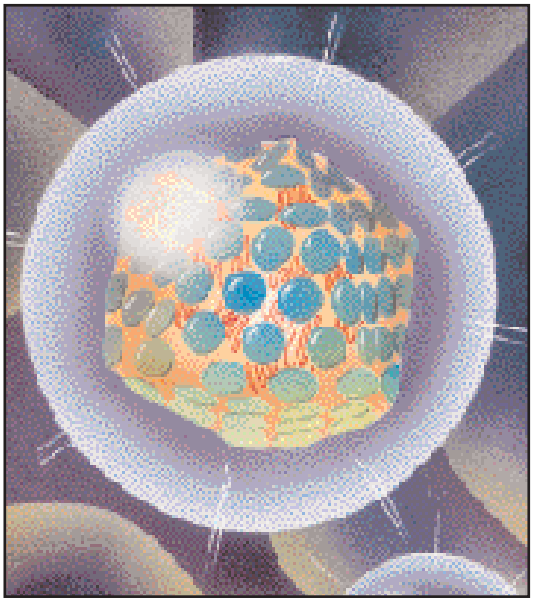


Diseases: New and Emerging

Canadian health-care workers face the challenge of finding ways to prevent, or minimize, the spread of new diseases, particularly those resistant to antibiotics, as well as those originating in other countries.

By Murray McQuigge, MD, Hon. BSc, CCFP, MPH

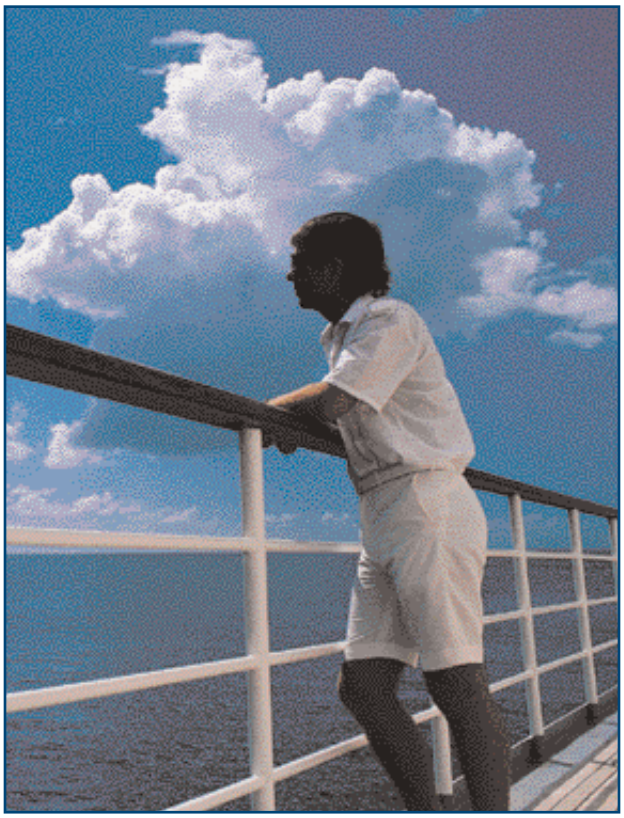
Hantavirus in Canada? Lassa fever in Germany? Reading about new and emerging diseases in the media and medical literature is now a regular occurrence. Some of the etiologies of these diseases, such as human immunodeficiency virus (HIV), prions in Mad Cow disease, and *Pfiesteria*, read like science fiction. Others remind us that the old bugs can adapt to new threats and change in virulence remarkably quickly.

Dr. McQuigge is clinical adjunct professor, University of Western Ontario, and Medical Officer of Health Bruce-Grey-Owen Sound Health Unit, Owen Sound, Ontario.

The definition of emerging infectious disease includes diseases whose incidence in humans has increased within the past two decades, or threatens to increase in the near future.

There are many individuals, organizations and private businesses tracking trends in infectious diseases. There is the potential for profit in the business of responding to such changes. Many excellent books have been written on new and emerging diseases. On the Internet, the Promed Listserve Group offers a daily update on diseases around the world.[1]

We have gone from responding to bacterial threats to responding to threats of smaller, simple viruses and simple proteins called prions. From a public health perspective, the change in infectious diseases and the emergence of new ones is both fascinating and alarming.



