INVISIBLE ENEMY: THE SUPERBUG THREAT

Introduction

Medicine faces some major problems at the beginning of the 21st century. In the last 25 years, 30 previously unknown human diseases have been identified for which no cure exists (among these are two of major concern to Canadians, SARS and West Nile virus). And at least 20 major maladies, including tuberculosis and malaria, have re-emerged in more deadly or drug-resistant forms.

Most alarmingly, we are on the verge of losing a battle long considered to have been won: the fight against bacterial infection. In 1928, when Alexander Fleming first discovered penicillin, a fungal spore capable of killing bacteria, a new age of medicine began. This was the beginning of the age of antibiotics. Its significance was confirmed in 1945 when Fleming received the Nobel Prize for medicine, along with Howard Florey and Ernst Chain, who had proven penicillin’s potential as a therapeutic drug.

By screening soil samples for substances that kill bacteria—the way in which most of these drugs were first developed—scientists created an arsenal of antibiotics to use in the fight against infection. By 1960, because of the wide variety of antibiotics available, many thought the war against bacteria had been won. From the beginning, however, bacteria were already fighting back. A strain of Staphylococcus aureus (S. aureus) became resistant to penicillin shortly after it began to be widely used in the 1940s.

Random genetic mutation is the reason that bacteria become resistant. Some bacteria double in numbers every 20 minutes, and some of the new bacteria are slightly different from the rest. If the mutation is one that makes the bacterium resistant to the way in which it is targeted by an antibiotic, the mutated bacterium is given a huge competitive advantage over other bacteria, and thrives. The antibiotic has actually made the bacterium stronger, and contributed to resistance to itself.

Some bacteria can and have developed resistance to most, if not all, the antibiotics that are used against them. The biggest current menaces in hospitals, especially to surgery patients, are strains of none other than S. aureus that have become resistant to methicillin and many other antibiotics (MRSA – methicillin resistant Staphylococcus aureus). Recently, some strains of MRSA have even developed a resistance to vancomycin, a powerful antibiotic with frequent unpleasant side effects. Vancomycin was used for over 30 years as an antibiotic of last resort before resistance to it emerged.

One major reason for the development of antibiotic-resistant bacteria is the over-prescription of antibiotics, often for ailments they are powerless to fight. Patients see them as “miracle drugs” and demand them from physicians. Under pressure, physicians prescribe them, knowing full well that they will have no beneficial effect.

A second major reason is that patients fail to take the full dose prescribed, which is necessary to totally clear up the infection. Instead, they stop as soon as they begin to feel better.

When improperly used, antibiotics can have three major negative effects. They can:

• Lower the body’s immunity
• Destroy “good” bacteria in the body that help with digestion
• Lead to the development of antibiotic-resistant bacterial strains

Antibiotic-resistant bacteria have become a major problem in hospitals in Canada and around the world. In Canada alone about 200,000 hospital patients each year develop a hospital-acquired infection. Increasingly often the bacteria responsible are proving to be antibiotic-resistant. The reasons, in addition to the misuse of antibiotics, are many. Canada’s population is aging, and hospitals deal with more and more patients weakened by chronic disease. Surgical treatments are more aggressive, and surgical patients are the ones most susceptible to infection. Cost-cutting has reduced the number of available hospital beds, which means hospital are more crowded; crowding people together facilitates the spread of infection.

It has been estimated by experts in infection control that, for every dollar spent on infection control, five dollars are saved in future treatment costs. Unfortunately, it is impossible to tell, after the fact, if disaster was actually averted by prudent expenditure. As a result, infection control is rarely a priority expense with governments or hospitals. Meanwhile, the direct hospital costs of hospital-acquired infections in Canada are estimated to be $1.5-billion annually.

The fight against antibiotic-resistant bacteria continues on many fronts. Despite its problems, Canada is considered to be a leader in the fight against antibiotic resistance. The number of Canadians prescribed oral antibiotics has dropped and continues to do so. The U.S., with its higher percentage of resistant bacterial strains, is also beginning to cut back on routine antibiotic use. New prescriptions of antibiotics for children fell 25 per cent between 1995 and 2000. But, as Ronald Grossman of the University of Toronto School of Medicine said in 2002 (The Globe and Mail, January 20, 2002), “There’s still a core of individuals that have misconceptions about antibiotics and are using them inappropriately.”

