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Original article

The book reopened on infectious diseases

Maria Avila, Najwane Saïd, David M. Ojcius*

School of Natural Sciences, University of California, Merced, CA 95344, USA

Available online 10 July 2008

Abstract

Emerging infectious diseases represent a major challenge to human health worldwide. The risk of evolving new infectious pathogens has been intensifying due to urbanization, demographic changes, air travel, inappropriate use of antibiotics, and climate change. These pathogens can affect humans from urban centers to the remotest corners of the globe. Far from being a scourge of the past, infectious diseases are relevant for the world today.

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Keywords: Infectious diseases; Pathogens; Worldwide; Pandemics; History

1. Introduction

At the beginning of the twentieth century, infectious diseases were the leading cause of death worldwide [1]. A child born in 1900 had almost a 10% chance of dying between the ages of 1 and 4, often as a result of pneumonia or a diarrheal disease [2]. But with improvements in nutrition, housing, sanitation, hygiene, and the availability of safer food and water, the average life span increased tremendously. The discovery of antibiotics in the mid-twentieth century has also contributed to the increased estimated life span. With such phenomenal progress being made in combating illness, Surgeon General William H. Stewart informed the United States Congress in 1969 that it was time to “close the book on infectious diseases” [3]. However, when declaring such a victory, he never could have predicted the increase in emerging, re-emerging, and antibiotic-resistant infectious diseases that were witnessed in the subsequent 30 years [4]. This has led to growing concern regarding new and re-emerging infectious diseases.

This concern may come as a surprise to many. After all, we live in modern cities, protected by clean homes, antibiotics, and large jars of antibacterial gels. But the annual human

mortality rate from recent emerging diseases varies in degree from fewer than 100 deaths due to avian flu (H5N1 strain) to 2.1 million AIDS-related deaths in 2007 [5].

2. Vaccination and other public health advances

In the late 1700's, Doctor Edward Jenner had a variety of career options but he chose to become a Surgeon under John Hunter at George's University of London, starting a journey that led him to helping to launch the modern era of public health [6]. Following the realization that milkmaids were typically immune to small pox after their exposure to cowpox, Jenner vaccinated James Phipps using the contents from a cowpox lesion on the hand of milkmaid Sarah Nelmes [7]. After this first recorded immunization – and unsuccessful attempts to infect Phipps with smallpox at a later date demonstrated his immunity – the vaccination era had begun. Although Jenner lacked an understanding of modern immunology, his clinical observations had convinced him that milkmaids were protected from smallpox because of their previous exposure to cowpox, and he acted to see if nature could be replicated [6].

Public health is considered the first line of defense in the battle between humans and microbial pathogens. Probably the most difficult part of fighting infectious disease was the acknowledgment of its existence and spread. A well-known

* Corresponding author. School of Natural Sciences, P.O. Box 2039, University of California, Merced, CA 95344, USA.

E-mail address: dojcius@ucmerced.edu (D.M. Ojcius).

account of early endeavors in the public health arena show Louis Pasteur attempting to educate the people of France regarding the existence of microorganisms and their spread of disease through foul odors and general filth [8]. Louis Pasteur's research in the 19th century led to the proposal of the germ theory, which opened the door to the pursuit of better-informed solutions to the spread of infectious diseases [8].

Arguably, an invention with the largest impact on human health was due to British patent 4990, issued in 1898, for the “silent valveless water waste preventer”, better known as a flushable toilet [9]. Over the years, there has been much discussion as to whether the true inventor of the flushable toilet was Thomas Crapper or Albert Giblin. However, as interesting as this debate has proven to be, the importance of the flushable toilet invention as an effective means of human waste removal from urban residences remains significant for its immense improvement in public health, regardless of the inventor.

The foremost figure in the modern fight against infectious disease is Alexander Fleming, the discoverer of penicillin, the first antibiotic, in 1929 [6]. After serving time fighting infection in World War I, Alexander Fleming returned to his alma mater, St. Mary's Hospital, London, and continued to study infection. At age 47, he observed that a mold, *Penicillium*, had inhibited the growth of bacteria, which led to the subsequent identification of penicillin [10]. This discovery was a tremendous advancement in public health. It gave the world a “miracle drug” and spawned research that resulted in a vast array of other antibiotics [7]. The life expectancy in the United States and Western Europe had increased by at least 30 years in the last century due to such improvements in public health, one major reason being the use of antibiotics to treat childhood infections.