Health-care workers must now keep track of trends in diseases in other countries and maintain a high index of suspicion of symptoms appearing in a patient who has recently traveled.

There will not be enough space in this article to delve into the science of molecular biology, polymerase chain reaction (PCR) testing and the enhanced ability to detect, and genetically track, new and emerging diseases. Consider reading the books referenced at the end of this article (particularly *Plagues* by Christopher Wills).[2] It is not often you will get a chance to sit back and look at the "big picture" in global trends in disease. These books are easy and interesting to read, and will start you down the path to discovery.

The objective of this article is twofold: first, to give you a Canadian overview of new and emerging diseases and, second, to make you aware of those factors shaping trends in these new diseases.

This article is not meant to cause an "Outbreak Panic." The real killers in the world remain acute respiratory and diarrheal diseases in those under the age of five, as well as tuberculosis (TB), malaria, measles and hepatitis B.

Most of the emerging diseases in this article are not new, but have taken on new characteristics because of changes that are occurring in our ability to detect them, or because of changes in the environment and demographics.

Travel

It is now possible to travel almost anywhere within 24 hours. This convenience brings with it the risk of asymptomatic travelers arriving back in their country of origin with a deadly disease that they are incubating. Many countries have developed, or are developing, contingency plans that will hopefully limit, or contain, the spread of "hot virus" diseases. Health-care workers must now keep track of disease trends in other countries and maintain a high index of suspicion of symptoms appearing in patients who have recently traveled abroad.

Ebola Fever

This hemorrhagic virus, and one of the so-called "hot viruses," was first discovered in August 1976, in Zaire, during an outbreak of 318 cases, which had a case-fatality rate of 90%. Smaller outbreaks continue to appear periodically, par-

Quick Facts

The Spread of Infectious Diseases

Some demographic and environmental conditions that favor the spread of infectious diseases include:

- Global travel.
- Globalization of the food supply and centralized processing of food.
- Population growth and increased urbanization and crowding.
- Population movements due to civil wars, famines, and other man-made or natural disasters.
- Irrigation, deforestation, and reforestation projects that alter the habitats of disease-carrying insects and animals.
- Human behaviors, such as intravenous drug use and risky sexual behavior.
- Increased use of antimicrobial agents and pesticides, hastening the development of resistance.
- Increased human contact with tropical rain forests and other wilderness habitats that are reservoirs for insects and animals that harbor unknown infectious agents.

Adapted from: *www.cdc.gov* *www.cdc.gov* (Centre for Disease Control in Atlanta Georgia).

ticularly in eastern, central and southern Africa. Outbreaks have resulted from person-to-person transmission, nosocomial spread or laboratory infections.

The virus spreads through the blood and replicates itself in many organs. The histopathologic change is focal necrosis in these organs, including the liver, lymphatic organs, kidneys, ovaries and testes. The resulting manifestations are bleeding, especially in the mucosa, abdomen, pericardium and vagina. Patients die in intractable shock. Those with severe illness often sustain high fevers and become delirious, combative and difficult to control. Specific antiviral therapy currently does not exist, nor does interferon have any effect.

In 1989, a hemorrhagic disease was recognized among cynomolgus macaque monkeys that were imported from the Philippines into Reston, Virginia, about 16 km west of Washington D.C. Serological testing proved the virus to be a variant of Ebola virus. This variant virus infected the monkey handlers, but did not kill them. It was a close call. A book called the *The Hot Zone* was written about this event.[3]

Serologic studies in the Philippines and elsewhere in Southeast Asia indicated that Ebola virus is a common cause of infection among macaque monkeys. Despite intensive efforts, no known host for Ebola fever has been found, and there is currently no vaccine against this disease.

Lassa Fever

Lassa fever is caused by a virus that is transmitted to humans from a small rat common in African dwellings. The virus is transmitted

Ebola spreads through the blood and replicates itself in many organs. The resulting manifestations are bleeding, especially in the mucosa, abdomen, pericardium and vagina. Patients die in intractable shock.

mainly through food contaminated with rodent excrement. Human-to-human transmission is uncommon, but is possible under poor hygienic conditions, through direct contact with the blood, saliva, vomitus or urine from diseased individuals. Most infected individuals only become infectious when they reach the acute febrile phase. The disease, a so-called viral hemorrhagic fever, can lead to a severe bleeding disorder with shock and circulatory collapse. In hospitalized patients, mortality is about 15%. Often, the disease may run a mild or asymptomatic course. There is currently no vaccine.