In addition to public education about antibiotic use, there is a new emphasis on hygiene in many institutions. New therapies, drugs, and vaccines are under development. There is a real awareness among medical professionals that this is a critical war. No one wants to go back to the times before antibiotics, when almost all seriously ill hospital patients died from bacterial infection.

For Reflection

What would your world be like without effective antibiotics? Have you, your friends or members of your family been prescribed antibiotics for infections? Which ones? Why? Have any of these people experienced any form of resistance while taking one of these drugs?
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Video Review

1. How many Canadians die every year as a result of hospital infections? ____
2. How many become ill? ______________________________________________
3. Where does hospital infection rank among the leading causes of death in Canada? ______
4. According to Dick Zoutman, how is MRSA spread?

5. What does industrial hygienist Ugis Bickus say hospitals need to do to rid themselves of infections or germs?

6. How much extra time does an infected patient spend in hospital? ______
7. What is the total cost to Canadian hospitals of extra care for infected patients?

8. According to reporter Susan Ormiston, what is the “number-one defence” against the spread of superbug infections?

9. Guidelines require one infection control professional per 100 beds. What percentage of Canadian hospitals do not meet this guideline? ______ %
10. How many cases of community-acquired MRSA had appeared in Calgary by October 2004?

11. In Chicago, what percentage of children admitted to hospital with Staphylococcus infections have MRSA? _____________ %
12. The presenter finishes this video presentation by giving two tips that doctors say are “the best ways to protect ourselves.” What are they?

13. How does this information affect your view or possible use of hospitals? Explain.

Further Research
To stay informed about current health issues facing Canadians, consider a visit to Health Canada at www.hc-sc.gc.ca.
By the mid-1940s, penicillin, the first antibiotic, was regularly being used to control infections, and by the mid-1950s some bacteria were already showing resistance to the drug. Pharmaceutical companies rapidly began developing new and stronger antibiotics, and doctors used them with enthusiasm. But bigger problems soon began to appear.

“As recently as the 1980s, doctors thought they had bacteria licked,” wrote Anna Kuchment in *Newsweek*, December 6, 2004. “But the microbes have bounced back with a vengeance, developing resistance to the strongest of antibiotics. A study released over the summer reports that 70 per cent of infections acquired in hospitals—the hot zone for disease transmission—can defy at least one drug.”

The problem is an international one, and the statistics we have are truly alarming. Complicating our understanding of the problem of hospital-acquired infection is the fact that, at least in Canada and the United States, hospitals are not required to report all cases of infection by drug-resistant bacteria. However, what we do know is scary enough. Here are some examples:

**United States**

In the U.S., between 5 and 10 per cent of all patients admitted to acute-care hospitals (that is, those hospitals that deal with non-chronic conditions) acquire one or more infections while they are there. This means that approximately two million U.S. patients are infected every year. Of these, 90,000 die as a result of their infection.

**Britain**

In Britain the most severe problem is MRSA, or methicillin-resistant *Staphylococcus aureus* (see “Five Deadly Profiles,” on page 40). In 1994, only two per cent of staph infections in hospital patients were MRSA; that figure has now risen to 40 per cent. Every year 300,000 British patients pick up a potentially life-threatening infection in hospital; 5,000 of these will die. In 2002, 800 patients died from MRSA alone.

**Canada**

Canada has a better record with some hospital infections than both the U.S. and Britain, but the trend is worrisome. In 1995, for example, the percentage of staph infections that were MRSA was one per cent; this figure had risen to eight per cent by 2000. Each year, about 200,000 Canadians suffer from a hospital-acquired infection; somewhere between 8,500 and 12,000 die. Canada’s most notorious problem with hospital-acquired infections involves *Clostridium difficile* (*C. difficile*), which has been especially prevalent in Quebec hospitals. In the year between April 1, 2003, and March 31, 2004, there were 7,004 cases of *C. difficile* in Quebec hospitals. After being infected, 1,270 patients died. Not only has the infection rate risen dramatically in recent years, so has the death rate—by almost 60 per cent. In 2000-01, 12 per cent of infected patients died. By 2003-04, 18 per cent of those who acquired the infection died.

