# Chapter 1
# Infectious Diseases, Introduction

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Infectious diseases of humans and animals are illnesses resulting from an infection caused by the presence or growth of a biological organism, often termed a pathogen, for its disease-causing behavior. The term derives from the transmissibility of the pathogen to others and when this results in large numbers of infections in a region can be responsible for epidemics. Pathogens responsible for infectious diseases can be viruses, bacteria, protozoa, fungi, multicellular parasites, and prions. While antibiotics and vaccines have made major progress in the treatment and prevention of major infectious diseases, largely in the developed world, the developing world still bears a significant burden of disease due to infectious disease pathogens such as malaria, tuberculosis, and the Human Immunodeficiency Virus (HIV). Changes in the environment, zoonotic pathogens and their interaction with human populations, and medical practice including treatment and vaccines are just some examples of determinants that can modulate the impact of infectious diseases, in terms of spread, ability to cause disease, or even response to prevention or treatment measures. The ever-changing dynamic nature of infectious diseases is not only due to some pathogen's intrinsic propensity for diversity and fitness but also complex lifecycles involving intermediate nonhuman hosts. Therefore, our ability to control or eradicate various infectious diseases must entail new technologies and analytic methods.

There is significant disparity in the burden of infectious diseases globally. According to the 2008 Global Health Observatory report, infectious diseases only account for one of the top ten causes of death in high-income countries of the world, whereas in low- and middle-income countries, four of the ten leading causes of

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death are infectious diseases [1]. However, the mobility of populations globally has resulted in infectious disease outbreaks such as the H1N1 influenza outbreak in Mexico in March 2009 that led to 28,000 confirmed cases in the United States just 3 months later. The WHO raised the pandemic alert level to phase 6, the highest level indicating a global pandemic, because of widespread infection beyond North America to Australia, the United Kingdom, Argentina, Chile, Spain, and Japan. Six months after the initial outbreak in Mexico, H1N1 infection had been confirmed in over 200,000 people from more than 100 countries and several thousand deaths [2]. While influenza virus infections are found in both high- and low- and middle-income countries, the virus responsible for this pandemic appeared to be a novel virus with characteristics of North American and Asian swine influenza viruses, as well as human and avian influenza viruses. Thus, the viruses' propensity for variation through genetic reassortment, various animal reservoirs and their contact with human populations, and the mobility of populations led to an epidemic of global proportions in a short time period.

In the past decade, international donor agencies have supported large-scale programs to address the gap in prevention and treatment of HIV/AIDS, malaria and tuberculosis. The burden of these three infectious diseases is disproportionately high in Africa, where health systems are weak and heavily dependent on foreign aid. The President's Emergency Plan For AIDS Relief initiated in 2005 is the single largest funded program for a disease in the history of US government support, active in 30 countries primarily in Africa and responsible for the initiation of antiretroviral therapy to 3.2 million adults and children with AIDS. A summary of the "HIV/AIDS Global Epidemic" describes the many challenges posed by the HIV virus, first described in the early 1980s. The HIV/AIDS epidemic most severe in Africa has also led to a concurrent increase in tuberculosis, where the presence of either infection increases the risk of coinfection, and as a result in the past decade, TB incidence has tripled. HIV and TB coinfected patients are more difficult to treat and are responsible for the highest mortality rates in both untreated and treated populations. The complex "Tuberculosis, Epidemiology of" described by Mario Raviglione and colleagues illustrates both the severity of the public health problem and the efforts by the WHO Stop TB alliance in its control. Development of improved, cost-effective, and point-of-care diagnostics is an emphasis for all three of these pathogens.

The development of drug resistance is another feature common to many infectious disease pathogens. The widespread use of chloraquine to treat malaria in the 1940s and 1950s, led to the detection of chloraquine resistant malaria first in South America and Asia and later in Africa by the late 1970s. It became widespread across Africa within a decade. Continued surveillance for drug resistance is critical to adjust treatment policies and the need for more effective drugs is ever present. In 2006 in Tugela Ferry, South Africa, the interaction between tuberculosis and HIV resulted in the recognition of an "extensively drug resistant" tuberculosis strain (XDR), where the bacteria was not only resistance to the common first line drugs, rifampicin and isoniazid but also to drugs in the quinolone family and at least one of the second line drugs [3]. The XDR tuberculosis epidemic in Tugela Ferry was unusually severe with rapid ($\sim$2 weeks) mortality, demonstrating the grave