On Jan. 7, 2000, a 23-year-old female German student arrived in Germany by plane, having vacationed in Africa's Ivory Coast. She had a high fever before she left Africa. On Jan. 11, she was diagnosed with Lassa fever. All airplane passengers on the two flights this student took were being traced and told to go to hospital immediately if they had a fever > 38.5°C, headache, sore throat, coughing, or intestinal upset. The student subsequently died eight days after her arrival in Germany.[1] No further cases have been reported in Germany.

Human Immunodeficiency Virus

Who could have imagined the emergence of a virus that specifically targets and destroys the very cells in humans that are responsible for maintaining our immune system, or that this virus would quickly spread worldwide? It is transmitted from person to person by sexual contact, exposure to blood and the transplantation of HIV infected tissues or organs. Acquired immune deficiency syndrome (AIDS) has killed more than 16 million people worldwide since the pandemic began, and a total of 50 million people have been infected with HIV. In Canada, AIDS is clearly now a heterosexual disease, and there is great concern about the increasing number of cases among intravenous drug users.

AIDS is a disease unlike any other that has challenged our species. It illustrates many of the features of the emerging diseases. Although discovered in 1981, HIV has been around for decades before that time. It probably was harbored in monkeys, mutated, and infected humans. It quickly spread around the world. AIDS also illustrates the barriers to an effective prevention strategy: fear, biases, prejudice

and political inaction.

The appearance of AIDS and the discovery of HIV have markedly accelerated viral research and the quest for anti-viral medications, many of which are now starting to appear on the Canadian market.

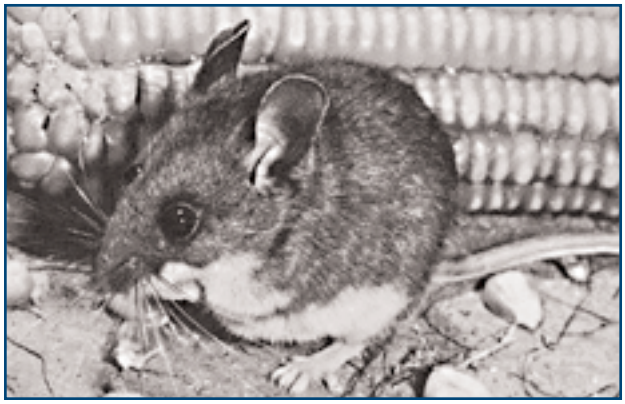
Raccoon Rabies

In 1977, a new variant of rabies appeared in raccoons in Virginia, USA, and it has been steadily travelling northward. Intensive efforts were made to try and stop raccoon rabies from crossing the border into Ontario. Unfortunately, there have been several cases of racoon rabies reported in the past two years.[5] This is serious because this variant has readily spread among populations of raccoons—an animal that is numerous and has adapted well to urban life. The current human rabies vaccine is effective against raccoon rabies.

Hantavirus

Hantavirus first came to attention in 1951-54 because of the death of over 2,500 GIs during the Korean War. The soldiers died of kidney failure caused by a previously unknown virus. It took over 20 years to successfully isolate the virus — dubbed Korean hantaan. Subsequently, many other types of Hantavirus have been discovered around the world.[6]