It is important to note that some countries have even higher rates of...
Community-based Infection

The October 9, 2004, issue of *New Scientist*, reporting on a meeting of the Infectious Diseases Society of America, described an alarming new development: the rapid increase of antibiotic-resistant superbug infections outside hospitals. The culprit: methicillin-resistant *Staphylococcus aureus*, or MRSA (see “Five Deadly Profiles,” page 40). The rise in infections has been especially evident in segments of the population where large numbers of people (just as in hospitals) are concentrated together: prisons, the military, and athletic teams.

The superbugs are causing an entire range of problems, from skin boils in children to necrotizing fasciitis, or flesh-eating disease. “In one Texas hospital alone, cases of boils in children caused by MRSA shot up from nine in 1999 to 459 in 2003,” says *New Scientist*. “There were 14 cases of flesh-eating MRSA in Los Angeles last year, with several patients needing reconstructive surgery.”

Doctors, however, are especially concerned that MRSA is now causing fatal pneumonia in otherwise healthy young people. In one group of 17 people who developed MRSA pneumonia, five died—and their average age was 28.

Discussion

Many medical authorities are predicting significant outbreaks of antibiotic-resistant, community-based infections in many parts of Canada. How might public health departments prepare for them? Are there any recent experiences, Canadian or international, that might serve as templates for how an outbreak might behave, and how to respond? Has your community suffered any of these outbreaks recently?
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Five Deadly Profiles

Many different types of bacteria have developed resistance to at least one commonly prescribed antibiotic. Some strains have gone on to develop resistance to a whole variety of antibiotics. Here are profiles of some that are most worrisome for scientists and medical workers, and are common sources of hospital-acquired infections.

1. Staphylococcus aureus (S. aureus, Staph)

*Staphylococcus aureus* is a bacterium that is found on the skin and on mucous membranes, especially in the nose. If it has an opportunity to enter the body it can cause a variety of infections—skin, wound, urinary tract, and blood stream infections, and pneumonia. It can also cause food poisoning. A serious staph infection causes a high fever, attacks vital organs, and lowers blood pressure, ultimately causing the patient’s death. Before antibiotics, infections killed the majority of seriously ill hospital patients; the usual cause of these infections was staph.

Methicillin is the most commonly used antibiotic to treat staph infections. However, *S. aureus* has rapidly developed a strain that is resistant to methicillin. It is known as methicillin-resistant *Staphylococcus aureus* (MRSA). In 1990, only two per cent of *S. aureus* infections showed such resistance; by 2002 over 30 per cent of hospital staph infections in North America were caused by MRSA. Hospital-acquired MRSA can often only be treated with vancomycin, the drug that doctors often call the “antibiotic of last resort.” Cases of MRSA resistant to vancomycin are beginning to appear.

Also emerging is a new strain of MRSA that spreads through skin contact and even affects healthy people. It first appears as small sores that look like insect bites. These later turn into boils and major abscesses.

2. Enterococcus

*Enterococcus* is a bacterium that lives in the human digestive tract. Normally benign, it does not cause problems for healthy individuals. It can, however, cause infections in those with compromised immune systems if it enters the bloodstream or urinary tract through a wound. It is a common hospital problem.

Especially dangerous is VRE, or vancomycin-resistant *Enterococcus*. It causes life-threatening illnesses in the very young, the very old, and the seriously ill. It also readily transfers its resistance gene to both *Staphylococcus* and *Streptococcus* bacteria.

3. Streptococcus pneumoniae (Strep)

*Streptococcus pneumoniae* is the leading cause of inner ear infections, sinusitis, pneumonia, and meningitis. Strep was once easily treated with penicillin, but many strains have developed a resistance to it and other antibiotics. In fact, the resistance rate continues to climb rapidly. The routine dosage of antibiotics required to treat childhood ear infections from strep doubled between 1996 and 2001.