3. Major events in the history of infectious diseases

When humans began domesticating animals and crops about 11,000 years ago, a huge benefit was the increase in the size of human populations across Asia, Europe, and Africa [11]. Coupled with this advance was the ease of infectious agents' crossing over the species barrier and humans becoming the hosts for an entire new class of microorganisms. The plague, tuberculosis (TB), flu, and smallpox are the best documented and most relentless infections that humanity has co-existed with these many millennia [12].

During human dispersal throughout the world, human impact on ecology and interactions with other species have profoundly influenced the subsequent patterns of infectious disease [2]. The spread of humanity into unfamiliar terrain exposed people to new infectious agents in addition to facilitating the radiation of existing infectious diseases. Along with increased social exchanges, pathogens were freely shared between populations [13].

The plague is an infectious disease of animals and humans caused by a bacterium, *Yersinia pestis*, which is typically transferred from rodents to humans through the intermediary of fleas [14]. The first recorded account was an outbreak among

the Philistines in 1320 BC. In the last 2000 years, plague has become widespread, affecting a large number of countries on most continents during several pandemics. To date, there have been three reported plague pandemics. The first plague lasted from 542 to 546 AD. The second, the “Black Death” of the 14th century, from 1347 to 1350 AD, decimated 30–60% of the population of Europe. And the third, beginning in Hong Kong in 1894, destroyed communities for 10 years on five continents, killing untold millions [15].

TB is caused by *Mycobacterium tuberculosis* and is transmitted from humans to humans through aerosols. The earliest detection of *M. tuberculosis* is from bison remains from 18,000 years ago. But it remains to be established whether TB originated in cattle and was then transferred to humans, or diverged from a common ancestor [16]. The remains from prehistoric humans (4000 BC) and mummies (3000–2400 BC) show evidence of TB [17]. By the mid-nineteenth century, humans finally appeared to be winning the battle in the war against TB. Due to advances in antimicrobial therapies, a worldwide eradication program ensued [15]. However, even today, over one-third of the world's population is still exposed to *M. tuberculosis*, which in most cases gives rise to asymptomatic, latent TB [18]. But about 10% of latent infections develop into active TB, which can result in death of over 50% of subjects.

The 1918 influenza pandemic, or “Spanish flu”, is believed to have started on March 11, 1918, in Camp Funston, Kansas. The name of the pandemic was due to the early mortalities observed in Spain, where 8 million people are estimated to have died in May, 1918 [19]. The earlier wave of influenza in Kansas was barely noticed in the midst of World War I. The virus continued to mutate and by the end of 1918, it had circled the globe in three waves, taking more lives in its 1st year than the entirety of the “Black Death” [7].

The tables seemed to have turned on infectious diseases with the first successful disease eradication program. The concept of the global eradication of smallpox was initially proposed in 1953 by the first Director-General of the World Health Organization (WHO) [20]. The global eradication program was a coordinated effort that included standardization of vaccines, vaccination technique, laboratory diagnosis, and approaches to outbreak control lasting from 1960 to 1979. This program is judged to be one of the greatest successes in the history of public health. The climax occurred in 1979, when the WHO declared smallpox eradicated [21].

It appeared that the world was going to be rid of the scourge of smallpox and TB, and, with the increased use of antibiotics, these eradication programs heralded the end of infectious disease. But following these health successes, the public health systems of the world were dealt a harsh blow in the early 1980's, with the advent of AIDS [12], followed by an increase in multi-drug resistance tuberculosis (MDR-TB) and other drug-resistant infectious diseases. WHO reports approximately two million deaths due to TB worldwide each year, many of which could have been prevented with appropriate drugs. Moreover, there are an estimated 450,000 new cases of MDR-TB every year, which may be a conservative number due to

inadequate surveillance [15]. Worse yet, WHO estimates that each person with MDR-TB infects up to 20 other people on the average during his or her lifetime.

With increasing antibiotic resistance and a new wave of emerging infectious agents, including the re-emergence of familiar agents, the public health agencies began a new era of challenges facing the world populations.

4. Recent emerging infectious diseases

The key players in global health management are the WHO, the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE). The emergence of new diseases, many of which are zoonotic, is drawing these historically independent organizations together as never before. These public health watch dogs have observed the current evolution of infectious disease occurrence and their increasing pace of proliferation. Beyond AIDS and MDR-TB, recent emerging diseases include Ebola, Legionnaires' disease, Lyme disease, cryptosporidiosis, West Nile virus, and severe acute respiratory syndrome (SARS) (Table 1).

In 1976, the Ebola virus was first recognized in the Congo by its ability to cause aggressive lethal hemorrhagic fever in humans and non-human primates. Since this time, there have been numerous outbreaks in Africa, with mortality rates from 50 to 90% [22]. Ebola is known as a quickly-progressing disease which has complicated the study and characterization of the disease. Currently there is no effective treatment against Ebola in humans [23].