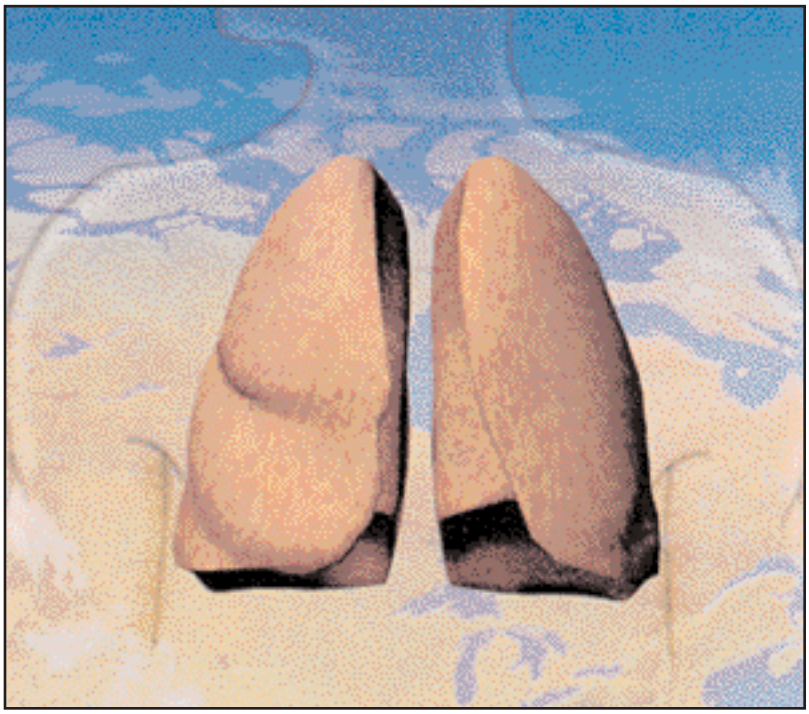
In mid-May 1993, residents of Four Corners, New Mexico, started dying of acute respiratory distress. Within weeks, the cause had been found to be a variant of the Korean Hantavirus. Through excellent biological detective work, it was soon shown that the virus was a natural pathogen in a number of rodent species, and was particularly common in a cute little white-footed deermouse, *Peromyscus maniculatus*. The virus was found to be responsible for many subsequent respiratory cases throughout the western US.[6]



Through excellent biological detective work, it was shown that the Korean Hantavirus was a natural pathogen in a number of rodent species, and was particularly common in a cute little white-footed deermouse, Peromyscus maniculatus.

Hantavirus disease also exists in Canada. As of Jan.1, 2000, the number of recognized cases are: 20 in Alberta, six in British Columbia, five in Saskatchewan and one in Manitoba. Hantavirus infected mice have been found in every province, except Prince Edward Island and Nova Scotia.[7] Person-to-person spread has not been documented in North America.

There is no treatment for Hantavirus other than supportive care, and there is no vaccine. Mortality is about 35% for the North American pulmonary variety. This virus is common in Europe, Asia and South America and is an expanding health problem in China, where about 40,000 to 100,000 cases are reported annually.



The number of cases of asthma has skyrocketed, with a 75% increase since 1980. Despite the advent of new treatments, the decrease in mortality has been relatively small, and there has been less than the forecasted reduction in morbidity.

Lyme Disease

The causative spirochete of North American Lyme disease, *B. burgdorferi*, was identified in 1982. The clinical symptoms are numerous in the short and long term. Lyme disease is found in the US as well as in Canada, where it is reported in Ontario and British Columbia. The reservoir for the spirochete is in ixodide ticks. Lyme disease can be treated with antibiotics and there is a vaccine available.

Plague

Plague, as in bubonic plague, still occurs regularly in the world, and several endemic cases a year are diagnosed in the US. The causative bacterial agent is *Yersinia pestis*. It generally is transmitted to humans from the bites of fleas infected by dead or dying rodents. Symptoms include chills and fever; painful, swollen lymph nodes in the groin, armpit or neck; and sometimes, headache, vomiting and diarrhea. Plague is treatable with streptomycin.

Influenza Pandemic

The last serious flu pandemic occurred in 1919 and killed 20 to 40 million people worldwide. Unlike the normal seasonal flu that occurs with deaths mainly in infants and the frail elderly, pandemic flu kills young healthy adults. The 1919 pandemic spread around the planet in about four months. Flu pandemics occur every 20 to 50 years. We are overdue for one.

We now know that the flu virus that occurred in Hong Kong in 1997 was close to the start of a flu pandemic. The virus had all the classic features. It was a new flu virus variant that started in fowl, was transmitted to humans, and killed children. Luckily, this flu virus variant did not transmit well from person to person. Good surveillance and the slaughter of millions of chickens and domestic ducks stopped this new flu before it could spread. The federal government and the provinces are working on plans to meet the threat of a flu pandemic.

Air

Air has been a vector for disease spread for millennia, but some recent concerns have made this vector even more prominent.

Asthma

The number of cases of asthma has skyrocketed, with a 75% increase since 1980. Despite the advent of new treatments, the decrease in mortality has been relatively small, and there has been less than the forecasted reduction in morbidity.