4. Campylobacter

*Campylobacter* bacteria cause diarrhea, cramping, abdominal pain, and fever within two to five days after exposure to the organism. The diarrhea may be
bloody and can be accompanied by nausea and vomiting. The illness typically lasts one week. In persons with compromised immune systems, *Campylobacter* occasionally spreads to the bloodstream and causes a serious life-threatening infection. This is the disease that is most commonly a result of handling uncooked or improperly prepared chicken.

The antibiotics most commonly used to treat severe cases of *Campylobacter* are erythromycin and quinolones like fluoroquinolone. *Campylobacter* in North America is beginning to show resistance to quinolones, which are a class of antibiotic given to both humans and animals.

5. *Clostridium difficile* (C. difficile)

*Clostridium difficile* causes intestinal difficulties ranging from diarrhea to colitis. *C. difficile* is one of the most common causes of hospital infections, and has become a major problem in hospitals in Quebec, especially in the Montreal area. There were 1 406 cases in 88 Quebec hospitals between August and November 2004 alone. Over 1 200 patients with *C. difficile* died in 2003—18 per cent of those who developed an infection.

*C. difficile* is notorious because the use of antibiotics actually increases chances that patients might develop it. When antibiotics are used to treat infections, they lower the number of good bacteria in the intestines and colon. *C. difficile* can then thrive and flood the digestive tract with infection-causing toxins. The number of hospital patients receiving antibiotic therapy makes them especially vulnerable. A recent study has indicated that the strain currently active in Quebec may be one especially resistant to treatment.

**Analysis**

Complete the following chart based on the information in this reading. Rank the “superbugs” from 1 (most dangerous) to 5 (least dangerous).

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<th>Name of Superbug</th>
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In the European Union, the use of most antibiotics to promote growth in animals has been banned since 1999. Four remaining antibiotics will be phased out in 2006. Agricultural use of antibiotics is still widespread in the U.S. and Canada, and evidence is piling up that, as a result, bacterial resistance is increasing. Studies have also shown that the use of antibiotics to promote growth in farm animals accelerates the end of their medical effectiveness. In 2002, a special committee—the Advisory Committee on Animal Uses on Antimicrobials and Impact on Resistance and Human Health—presented Health Canada with a 150-page report investigating the uses of antibiotics by Canadian farmers. The committee observed (reported by Gail Powell in *Food in Canada*, October 2002):

- Farmers have over-the-counter or feed mill access to many antibiotics without prescription.
- The food-borne infections that people get generally come from animals; antibiotic resistance in the bacteria that cause these infections also comes from animals.
- Animal-source bacteria can pass their resistance genes to human bacteria.
- Antibiotic resistance can be passed from animals to humans either through the food chain or through the environment (water, soil, or air).

Committee recommendations included:

- Antibiotics for treatment and control of disease in farm animals should only be available by prescription.
- Antibiotics not approved by Health Canada should be prohibited from importation, sale, or use.
- Any antibiotics that are important in human medicine or that impair the effectiveness of human drugs should be rapidly phased out of animal use.
- A permanent national surveillance system should be created to monitor antibiotic resistance in farm-animal production.
- Resistance risk should be included in any review of new or existing antibiotics for agricultural use.

After an in-depth investigation of the U.S. poultry industry conducted by *Consumer Reports* (January 2003), the editors made similar recommendations:

- The U.S. government should require companies to monitor data on the use of antibiotics in food animals.
- The use of medically important drugs for anything other than the treatment and control of disease should be prohibited.

To Do

In a well-written paragraph indicate whether you support or reject the recommendations outlined above.
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Fighting Back

As early as 1996 a group of Canadian health professionals, recognizing the threat from antibiotic-resistant bacteria, began a campaign against over-prescription and misuse of the drugs. The message they have tried to get across is simple:

• Antibiotics should only be prescribed for conditions for which they are effective. Viruses such as colds and flu do not respond to antibiotics; the drugs are useless.
• If one is prescribed an antibiotic, it is important to take the full dose prescribed and to not stop as soon as one is feeling better.

The campaign has been successful, and prescriptions for antibiotics in Canada are continuing to decline. Meanwhile, the rate of hospital-acquired infections has remained the same or increased. The bacteria causing these infections have become harder and harder to treat.