Most lay people may assume that emerging pathogens are first detected mainly in developing countries, but the following severe illness to appear was Legionnaires' disease, which was

first reported in 1982 in Pennsylvania among American Legion members who fell ill with an acute respiratory illness [24]. In fact, many new pathogens are detected in the United States or Western Europe. The causative agent of Legionnaires' disease, *Legionella pneumophila*, had been infecting only amoeba in its natural environment for thousands if not millions of years, before modern technology provided us with air conditioners that could transmit *Legionella* via aerosols into the alveolus of the lung. The natural sources of the bacteria are ponds and creeks, but modern-day reservoirs include cooling towers and water fountains [24].

In the mid-1970's a geographic clustering of juvenile rheumatoid arthritis was identified and was often preceded by a distinctive skin rash, erythema migrans, in some leading to neurological and cardiac abnormalities. These symptoms were associated with tick bites and in 1982, Lyme disease (caused by the spirochete, *Borrelia burgdorferi*) was added to the ranks of known infectious diseases [25]. Lyme disease – named after Lyme, Connecticut – is transmitted to humans through the bite of infected ticks, whose natural hosts are rodents.

By 1983, AIDS was viewed as a potential pandemic, and to this day, the number of infected people only continues to rise throughout the world. The first appearance of AIDS in a human was reported in the 1950's, although it may have existed before this time in isolated locations. It is generally agreed that the human immunodeficiency virus (HIV), the causative agent of AIDS in humans, originated from a series of mutations in a related simian immunodeficiency virus (SIV), which resulted in its ability to infect humans [7]. Due to the committed work of Luc Montagnier and Robert Gallo, a tool was developed in 2 short years from its first confirmed appearance to diagnosis [7].

After the slow public policy start to address the pandemic of AIDS in the late 1980's, the global health agencies began creating procedures to improve communication and strategies for dealing with outbreaks of infectious diseases globally [2]. By the 1990's, the WHO identified MDR-TB, and more recently, extreme drug-resistant tuberculosis (XDR-TB) [26]. The emergence of XDR-TB is a prime example of the need for strong health systems to improve public health security, since the emergence of drug-resistant pathogens is essentially a man-made problem. According to the WHO, from January 2005 to March 2006, 221 cases of MDR-TB were identified at the district hospital in Tugela Ferry, Kwa Zulu-Natal Province, South Africa [26]. Many of these patients were found to also be infected with HIV. In fact, widespread infection in Africa with HIV has provided fertile ground for the transmission of all forms of TB [26] and other infectious diseases.

In 1998, avian flu virus (strain H5N1) caused great alarm due to its structural similarity to the Spanish flu virus responsible for the 1918 pandemic. All the necessary players seemed to have been in place to allow the transition from bird-to-bird transmission to human-to-human transmission [4]. From April 2003 to April 2007, a total of 291 confirmed cases were reported to the WHO, and 172 (60%) of these cases were fatal [27]. Although sporadic cases of human-to-human transmission of the H5N1 strain have been confirmed [28],

Table 1
Examples of pathogens discovered since 1973 and the diseases they cause

Year	Microbe	Type	Disease
1977	Ebola virus	Virus	Acute hemorrhagic fever
1977	<i>Legionella pneumophila</i>	Bacterium	Legionnaires' disease
1980	Human T-lymphotrophic virus I (HTLV 1)	Virus	T-cell lymphoma/leukemia
1982	<i>Escherichia coli</i> O157:H7	Bacterium	Hemorrhagic colitis; hemolytic uremic syndrome
1983	Human immunodeficiency virus (HIV)	Virus	Acquired immuno-deficiency syndrome (AIDS)
1983	<i>Helicobacter pylori</i>	Bacterium	Peptic ulcer disease
1989	Hepatitis C	Virus	Parentally transmitted non-A, non-B liver infection
1992	<i>Vibrio cholerae</i> O139	Bacterium	New strain associated with epidemic cholera
1999	West Nile virus	Virus	Encephalitis
1996	Misfolded prion	Prion	New variant Creutzfeldt–Jakob disease
1998	H5N1	Virus	Influenza (avian flu)
2002	<i>Cryptosporidium hominis</i>	Protozoan	acute gastroenteritis and diarrhea
2003	SARS coronavirus	Virus	Acute respiratory syndrome

large-scale transmission between humans fortunately has not been observed. Nonetheless, the likelihood that this or another avian flu strain in the future will develop into a human pandemic remains high.

