.

**Klebsiella pneumoniae (K. pneumoniae):** A bacterial species typically found in the intestinal tract and responsible for many nosocomial infections.

**MRSA:** A type of *Staphylococcus aureus* bacterium resistant to methicillin and other beta-lactam (penicillin and cephalosporin) antibiotics. No longer confined to hospitals, MRSA has caused infectious outbreaks in some community groups.

**Narrow-spectrum antibiotics:** Antibiotics that selectively kill only Gram-positive or Gram-negative bacteria.

**Nosocomial infection:** An infection acquired in the hospital, excluding infections incubating at the time of admission.

**Ribosomal protection:** Resistance mechanism that allows bacteria to interfere with an antibiotic's ability to prevent the bacteria to make proteins necessary for their survival.

**Selective toxicity:** A drug's ability to target pathogens, such as bacteria or viruses, without damaging the host organism.

**Static activity:** An antibiotic's ability to disarm bacteria without killing them.

**Superbugs:** Bacteria with resistance to several commonly used antibiotics.

**VRE:** A type of enterococcus bacterium resistant to the antibiotic vancomycin. VRE can enter the bloodstream and may cause death in people with weakened immune systems.



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