Prevention: Hygiene and Infection Control

The most effective way to fight hospital-acquired infections is to prevent them in the first place. The major weapons used in Canadian hospitals are to increase infection control methods and to improve environmental hygiene.

Bacteria can be spread in several ways, but health-care workers themselves are one of the major transmitters. Bacteria can be spread to a patient by doctor or nurse hand contact, on a stethoscope, or left on a patient’s bed rail. Cleanliness, especially clean hands, is a key to preventing this transmission.

In 2002, the Centers for Disease Control and Prevention (CDC) developed a “Guideline for Hand Hygiene in Health Care Settings” to assist health-care professionals in preventing hospital-acquired infections. Unfortunately, as one study demonstrated, the new guidelines are not always followed: 50 per cent of the doctors in Chicago hospitals failed to adhere to the guidelines.

William Bowie, a professor of infectious diseases at the University of British Columbia, wrote the following for The Globe and Mail (May 28, 2003) during the SARS crisis in Toronto:

“Most hospital-transmitted infections go from hospital staff or equipment to patients. We must pay more attention to the staff’s hand hygiene, to the equipment used to deliver medicines or oxygen, and to proper surgical technique. Such attention will not happen without monitoring and even haranguing. For that, we’ll need staff with the skills, the time, and the mandate to teach, evaluate, track trends, and intervene. And for that, we’ll need more infection-control practitioners.”

According to many health-care professionals and critics, Quebec’s recent problems with Clostridium difficile are partly a result of a shortage of infection-control supervisors. The Quebec government’s response has been aimed at funding more nurses dedicated to infection control. A ratio of one nurse per 130-150 acute-care beds is the aim; this is still below the national standard of one infection-control specialist per 100 beds.

The Quebec government announced other basic measures to bring the problem under control. According to the CMAJ: Canadian Medical Association
Journal (September 28, 2004), these included “increased handwashing, disinfection of rooms, isolation of infected patients and a rigorous appraisal of the use of antibiotics.”

The Dutch Response: Search and Destroy

One of the lowest rates of antibiotic-resistant hospital-acquired infections belongs to the Netherlands. The technique they use can best be described as “search and destroy.” The Dutch screen all patients for such infections, and isolate any cases they find. They also screen all hospital staff, and treat any who are found to be carriers. Both patients and staff are “decolonized” with antibiotics until completely rid of the infections. Wards and critical-care facilities where infections have been found are closed to new admissions, and thoroughly cleaned before they are reopened.

The success of the Dutch approach is unparalleled. While the rate of methicillin-resistant Staphylococcus aureus (MRSA) infections in England rose from two per cent in 1994 to 40 per cent in 2004 (and from one per cent in Canada in 1995 to eight per cent in 2000), the Dutch held their rate to one per cent. Dutch doctors insist that it is their extensive screening of patients and health-care workers alike that is responsible for this success.

To Consider

1. Do you think that the Dutch approach could be adapted to Canadian hospitals? Could most hospitals afford to close an entire ward for a period of time if an infection were discovered?

2. What other measures do you think hospitals might take to reduce infections?

3. What personal measures of hygiene could you take to lessen your risk of bacterial infection?
While bacteria are fighting back against some of our strongest weapons, doctors and scientists are not about to give up the fight against them. In addition to controlling and refining the use of currently available antibiotics, they are developing new weapons to assist in the fight. Most of the major pharmaceutical giants have given up on antibiotic research to concentrate on more profitable chronic disease treatments. Smaller biotechnology companies, however, are trying old, new, and sometimes radical solutions to the antibiotic-resistance problem. Here are some of the more promising directions their research is taking.

**Phage Therapy**

Phage therapy has been around for over a century, but was largely abandoned by Western medicine because of the initial overwhelming effectiveness of antibiotics. The technique survived in Eastern Europe, where it is still used in a number of countries.

Bacteriophages are viruses that attach themselves to the outer surfaces of bacteria and inject their own DNA, hijacking the cellular machinery of the bacterium and forcing it to make phage proteins and more phage DNA. New phages are formed, which explode out of the bacterium and destroy it in the process.

Phage therapy advantages are many. Phages are specific to individual bacteria species, and do little harm to the “good” human bacteria. Phages breed rapidly in the body, increasing in strength as needed; but they also die away as the harmful bacteria are destroyed.

