

A new century of new challenges – Infection Research faces new threats

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Infection research is experiencing something of a rebirth. The century-long decline in rates of infectious diseases has flattened out and in some cases risen over the last two decades. Many diseases that were once well-controlled have remounted their attack, and a host of new sicknesses have come to the fore. In addition, the body of scientific data has provided a crystal ball through which scientists conjure future diseases - though researchers don't when or if these new scourges will appear and how devastating they will be.

As scientists grapple with understanding how infectious diseases strike and how they spread, they also struggle to keep pace with effective treatments or preventive measures. Existing viruses and bacteria quickly morph to escape the best drugs, and new effects agents emerge that require new strategies.

Reducing the number of deaths from infectious diseases is one of the great health triumphs of the 20th century. The discovery of antibiotics, development of vaccines, and improvements in sanitation profoundly alleviated the toll exacted by infectious diseases, and deaths from infectious diseases plummeted in developed nations over the course of the 20th century.

But infectious disease is not a waning threat. It remains a significant killer in the developing world, where sanitary conditions often remain poor and access to modern medicines is limited. And in the developed world, uncertainty remains about whether treatments will keep pace as new diseases appear, existing diseases morph, and a global economy speeds the spread of infectious agents.

The global nature of travel and economy help create an environment that cultivates infectious disease. No longer geographically isolated, infectious agents can spread rapidly around the world and hamper investigations into where and how an epidemic starts--although instant communication means that, with effective surveillance programs in place, officials should be more adept at tracking diseases than ever before. And climate change will likely alter the distribution of diseases on the planet.



The (re-)emergence of old and new infectious diseases is plaguing the world and might bring it out of balance. Arnold Böcklin, 'Die Pest' (The Plague), 1898.

Old Enemies, New Threats

To tackle infection, researchers and doctors must confront a myriad of invaders. Infectious agents take on varied forms such as bacteria, viruses, fungi, and parasites, and can be transmitted through the air, in water, or by animals or insects. They range from near-instant killers to loiterers that lurk in bodies for decades. They can hide from the immune system, or trigger out-of-control inflammatory responses that destroy the host's own tissues.

And many infectious agents subtly change their genetic and molecular makeup to stay one step ahead of human defences. The variety means that doctors need many tools to fight infectious diseases, not just one cure all. But it also provides a never-ending supply of fascinating biological questions for researchers to dig into, and we will explore many of these questions in Infection Research.

Although the death rate from infectious diseases dropped dramatically over the 20th century, humans have had to battle a range of new and changed threats in recent decades. As HIV emerged and spread during the 1980s, overall death rates crept slightly upward, suggesting that limiting the impact of infectious diseases was not a matter of simply defeating known illnesses, but adapting to new ones.

Other diseases that have emerged are more familiar. For instance, carrying the HI virus increases the risk of acquiring other diseases, such as tuberculosis, and the spread of HIV has resulted in a surge in the respiratory disease. Compounding the problem, strains of tuberculosis resistant to antibiotics are spreading, hampering treatment of the disease.

Animals spread infectious diseases

Other new threats are making the hop from animals to humans. West Nile virus, a virus that infects birds and is transmitted by mosquitoes, has hopped to humans in various regions of the world at several points during the 20th century, and appeared for the first time in North America in 1999, showing that developed countries in temperate climates are not immune to changing threats in infectious disease.

And scientists struggle with new diseases that haven't yet reached epidemic proportions. In 1997, H5N1, the so-called bird flu, struck 18 people in Hong Kong. In the mid-2000s, the virus spread and killed birds across Asia, and in Africa and Europe. A second human outbreak occurred in China in 2003. Since then, 172 people in 12 countries have died, according to the World Health Organization.

Human infections seem to have resulted from direct contact with infected poultry. Though the virus doesn't seem to transfer readily between humans, researchers fear that with only a few genetic changes the virus could hop easily between people, triggering a world-wide epidemic, or pandemic. They fear a pandemic even more deadly than the 1918 Spanish flu outbreak, which by some estimates killed as many as 50 million people worldwide.

In particular, the 1918 flu virus also originated in birds, and bears some resemblance to H5N1. Researchers are currently working to develop vaccines that would protect against such a prolific virus, and identify antiviral medications that could help people who are struck with the flu. At

the same time, governments struggle with how to properly prepare for a new flu pandemic, without fostering panic.

Updated Antibiotics

To fight infection, we rely on multiple defences. When our bodies confront a bacteria or a virus we haven't experience before, we rely on innate immunity, which recognizes general chemical patterns commonly seen on infectious agents and spurs immune cells to devour anything with that pattern. This system is thought to be evolutionarily ancient; it is found in mammals, insects, and even plants.

