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# ANCIENT AND NEWLY EMERGED DISEASES AFFECTING THE COURSE OF HUMAN HISTORY

**B. Chakarova[1*], K. Kichukova[2]**

[1]Department of Hygiene, Epidemiology, Microbiology, Parasitology and Infectious Diseases, Faculty of Medicine, Trakia University, Stara Zagora, Bulgaria
[2]Medical College, Trakia University - Stara Zagora, Bulgaria

**ABSTRACT**

Throughout the relatively long history of mankind, pandemic outbreaks have succeeded in wiping out entire communities, condemning large groups of people to hermitage, and deciding the outcomes of wars. These processes have significantly affected the lives of people in various fields - political, economic and social and have changed human civilization, and their results have often lasted for centuries. The emergence of new outbreaks has defined some of the basic principles of modern medicine, provoking the scientific community to develop the basic principles of epidemiology, prevention, vaccine prophylaxis and antibiotic therapy. Paradoxically, in the course of epidemics significant changes in almost all aspects of life have also occurred and have succeeded in making the way for innovation and progress in sciences. The foundations of medicine as a science were laid, occupying an essential place in people's lives, and public health acquired a qualitatively new meaning. Changes in the social life of the ancient societies have repeatedly led to reconstructions of political systems and economic transformations. Both in the past and now, the emergence of new, unknown diseases confronts humanity with unforeseen problems, severe trials and challenges with unclear dimensions.

The purpose of this review is to trace the emergence and evolution of some ancient and emerging diseases that have affected the course of human history.

**Key words:** infectious, parasitic, tropical diseases, epidemic, pandemic, malaria, plague, influenza, COVID-19

Every day the world faces the unpredictable power of nature. This is most vividly manifested in the continuous evolution of new infectious agents threatening human health. These often appear without prior warning and, in most cases, catch the mankind unprepared. During the first two decades of the 21st century, the world and people on a global scale have repeatedly encountered known and new pathogens to which they are vulnerable. In the 1970s and the years since then, the remarkable advances in science and medicine, with the development of new vaccines, antibiotics and other treatments and technologies, have led to an illusory sense of victory over germs. Many experts believe that "the time has come to close the book on the problem of infectious diseases"(Jesse Steinfeld, MD, US Surgeon General, 1969) (1).

The unexpected events that followed prove that the germs have not disappeared but have only hidden from our view and the new situations are catching many health institutions and decision makers unprepared. Over 1,500 new pathogens have been discovered in the last 50 years, 70% of

***Correspondence to:** *Assoc. Prof. Borislava G. Chakarova, MD, PhD, Department of Hygiene, Epidemiology, Microbiology, Parasitology and Infectious diseases, Faculty of Medicine, Trakia University - Stara Zagora, Bulgaria, Cell: + 359 888 871 601, e-mail: borislavachakarova@gmail.com*

which appear to be of animal origin. Not all of them had the scale of an epidemic and did not have a significant impact on public health, but some of them, such as the Ebola virus, identified in 1976, reappeared today, the human immunodeficiency virus (HIV), diagnosed in 1983, and SARS-CoV-2, which is taking over the world today, shook the medical community with its potential to devastate life (2). WHO Director-General Dr Tedros Adhanom Ghebreyesus declared COVID-19 disease caused by SARS-CoV2 a pandemic on March 11, 2020 (3). As of December 1, 2021, the total number of infected people in the world is 263,246,956, and over a 24-month period, the number of deaths is 5,237,048 (4), or 3.3% of the world's population is infected and 0.003% have died, with a lethality rate of 2.00%.

History, however, handles more sinister figures describing diseases that have changed the course of human history many times over. Cholera, bubonic plague, smallpox, influenza are some of the most ferocious killers in human history. The outbreaks of these diseases crossing international borders have been defined as pandemics.

**Plague**

The name plague comes from the Greek word plaga (plague), caused by Yersinia pestis, a highly virulent febrile disease transmitted by fleas. The word is used as a synonym for any epidemic disease with high lethality or in a broader sense, as a metaphor for any sudden outbreak of catastrophic evil or suffering. Science calculates at least three pandemics of human plague, Justinian plague, Black Death and the third plague (5).