consequences of pathogens that readily evolve under drug pressure. As a result of these biologic propensities, the need for new drugs that target resistant strains is an ongoing process. The cost of second and third line drug therapy is prohibitive in most low-income countries and the need for more efficacious and cost-effective drugs is an important priority. Unfortunately, despite the importance of these pathogens like malaria and TB primarily in low-income countries, major biotechnology firms do not prioritize these diseases agents for diagnostic, vaccine, or drug development. The example of malaria and the structural barriers to solutions for low-income (tropical) settings is well described by J. Kevin Baird in "Tropical Health and Sustainability."

It is widely believed that prevention measures including vaccines are the most effective means of combating infectious diseases whenever possible and this becomes of paramount importance in infectious diseases with high burden and mortality. In the case of malaria, the ubiquity of the mosquito vector, difficulty in its control, and prevalent drug resistance all lend support for the search for an effective malaria vaccine. As described by Christopher Plowe in "Malaria Vaccines," a study conducted in a single African village, documented more than 200 variants of blood stage malaria antigens. Thus evidence of the difficulty in developing vaccines that must elicit cross-protective immunity to an ever-expanding set of antigens, such as the multiple parasitic stages of malaria. Despite these many challenges, Christopher Plowe describes progress toward a malaria vaccine that would reduce parasite burden, rather than sterilizing protection, such a vaccine would be an important milestone to be reached in the short-term future of malaria control.

While effective vaccines against poliomyelitis have been available since the 1950s, the global eradication campaign is still in effect, with >99% reduction in the number of cases since 1988 and the inception of the Global Poliomyelitis Eradication Initiative by the World Health Assembly. Indigenous poliovirus remains in only four countries of the world, including Afghanistan, Pakistan, Nigeria, and India. "Polio and Its Epidemiology" by Lester Shulman describes the complexity of a disease system with both natural and vaccine strains of the poliovirus, and the many challenges to its future eradication. The use of the live oral polio vaccine has generated vaccine-derived poliovirus, which contributes to the complex molecular epidemiology of polioviruses in countries with residual infection. The cost and implementation considerations for polio's ultimate eradication are therefore far from simple. It is possible that alternative inactivated vaccines may need to be developed if the ultimate phase out of the current oral polio vaccine is to be considered.

Worldwide, one billion people are infected with pathogens termed neglected tropical diseases, largely in low-income countries. Many infectious diseases in this category are considered waterborne. A comprehensive review of major waterborne diseases is covered in "Waterborne Infectious Diseases, Approaches to Control" by Fenwick and colleagues. Where the water serves as the habitat for the intermediate animal host or vector and the proximity of human populations facilitates the lifecycle. These include diseases such as schistosomiasis, a protozoa transmitted by snails and guinea worm, transmitted by contaminated water, onchocerciasis or river blindness transmitted by flies, as examples. Protozoal and parasitic infections

often have complex lifecycles involving multiple hosts, creating challenges to prevention and treatment. Since 1986, the Carter Foundation has devoted its efforts to neglected tropical diseases such as guinea worm in Africa. More than 3.5 million people were affected by this parasitic roundworm untreatable infection caused by *Dracunculus medenisis* in the 1980s and today, the eradication of this disease through prevention is imminent, despite its neglect in the global health agenda.

Zoonotic diseases are infectious diseases transmitted from animals to humans, and constitute more than half of infectious diseases to humans [4]. There are examples of viruses, bacteria, protozoa, parasites, and prions (transmissible proteins) that are considered zoonotic diseases, where their biology and epidemiology are influenced by the animal host, its behavior, and ecology. Examples such as anthrax (*Bacillus anthrasis*), bovine tuberculosis (*Mycobacterium bovis*), brucellosis (*Brucella* sp), cysticercosis (*Taenia solium*, the pork tapeworm), echinococcosis (*Echinococcus* sp), and rabies virus are endemic in many developing countries of Africa, Asia, and South and Central America. Many of which have poor human and veterinary infrastructure to control these important pathogens. Interdisciplinary research is needed to develop novel and more effective control measures. The divided responsibilities between veterinary and medical governing bodies and resources needs to be further integrated as envisioned by the "One Health" initiatives that study the risks of biological pollution on wildlife and humans.