Asthma is a complex disease with multiple etiologies and, so far, there has not been a good explanation for the dramatic increase in asthma cases. Theories abound about the causes of asthma. It has been blamed on industrialization, air pollution, diet, food additives, carpets, allergen exposure, childhood infections and tire wear (the average latex tire is worn down at the rate of about four pounds per year, and the particles produced are so small that they act almost like a volatile gas).[8]

Toxogenic Moulds

The role of indoor fungi attributed to indoor air quality problems has become increasingly controversial. In Cleveland, in 1993, a black mold called *Stachybotrys atra* was suspected in an unusually high number of infant cases of, and deaths due to, idiopathic pulmonary hemosiderosis. Since then, school portable classrooms have been identified as a source of *Stachybotrys* contamination and concern. However, there are no conclusive studies to date that determine the human toxic effects of inhaled fungal toxins in contaminated buildings. More research is necessary to establish a scientific basis for determining if there is a need for intervention.

Multidrug Resistant Tuberculosis

One in three people in the world is infected with tuberculosis. In some places (*e.g.*, Russian jails and in the inner-core of some cities), tuberculosis has become resistant to some, or all, of the mainstay drugs used to treat it. Canada has a multidrug- resistant TB rate of 1.2%.[9] While it is costly to treat a normal case of TB, it can cost upwards of $1 million to treat a case of multidrug resistant TB.

Pollution of groundwater, rivers and lakes, and supplying water through large communal sources has led to new disease.

Canada has much lower rates of TB than most other countries in the world. The incidences of TB are so few that many Canadian health-care workers do not know how to read a Mantoux test. However, TB rates in Canada have not decreased in the past several years, which is a worrisome sign. Health-care workers should continue to be aggressive about testing for, treating and containing this disease.

Food

Although Canada's food safety programs are among the best in the world, there are increasing numbers of diseases being spread by food in North America.[10] We enjoy a wide variety of exotic foods imported from other countries whose food safety practices may be at a lower standard than in Canada.

Legionnaires' Disease is difficult to diagnose because Legionella does not grow on routine cultures. Patients generally respond well to treatment with erythromycin, however, the disease has a high case-fatality rate of 39% in high-risk patients.

Multi-national companies that are vertically and horizontally integrated are involved in agriculture. These companies control production of food from beginning to end (*e.g.*, crops, livestock, trucking, processing and retailing). This means it is increasingly possible to have potentially contaminated food that is widely distributed. Although too numerous to document in this article, outbreaks of *verotoxigenic E. Coli* in ground beef, antibiotic-resistant *salmonella* in chicken, *cyclospora* in raspberries and *Listeria* in soft cheeses are some examples of the problems with the way our food is processed, traded and distributed.

E. coli 0157:H7 disease was discovered in 1982. Shortly after that, a Canadian, Dr. Mohammed Karmali, discovered the connection between hemolytic uremic syndrome (kidney failure) and the *E. coli* 0157:H7 bacteria. A total of 95% of disease caused by this organism comes from contaminated food. Since the Walkerton, Ontario water-borne disaster of May 2000, however, we now know that municipal drinking water systems, if not protected and maintained, can be contaminated with this deadly bacteria.

Variant Creutzfeldt-Jakob Disease (vCJD)

The phrase "you are what you eat" has new meaning when it comes to prion diseases — the newest of foodborne emerging diseases.

It is being recognized slowly that there is a much closer connection between animal and human disease than once assumed. The infectious agent for vCJD is thought to be prions — unique proteins that replicate by a yet unknown mechanism. Dr. Stanley B. Prusiner discovered prions.[11] In prion diseases, he noted that some unknown trigger causes prions to change shape from a normal spiral into an abnormal conformation, which can produce disease by destroying brain cells.

There are four known prion diseases in animals: scrapie in sheep and goats, transmissible encephalopathy in mink, chronic wasting disease of American mule deer and elk, and bovine spongiform encephalopathy (BSE).[12] During the

past decade in the UK there have been reports of thousands of BSE cases in domestic cattle. The theory is that these cattle were fed scrapie-infected sheep remnants and developed BSE. In turn, humans who ate the BSE-infected beef are thought to have been at risk for vCJD. So far, over 50 people in countries, such as the United Kingdom, Ireland and France have died of vCJD. There are now reports of cows carrying vCJD in many countries.