In vertebrates, a second branch of immunity provides animals with a memory of what agents have infected them. This system uses antibodies and specialized cells that are fine-tuned to particular agents, which kick into action if those agents infect a person again. Most of the time, the human immune system efficiently battles back infections--so effectively, we may not even know that we were infected. But when our immune systems falter, we need extra help. Scientists have devoted decades of effort to generate additional weapons

The discovery of antibiotics in 1940 revolutionized the treatment of bacterial infections. Suddenly, diseases that once spelled certain death became almost trivial to treat. But just as quickly, microbes developed capacities to circumvent antibiotics. The problem of antibiotic resistance is now especially profound. Hospital patients are frequently infected by *Staphylococcus aureus*, and now, almost all strains of *S. aureus* in hospitals are resistant to penicillin.

Even worse, perhaps half of those are so-called multi-drug resistant *S. aureus* (MRSA) strains and are impervious to methicillin, a second-generation drug developed to tackle penicillin-resistant strains. Thus, the principle weapons doctors possess to battle hospital infections are dulling. And it's not just a problem in hospitals. Many prominent infectious bacteria are developing resistance in the general human population, including those that cause pneumonia, tuberculosis, malaria, and salmonella poisoning.

At the same, the development of new kinds of antibiotics has come to a virtual standstill. Scientists must invest huge effort to devise increasingly subtle twists and tricks to foil infectious agents. Yet the apparent success of existing drugs means that companies and government are reluctant to invest money into truly novel drugs. To create new antibiotics, researchers commonly make subtle changes to the chemical structures of existing drugs, meaning bacteria can quickly adapt to circumvent novel treatments.

Since 1963, doctors have not had access to any truly new kinds of antibiotics, except for linezolid, a so-called oxazolidinone approved for human use in 2000, and daptomycin, a so-called cycle lipopeptide introduced to medical practice in 2003. Because existing drugs appear so successful, pharmaceutical companies and funding agencies have shown little interest in devoting significant resources to generate new classes of antibiotics.

As advocacy organizations lobby for more support for antibiotic development, researchers continue to delve into the biology of bacteria and the diseases they cause for leads on new treat-

ments. For instance, scientists are probing the variety of mechanisms that bacteria use to counteract antibiotics and how those mechanisms evolve in bacteria or how the genes responsible hop between organisms.

Researchers are also delving into how bacteria organize themselves to look for new clues. Bacteria use control mechanisms known as quorum sensing to communicate and to adjust their growth. Among other things, these mechanisms help bacteria form biofilms, slimy sheets of cells that function much like tissues, with different regions of the biofilm carrying out different functions. Biofilms can spur disease, such as in cystic fibrosis. Scientists are teasing apart the molecular strategies that bacteria use to communicate with each other and form biofilms; short-circuiting these processes might be a fruitful approach to preventing disease.

Vaccine View

Along with the discovery of antibiotics, the generation of vaccines represented one of the great public health triumphs of the 20th century. Thanks to vaccines, once widespread diseases such as smallpox, measles, and polio virtually disappeared. Smallpox has been eradicated, but measles and polio outbreaks still occur, in some part because vaccine programs wane or because vaccines are unavailable in developing countries.

Researchers continue to apply the vaccine strategy to countervail modern diseases. Influenza vaccines are common, although scientists and public health experts continue to struggle to predict which strain will be most prevalent in a given year. And researchers continue to devise other ways to make flu shots work better. For instance, flu vaccines don't protect the elderly as well as younger patients. Scientists are striving to understand what is different about immunity in the elderly and to invent new formulations that make flu shots more effective.

Other diseases are also in the sights of vaccine makers. Scientists have generated drugs that prevent death from AIDS and allow patients to live many healthy years while carrying the virus. But HIV continues to spread, especially among impoverished groups in developed countries, and through populations in developing nations. Researchers have struggled to create a vaccine against HIV for more than two decades, but with little success, and to date no vaccine is yet commercially available. HIV morphs quickly and employs mechanisms to cloak itself from a host's immune system, making it difficult to pinpoint a molecule that will prime the immune system to fight HIV.

Scientists continue to tease apart how HIV and the human immune system interact, and devise new strategies for vaccine design. But HIV vaccine development will continue to face the challenge of the expense of testing and the logistics of carrying out trials in developing countries, where vaccine demand is the greatest. And if an effective vaccine emerges, we will need to solve the problem of how to get it to populations with the greatest incidence of HIV.