Climate change has long been considered an important determinant of many infectious diseases but the field has been recently expanding in its scope. Pathogens requiring an intermediate host or insect vector may be particularly sensitive to climate change. Warmer temperatures will be predicted to provide an expanded environment for vectors such as mosquitoes, potentially changing the distribution of vector borne human disease. Climate change has also been associated with the frequency or magnitude of outbreaks of food poisoning due to salmonellosis in meat or Vibrio infection in shellfish. This field is expanding to consider infectious diseases that are nonvector borne with consideration of climate's impact on seasonality, pathogen replication, dispersal, and survival. However, as described in "Infectious Diseases, Climate Change Effects on" by Matthew Baylis and Claire Risley, the methodology for predicting climate change's impact on disease is yet to be fully developed and more research is needed to collect data on pathogens that might be influenced.

Disease control in humanitarian emergencies should rely on joint situation analysis and technical support involving experts from related specialties and include the development of standards, guidelines, and tools adapted for field use. Communicable disease epidemiological profiles and risk assessments specific to countries or crisis situations prioritize interventions and provide policy guidance to national authorities and humanitarian partner agencies for the control of communicable diseases in specific settings [5]. As an example, in an 8-week period in 2011, a cholera outbreak was reported in the Democratic Republic of Congo (DRC) and Republic of Congo, a poliomyelitis outbreak in Pakistan, and cases of avian influenza in humans in Egypt. Thus highlighting the ever-changing threat of infectious disease infections on a global and temporal scale.

The dynamic nature of various infectious disease agents is thus evident from a variety of examples, and the harnessing of new technologies for the rapid diagnosis and response to infectious disease agents is described in "Infectious Diseases, Vibrational Spectroscopic Approaches to Rapid Diagnostics" by Jeremy Driskell and Ralph Tripp. These new high-resolution approaches are being developed and evaluated for both bacterial and viral pathogens. Their further instrumentation and commercialization envisions point-of-care, mobile, and cost-effective spectroscopic based diagnostic methods, which has great potential for the sustainability of infectious disease agent control in our ever-changing environment.

The development of new treatments for current, emerging, and drug resistant infectious disease pathogens is also a priority. In "Antibiotics for Emerging Pathogens," Vinayak Agarwal and Satish Nair describe improvements and innovations to the approach of identification of antibiotics through metabolic connections between the host and microbe, as well as synthesis and mining of new potential antibiotic candidates. Added to these more conventional approaches is the use of genomics and bioinformatics to identify antibiotic gene clusters and microbial ecological evaluations to better understand the interactions of natural antibiotic with their microbial targets. Future emphasis on narrow spectrum antibiotics coupled with more discriminating diagnostic methods may reduce the emergence of drug resistance already associated with use of broad-spectrum agents.

"Infectious Disease Modeling," as described by Angela McLean, has become an important methodology to characterize disease spread, both in populations and within a single host. While within-host modeling, often considers the spread of infection within an individual and its interface with the host's immune responses, newer models employ multiple levels simultaneously; such as within-host dynamics and between host transmissions. Modeling has become an even more important tool in characterizing infectious diseases particularly with the challenges of growing population and densities. These methods can organize available data and identify critical missing data. Perhaps most important is the use of modeling techniques to compare or project the impact of various intervention strategies.

To complete the coverage of this volume, we are pleased to have contributions on Human Bacterial Diseases from Ocean; Marine and Freshwater Fecal Indicators and Source Identification; Waterborne Diseases of the Ocean, Enteric Viruses; and Waterborne Parasitic Diseases in Ocean.

Globally, infectious diseases account for more than 17 million deaths each year. While modern medicine and technology have diminished the threat of many of these pathogens in high-income countries, the ever present threats of reemerging infections, population mobility, and pathogen genetic variability are but some of the reasons for the dynamic threat of this broad category of risks to human health. The majority of infectious disease burden remains in the tropics, in low- and middle-income countries with scare resources, infrastructure, and health systems to mount or sustain control efforts in the absence of outside support. It is therefore critical that efforts from the scientific research community and international donor agencies continue to increase their efforts with integrated goals of vigilant surveillance, improved and cost-effective diagnostics, and treatment with a goal of sustainable control.

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