Soon after, the West Nile virus, previously associated with Africa and the Middle East, appeared in New York City. It spread rapidly and, by early 2004, had become endemic in the United States. The virus is transmitted via mosquitoes, which have already infected various species including birds, horses, and humans [2]. Human West Nile virus infections never took off in Europe, due apparently to the promiscuity of *Culex pipiens* mosquitoes in North America, which infect humans and birds, unlike their European counterparts [29].

In November 2002, a case of severe acute respiratory syndrome (SARS) was first reported in China. It was the result of transmission from a captive animal to a human by a previously unknown coronavirus [4]. Throughout the world, the movement to deal with the SARS outbreak was quite rapid, most likely a result of all the criticism that the health organizations took over the slow and bureaucratic approach to the AIDS epidemic [30].

With the development of rapid detection techniques, accurate diagnosis methods, and application of control measures to minimize infections [31], it should be possible to bring many new emerging infectious diseases under control more rapidly. However, the WHO estimates that at least one new emerging pathogen appears each year [32], and the infections are becoming harder to treat. Chances are high that the world will face a new threat similar to AIDS, SARS or Ebola within a decade.

5. Association between infectious diseases and chronic diseases

Microbial pathogens were previously studied mainly with regards to the direct effects of infection. But infectious diseases are now also known to be associated indirectly with the main types of chronic diseases found in developed countries. Examples include hepatitis B (HBV) and C (HCV) infections, which cause liver complications and hepatocellular carcinoma; the human papillomavirus (HPV), causing cervical cancer; Epstein–Barr virus, causing nasopharyngeal carcinoma; and *Helicobacter pylori*, causing gastric ulcers and gastric cancer [27,33]. In a general way, inflammation, caused by overt or persistent infections, is responsible for half of the risk of developing cardiovascular disease [34] and may contribute to development of some cancers [35]. Moreover, there may be a more direct association between atherosclerosis and infection by some pathogens.

Chronic diseases are the leading causes of death and disability in the United States. Accounting for 70% of all deaths in the United States, chronic disease is responsible for 1.7 million deaths each year. These diseases also cause major limitations in daily living for almost one out of 10 Americans or about 25 million people [36].

Many common cancers and cases of heart disease develop as a consequence of years of chronic inflammation. Increasing evidence indicates that the inflammation may result from persistent mucosal or epithelial cell colonization

by microorganisms [33]. Infection with certain chronic persistent microbes is also thought to promote or amplify some human autoimmune diseases [37].

A prevalent example of a chronic disease due to infections is ulcers. This disease was treated mainly with Zantac, which inhibited gastric acid secretion and was the largest-selling prescription drug in the world. But now ulcers are known to be caused by *H. pylori*, which is found in 50% of the world's population. Approximately 20% of this population suffers from diseases ranging from gastritis, an ulcer disease, to gastric cancer [33]. Rather than treating symptoms of ulcers, as Zantac might do, elimination of the bacteria addresses the cause of the disease.

Another pathogen associated with chronic disease is HBV, which is estimated to have approximately 350 million chronic carriers. Patients with chronic HBV infection are at risk of developing liver cirrhosis, which is associated with a high rate of mortality because of complications due to portal hypertension and carcinoma [38].

There are currently 120 different types of human papillomavirus (HPV) that are molecularly identified and cause a range of symptoms from warts to conjunctival carcinoma [39]. Other cancers known to be associated with HPV infections include cancers of cervix uteri, external female genitalia, the penis, and upper gastrointestinal tract [39].

Researchers are discovering an increasing number of chronic diseases that are caused by microbial pathogens [40,41]. One such example is diabetes mellitus (DM). The evidence for an infectious cause is strong between DM and HCV [27], but not enough resources have been applied to characterize the mechanisms linking these diseases. Another candidate for causative agent of chronic disease is *Chlamydia pneumoniae*, which is thought to increase the risk of atherosclerosis [42]. Nonetheless, despite considerable research, several important questions still remain unanswered with regards to the connection between *C. pneumoniae* and atherosclerosis; importantly, we do not yet know if *C. pneumoniae* is an innocent passenger aboard atherosclerotic tissue or whether it is actively involved in the initiation or progression of atherosclerotic disease [43]. In time, other relationships between infectious agents and chronic disease will inevitably be identified and explored.

6. Some reasons for emerging diseases

Wherever we may happen to be, we are surrounded or covered with microorganisms — but for the most part, these are not pathogenic for humans, as in the case of commensals. However, through urbanization, demographic changes, air travel, the abuse of antibiotics, and climate change — and enough time — new infectious agents are bound to evolve.