Good Neighbors

Microbes get a bad rap, but we can't live without them. In fact, for every human cell in our body, we carry ten microbes. Some of these microbes are crucial for healthy human growth. In the womb, developing fetuses don't have gut bacteria, for instance; newborns acquire them during and after birth, and establishing this gut colony is crucial for health. The right assortment helps establish a robust immune system and extract the most energy from food.

Research over the past few years is just beginning to reveal the diversity of microbes that we carry. Scientists are probing the genomes of the microbes in our guts to figure out who resides there. And they are now investigating how changes in the assortment of those microbes influence susceptibility to diseases. For instance, recent studies suggest that obese rodents were less likely to harbor one type of bacteria in their guts than were slimmer animals, and early reports suggest the same holds true in humans. Because gut bacteria also represent the first line of contact between humans and invading microbes, the variety of microorganisms there could alter whether we resist an infection or fall ill. That knowledge could lead to ways of altering the flora inside us for optimum health.

Diving Into Immunity

As we discover more about the microbes in and around us, researchers are also gaining new knowledge about how our immune system responds to them. For instance, scientists have made significant progress in the last decade in understanding innate immunity, the web of cells and molecules that provide the first line of defence against infections. Scientists have identified receptor molecules in humans that recognize molecular patterns on invading microbes. After detecting such patterns, these so-called Toll-like receptors trigger an inflammatory response that kills the interlopers.

The innate immune system provides a blunt instrument to destroy things that look like they don't belong. But researchers are now finding that the innate immune system is more complicated than that simple picture. It is also intimately entwined with the adaptive immune system, the branch of the immune system that provides long-lasting defences against specific infectious agents. For instance, innate immunity activates the cells that generate a more focused adaptive immune response.

As innate immunity's complexity comes to light, researchers are investigating whether tweaking innate immunity could provide a new route to resist infection. For instance, molecules that prod Toll-like receptors could prime the immune system and help vaccines work better. And shutting down Toll-like receptors could quench chronic inflammation, in part a product of an overactive innate immune response.

Infection Connection

Infections don't just foster diseases like flu and pneumonia; increasing evidence links infections to chronic diseases, including ulcers, cancer, heart disease, and diabetes. The idea that infectious agents trigger chronic conditions has been floating around for perhaps centuries, but the first solid validation of the idea came in the 1980s when researchers showed that *Helicobacter pylori*

caused ulcers. Stress and diet had formerly been considered the primary causes, but the new discovery revealed that the disease disappeared only when the bacterium was eliminated. The debilitating disease could be cured with a simple course of antibiotics.

H. pylori has also been connected to stomach cancer, and numerous cancers have infectious triggers. The human papilloma virus (HPV) spurs cervical cancer, for instance. In 2006, the United States Food and Drug Administration approved the first vaccine against the sexually transmitted virus, and officials have recommended vaccination for 9- to 26-year-old females. In fact, numerous states in the U.S. have explored the idea of mandating the vaccine. However, some critics have railed against such policies, saying they would promote promiscuous sexual behavior.

Nevertheless, the vaccine could drastically reduce the rate of HPV infection and cervical cancer. Although not all women with HPV develop cervical cancer, almost all women carry the virus at some point in their lives. The vaccine could even prevent a rare cancer in men. Vaccines already prevent other cancers, such as liver cancer caused by hepatitis B virus (hepatitis C virus also causes liver cancer, but no vaccine yet exists). Researchers are bolstering connections between other infectious agents and cancers; in addition, they are using their expanding knowledge of the immune system to devise tricks that prompt immune cells to attack tumors.

Other diseases also might have infectious origins. Individuals with cardiovascular disease often are infected by herpes viruses or *Chlamydia*, according to some reports, and carry antibodies to those microbes. The link remains tenuous, but the notion remains that an infection could be the start of clogged arteries. And diabetics tend to acquire infections, but infections might spur the disease in the first place. Some researchers have connected gum disease- a bacterial infection- to diabetes. Gum bacteria could access the blood stream and ignite an inflammatory response that spawns diabetes, the thinking goes. And infection by *Borrelia burgdorferi*, the cause of Lyme disease, can lead to lifelong arthritis and neurological problems.

In 1967 the United States Surgeon General proclaimed the end of infectious disease. But epidemiology, medicine, and basic biology over the last several decades have revealed that infectious diseases have not disappeared. Instead, the threat is a constantly changing one, and a concerted research effort from multiple fields is necessary to keep up with the challenge. Infection Research aims to keep scientists on top of this ever-changing field.