Water

Pollution of groundwater, rivers and lakes, and supplying water through large communal sources also has led to new diseases.

Pfiesteria

A marine toxic algae, *Pfiesteria piscicida*, sometimes acts like a plant and sometimes like an animal. It was first discovered in 1991, in connection with a massive fish kill in certain river estuaries in North Carolina. The organism was fully named and described by Dr. JoAnn Burkholder after a period of intensive study in 1996.[12]

These algae lie dormant in muddy coastal estuaries, until they chemically detect the presence of mullet and other finned fishes, whereupon they metamorphose into an active amoebic state, and attack the fish. Within hours, they produce toxins that stun fish and break down the fish tissue. They then digest their prey, reproduce, and return to their normal state. These algae can undergo some 24 different morphological states, making their initial discovery very difficult.[13]

As if this were not scary enough, fishers in these waters during the algae bloom, as well as researchers studying the algae, suffered sores, respiratory problems and neurological damage, such as memory loss and mood alterations, after long-term exposure to the toxins released by the algae bloom into the air. *Pfiesteria* is only toxic in the presence of fish excreta or secretions. Scientists are now trying to identify what specifically causes Pfiesteria to become toxic.

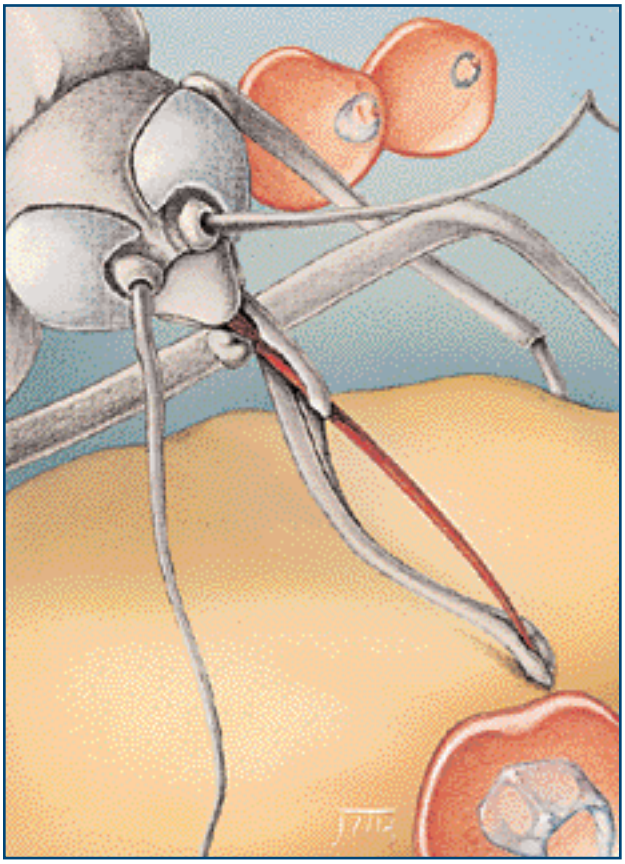
The history of penicillin-resistant bacteria illustrates how these antibiotic resistant bacteria can evolve rapidly and how it is possible to genetically track them back to their source and index cases.

Crytosporidium

This parasite has been recognized as a human pathogen since 1976. In 1982, the number of reported cases began to increase as a result of the AIDS epidemic. The fecal-oral route rapidly spreads this diarrheal disease in contaminated water or food. Several municipal waterborne outbreaks, including the 1993 outbreak in Milwaukee (400,000 cases, 100 deaths), have focused attention and concern on the potential for widespread waterborne transmission.

Legionnaires' Disease

The disease was first identified in 1977, after an outbreak of pneumonia-like illnesses amongst a group of US Legion members attending a conference at a hotel in Philadelphia. There were 34 deaths among the 221 cases identified. The source was traced to the cooling water tower



Two-fifths of the world's population is at risk of contracting malaria, 110 million new cases are diagnosed annually and the disease directly causes between one and two million deaths a year.

used for the hotel air conditioning system. Since then, the disease has been identified throughout North America, as well as in Australia, Africa, South America and Europe.