Urbanization and demographic changes have been recorded by the UN-Habitat 2006 Annual Report. It states that, as of 2007, the majority of people in the world are living in cities for the first time in history. One of the primary reasons for migration of populations is the urge to enter the cash economy, along with the international demand for both skilled and unskilled workers in a globalizing marketplace [2]. With the

movement of populations, comes the movement of their microbial agents. The effects of deforestation, along with associated land use changes and human resettlement, have also contributed to changes in diseases like malaria and its vectors throughout the tropics [44]. Similarly, high-rise housing structures in Hong Kong, a direct effect of urbanization, were found to be hot spots for SARS infections and AIDS [45]. Air travel has shortened the time necessary to travel across the globe, besides increasing the number of environments to which all people are exposed. The globalization of the food market has also accentuated the movements of pathogens from one place to another. A prime example of this was an outbreak of cholera in the US that was traced to imported frozen coconut milk and alfalfa sprout seeds that had been contaminated with *Salmonella* [2].

Antibiotics were first introduced into medical practice a little over 60 years ago. Since then, drug-resistant strains of bacteria have arisen in response to the selective pressure of their use [46]. Antibiotic agents have a wide range of modes of action ranging from interference with cell wall synthesis, inhibition of prokaryotic protein and nucleic acid synthesis, and inhibition of prokaryote-specific metabolic pathways [47]. However, bacteria, by virtue of both their rapid growth rate such that favorable mutations become very rapidly selected, and their access to a wide range of genetic material through horizontal gene transfer, have developed resistance to all known classes and groups of antibiotic agents by a plethora of mechanisms [47]. A variety of reasons can be cited for abuse of antibiotics, but often antibiotics are prescribed before the causative agent of an infection has been properly identified, and therefore, the most appropriate medication is not prescribed.

Interrupting antibiotic use before completion of treatment can also contribute to antibiotic resistance, as has happened with MDR-TB, which has already been documented in nearly 90 countries and regions worldwide [48]. Treatment for these patients requires use of second line drugs for ≥ 24 months. However, these drugs are more costly, toxic, and less effective than first line drugs used for routine TB treatment. As with other diseases, resistance to TB medications has resulted primarily from non-adherence by patients, incorrect drug prescriptions by providers, poor quality drugs, or erratic supply of drugs [49].

Drug resistance has also developed for viral pathogens. Thus, the prevalence of multi-drug-resistant HIV is increasing. While drug resistance is not associated with increased virulence [50], drug resistance is the leading cause of treatment failure among AIDS patients [51]. The emergence of drug resistance in treated populations and the transmission of drug-resistant strains to newly infected individuals are also important public health concerns in the prevention and control of infectious diseases such as influenza [52].

Global warming is projected to have an adverse impact on public health [53]. The frequency and geographical range of some plant and animal infectious diseases have reportedly changed over recent years, at least partly in response to climate change [54]. These changes are expected due to changes in the frequency or distribution of floods, heat waves,

and droughts [53]. Other less direct effects of climate change are on the ecosystem as a whole, in addition to water and food supplies [55]. Studies on infectious diseases due to climate change have mainly focused on the El Niño/Southern Oscillation, the strongest variability in weather currently observed on earth. Climate changes due to El Niño have been found to be related to the incidence of malaria in South America, Rift valley fever in East Africa, Dengue fever in Thailand, hantavirus pulmonary syndrome in the southwestern United States, childhood diarrheal disease in Peru, and cholera in Bangladesh. Currently, the WHO estimates that climate change-induced risk of various health outcomes will double by the year 2030 based on the projected increase of greenhouse gases [56]. The geographic distribution of disease-propagating vectors will also change with warmer climates, as recently noted with the “Tiger mosquito”, *Aedes Albopictus*. This mosquito transmits the Dengue and Chikungunya virus and is normally associated with tropical climates [57], but is now present in southern Europe, where an autochthonous case of Chikungunya has recently been documented [58,59]. A northward expansion in Europe of the vector for bluetongue, *Culicoides imicola*, has also been noted [60].

7. Concluding remarks

Emerging diseases represent a major challenge to the biological safety of the world [4], and it is commonly acknowledged that the factors that contribute to disease emergence will continue, if not intensify, during the next century. Renewed effort, resources, and new approaches in battling against infectious diseases are therefore needed. Besides development of more rapid methods for detecting and identifying novel pathogens, there is also a need for designing new drugs against “old pathogens” that are developing resistance against currently-used drugs. Heightened surveillance should minimize the chances of outbreaks spreading, while more imaginative policy measures may be required to contain pandemics.

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