The biggest potential problem with phage therapy is that some phages do not kill their host bacteria, but have a symbiotic relationship with them. Some of these phages can carry genes that may increase the bacteria’s toxicity. This is a potentially serious problem, should the wrong phages enter the body. Nonetheless, several firms are working on phage therapy, and trials are due to begin soon.

**Preventing Infection**

Developing anti-bacterial vaccines is another approach. One promising line of research recognizes that most bacteria begin invading their hosts by clinging to the cells of mucous membranes in the respiratory, gastrointestinal, or urinary tracts. It has been known for some time that there are compounds that prevent this. Some of these anti-adhesives occur naturally. For example, cranberry juice, an old folk remedy, has been used to prevent urinary tract infections for many years. Other compounds are being designed from scratch.

Cytovax, now merged with Millenium Biologix Inc., is an Edmonton-based biotechnology company recognized as a leader in this research. It has developed and clinically tested a vaccine against *Pseudomonas aeruginosa*, an antibiotic-resistant bacterium that causes 10 per cent of hospital-acquired infections in the U.S. It is believed that bacteria are less likely to develop a resistance to this type of therapy, which relies on thwarting rather than destroying the invader.
Human Antibodies to the Rescue
Rather than relying on chemistry, some companies are developing vaccines that use human antibodies to trigger the body’s immune system to destroy the invading bacteria. Inhibitex, a U.S. biopharmaceutical company, has developed such a vaccine to prevent hospital-associated infections in very-low-birth-weight (VLBW) infants. Because VLBW infants spend an average of two months in hospital neo-natal units, they are particularly susceptible to such infections. Inhibitex’s vaccine, Veronate, targets specific proteins on the surface of MRSA. It is now in its Phase III clinical study.

Improving Older Drugs
Some companies are re-engineering older antibiotics to work in new ways. One such company, Paratek Pharmaceuticals of Boston, is working to combine “resistance-reversing” drugs with tetracycline to create a new form of the drug. Tetracycline works by penetrating the cell walls of bacteria and then preventing them from reproducing. Resistant bacteria have developed mechanisms to expel the tetracycline or prevent it from disabling their reproductive system. Paratek has developed over 1 000 new molecules that are much harder for bacteria, including MRSA, to defeat. The company hopes that the drug will be approved for use by 2008.

These are only a few of the attempts being made to defeat bacteria in what Alison George (New Scientist, July 19, 2003) calls an “antibiotic arms race.” Without these drugs we would be very vulnerable indeed. “We go about our lives surrounded by billions of harmless bacteria on our skin, in our intestines, and in the environment. But if some of these same organisms manage to invade the body and multiply in the blood, the endotoxins that they produce can cause blood poisoning. For most of human history this would have been fatal.”

Without the new therapies, it could be fatal again.

Inquiry
Which of the above strategies aimed at fighting superbugs, do you think is likely to be most effective? Why?
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Protecting Family and Friends

All of us have family and friends who, from time to time, have to be hospitalized. While we tend to think of hospitals as places to go to be cured, for many individuals they have become places that make them more ill than when they went in.

More and more, patients are being asked to assume responsibility for guaranteeing the success of their treatment—by providing full information on their symptoms, by monitoring their reactions to treatments, by faithfully taking all required medications, and by asking questions to ensure they fully understand any procedure they will undergo.

For this exercise, prepare a list of at least five important things a member of your family or a friend should know or do before, during, and after a hospital stay. They should be things that would help that person to avoid the dangers of hospital-acquired infections. The list might include questions to ask, procedures to follow, or dangers to be aware of. When you have completed your list, compare it with those of other members of your class.

As a final step, compare your list with the “Tips for Adult Patients to Prevent Antimicrobial Resistance” from the Centers for Disease Control and Prevention at www.cdc.gov/drugresistance/healthcare/ha/tipsforadults.PDF; and to the “Tips for Surgery Patients to Prevent Antibiotic Resistance” at www.cdc.gov/drugresistance/healthcare/surgery/Tips_for_Surgery_Patients.pdf.

My List for Avoiding Hospital Infections

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