The causative agent is an aerobic gram-negative bacillus *Legionella pneumophila*. The organism is ubiquitous in the environment and proliferates well in warm stagnant water. Outbreaks recently have been traced to hot water systems, cooling towers, whirlpool spas, hotel and cruise ship water systems and decorative fountains. Legionnaires' Disease is difficult to diagnose because *Legionella* does not grow on routine cultures.

Patients generally respond well to treatment with erythromycin, however the disease has a high case-fatality rate of 39% in high-risk patients. *Legionella* is the cause of approximately 2% of community-acquired pneumonia.

Antibiotic Resistant Bacteria

Since post WWII, the focus of disease prevention has shifted to chronic disease prevention. Now with the rapid emergence of antibiotic resistant bacteria, that focus has, at least in part, returned to infectious disease prevention.

Micro-organisms that show increasing rates of resistance to commonly used antimicrobials include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), multiple antibiotic-resistant *Shigella* species, and extended-spectrum B-lactam-resistant enteric Gram-negative bacilli (Klebsiella-Enterobacter species).[14] Some strains of three bacterial species, *Entercoccus faecalis*, *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa*, already can evade every antibiotic in the clinician's armamentarium. There have been four deaths in the US from *staphylococcus aureus* that resisted vancomycin — the antibiotic of last resort.[15]

The history of penicillin-resistant bacteria illustrates how these antibiotic resistant bacteria can evolve rapidly and how it is possible to genetically track them back to their source and index cases.

More than 80% of antibiotic prescriptions are for acute otitis, pharyngitis and bronchitis.[16] Half of all antibiotics prescribed in North America are for otitis media.[5] In the Netherlands, national guidelines are followed, and acute otitis media is infrequently treated on initial evaluation. The Netherlands has one of the lowest oral antibiotic consumption rates per capita of any of the industrialized countries in the world and, not surprisingly, one of the lowest prevalence rates of antibiotic-resistant bacteria.[14,17]

Dr. Ross Pennie, in the September 99 issue of *The Canadian Journal of CME*, put forth a proposal for patients, child-care centers, and physicians to use an "Antibiotic Safety Zone" approach to rationalize antibiotic usage.[16]

What we know now is that overuse of antibiotics in humans, animal feed, veterinary medicine and even fish farms, runs the risk of the rapid development of antibiotic-resistant bacteria that quickly spread into the surrounding community.[18] This trend can be reversed if antibiotics are used to treat specific infections after diagnosis, based on careful clinical examination and microbiologic testing, and we severely limit their use for prophylaxis and as a growth promoter in animals.

Climate

World experts have finally agreed that global warming is occurring. This is not news to those who study world disease trends. There have been signs over the past decade that diseases endemic to the tropics may be moving north. A few degrees of global warming may significantly alter the pattern of disease in more northern climates.

West Nile Virus

In 1999, seven people in New York City died of encephalitis from West Nile virus (WNV). Investigation showed that these people were not epidemiologically linked to each other. The principal viral host is birds, and the virus is spread by mosquitoes. As of the fall of 2001, Ontario has seen many crows and blue jays tested, and some have tested positive for WNV. The range of those birds testing positive stretches from Windsor to Toronto, Ontario. Mosquito testing for WNV is under way, and no human cases have been reported in Ontario.

The emergence of new diseases elsewhere on the planet will have an impact in Canada sooner rather than later.

Malaria

In the Middle Ages, and even in the centuries that followed, malaria was widespread in England, Scotland and Scandinavia. The last malaria epidemic in Denmark took place in 1862.[19]

Malaria cases are now occurring in more northerly parts of the US. Malaria parasites cause immense damage. Two-fifths of the world's population is at risk of contracting malaria, 110 million new cases are diagnosed annually and the disease directly causes between one and two million deaths a year. Malaria para-

sites also are becoming resistant to current prophylactic and treatment medications.

Of Note

Toxic Shock Syndrome

Seen in the 1970s, and first defined in the US in 1987, toxic shock syndrome (TSS) is increasingly recognized in North America. The condition is due to invasive *group A Beta hemolytic streptococci* (GAS). The clinical picture ranges from that of bacteraemia to that of necrotizing fasciitis (the so-called "flesh-eating" disease. There is a new test being developed to detect the "super antigen-mediated disease" of streptococcal-induced TSS.[20]

The Link Between Chronic Disease and Infectious Agents

Several chronic disease etiologies are now either confirmed as, or under suspicion of, being due to an infectious agent (*e.g.*, duodenal ulcer [*H. pylori*], atherosclerosis [*chlamydia*] and breast cancer [mouse mammary tumor virus]).

Summary

It would seem that Darwin's theory of evolution is alive and robust, despite a recent denial by a state in the U.S. to the contrary. Humans continue to be part of the food chain (we are the largest meal around) and parasites and bacteria continue to evolve and respond to take advantage of this fact. The emergence of new diseases elsewhere on the planet will have an impact in Canada sooner rather than later. The challenge will be to find ways of preventing or minimizing the impact of these new organisms.

There needs to be a worldwide surveillance capability that looks for trends in new, and old, diseases. The surveillance system should be capable of providing sufficient warning time to respond to a threat. Health-care workers in Canada need to be well informed about world trends in disease and, ideally, should have a plan to deal with the arrival of a new and unexpected disease. CME

Acknowledgements:

- *The Infectious Disease Team of the Bruce-Grey-Owen Sound Health Unit, Owen Sound, Ontario.*
- *Dr. Harvey Artsob, Chief, Zoonotic Diseases and Special Pathogens, Canadian Science Centre for Human and Animal Disease, Winnipeg, Manitoba.*
- Dr. Susan Tamblyn, Medical Officer of Health, Perth District Health Unit, Stratford, Ontario.

References

1. *www.promed.com*
2. Wills, Christopher: *Plagues: Their Origin, History, and Future*. Flamingo,UK,1997.
3. Preston, Richard: *The Hot Zone*. Random House, Toronto, Canada 1994.
4. *www.cdc.gov* (Centre for Disease Control in Atlanta Georgia).
5. *www.ccdm.org*. (Raccoon rabies).
6. Garrett, Laurie: *The Coming Plague: Newly Emerging Diseases in a World Out of Balance*. Farrar, Straus and Giroux, New York, 1994.
7. Dr. Harvey Artsob: *Verbal Communication*. Canadian Science Centre for Human and Animal Disease and Special Pathogens, Winnipeg, Manitoba, 2000.
8. Tattersfield, AE: Limitations of current (asthma) treatment. The Lancet 1997; 350:Oct. pp. 24-27.
9. *www.hwcweb.hwc.ca* (Canadian Laboratory for Communicable Diseases Centre).
10. Fox, Nichols: *Spoiled: the Dangerous Truth About a Food Chain Gone Haywire*. Basic Books, USA, 1997.
11. Prusiner SB: The Official Mad Cow Disease Home Page: *www.mad-cow.org.*
12. Chin, James: Control of Communicable Diseases Manual. 17th

edition. American Public Health Association Publisher, Washington, DC, USA, 2000.

13. Barker, R: *And the Waters Turned to Blood: The Ultimate Biological Threat*. Simon and Schuster, 1997.
14. Conly J: Controlling antibiotic resistance. Can Family Med 1998; 9:1769-72.
15. Abraham C: Drugs Can't Stop Superbug That Kills: CDC. The Globe and Mail, Jan. 7/00, p. A2.
16. Pennie R: Welcome to the Antibiotic Safety Zone. The Canadian Journal of CME 1999; 11:51-68.
17. Cunningham A: Antibiotics for otitis media: Restraint, not routine. Contemporary Ped 1994; 11(3):17-30.
18. Levy S: *The Antibiotic Paradox: How Miracle Drugs Are Destroying the Miracle*. Plenum Press, New York, NY, 1992. Web site*: www.roar.antibiotic.org* (Antibiotic resistance).
19. Reiter P: *From Shakespeare to Defoe: Malaria in England in the Little Ice Age*. CDC Emerging Infectious Diseases Web site: *www.cdc.gov/ncidod/eid/vol6no1/riter.htm*
20. Verbal communication from Dr. Allison McGeer, Microbiologist, Mount Sinai Hospital, Toronto.

Suggested Reading

1. Peters CJ, Olshaker M: *Virus Hunter: Thirty Years of Battling Hot Viruses Around the World*. Anchor Books Doubleday, New York, NY, 1997.
2. Levy, Stuart B., The Challenge of Antibiotic Resistance. Scientific American (March 1998), pp. 46-53.