The oldest strain of Yersinia pestis ever found, RV 2039, was found in present-day Latvia, in the remains of a 5,000-year-old hunter. A genetic analysis published on 29 June 2021 reveals that this ancient strain was probably less infectious and less deadly than its medieval version. This ancient strain lacks the gene that allows fleas to be vectors for spreading the plague. This gene is responsible for the efficient transmission of the bacterium to human hosts, leading to the formation of pus-filled plague bugs in patients associated with the medieval bubonic plague (6). Plague occurs in three forms, bubonic, septicemic, and pneumonic, depending on the route of infection (7). The bubonic form is the most common and is the result of the inoculation of the bacterium when bitten by an infected flea. Justinian's plague originated in Egypt and spread throughout the Eastern Roman Empire and its neighboring territories (8). The technologically advanced Roman Empire facilitated the spread of the Justinian plague through its trade and military routes. Between 541 and 543, the plague killed about 100 million people in the Roman Empire, with its capital, Constantinople, being the most devastated.

The plague changed the course of the Empire's history, derailing Emperor Justinian's plans to unify the Roman Empire. After experiencing the horror of mass pestilence, Christianity spread rapidly through these lands. After this initial outbreak of the pandemic, for two centuries episodic outbreaks of plague appeared every 8 to 12 years and then disappeared for unknown reasons. (9). DNA analyses of dental pulp samples from plague victims identified Y. pestis as the etiological pathogen responsible for Justinian's plague (10).

The second plague pandemic, the Black Death, occurred in the Far East and traveled through Central Asia to Europe on the medieval land and sea trade routes of the Silk Road. (11). The genetic lineages of Y. pestis that cause the plague of Justinian and the Black Death differ from each other (12). Victims of the Black Death (1347-1351) were between 75 and 200 million people, more than ¼ of the population of Europe and Asia. In England one in four people died, in Florence one in two. Next came the plague waves in Milan (1630), the great plague in London (1665-1666) and the plague of Marseilles (1720-1722). It is supposed that the bacteria have existed in rodent reservoirs in Europe and reappeared periodically in the human population (13). Another hypothesis is that natural outbreaks of Y. pestis in Asian rodents - reservoirs are responsible for the new waves of plague arriving in Europe through the maritime trade network with Asia (14). Dubrovnik was the first city in Europe to establish a quarantine system in 1377 as protection against plague (15, 16). The separation of the healthy from the sick took place in camps, and then in plague hospitals called lazarettos. The word "quarantine" literally translated means "forty days". It is practiced as a

measure of prevention of the spread of plague (17). In Europe, there was no real understanding of the actual carrier of the disease, and the attempts for quarantine did not stop but only somewhat contained the scale of the disease. The plague in Russia penetrated the country in 1769 from Turkey, with which another war was then being fought. When in 1771 the disease swept across Moscow, the State Council, on the personal instructions of Catherine II (Catherine the Great), drew up a list of precautions to prevent the disease from spreading to Petersburg and other cities in the empire. The physician Danilo Samoilovich (then twenty-seven years old) played an essential role in the final victory over the plague in Moscow. He was convinced that the basis of the success of the eradication of the epidemic was the strict isolation of the healthy people from the sick and dying, as well as of those who had any contact with the sick (18, 19).

The Black Death fundamentally disrupted life in medieval Europe and had an irreversible impact on its socio-economic development, culture, art, religion and politics (20).

**The "Black Death" in the Bulgarian lands**

The Bulgarian lands also experienced the horrors of the plague epidemic of the 14th century, which devastated the villages and towns politics of Thrace and Macedonia. At the end of 1347 and the late spring of 1348, the plague epidemic affected the Bulgarian lands and raged for almost eight years and subsequently broke out periodically. Active trade with Genoa and Venice, lands where the Black Death was already raging, was one of the most important and rapid ways for the plague to spread in the Bulgarian lands. The consequences of the plague on the Balkans and for the Black Sea region were far more fatal, as they coincided in time with one of the most prolonged and dangerous invasions - the invasion of the Ottoman Turks (21, 22).

The last plague pandemic occurred in the mid-19th century in the Yunnan region (China), reached Canton and spread to Hong Kong (23). In 1894 Alexandre Yersin discovered the bacterium Y. pestis, in samples from plague patients and dead rats in Hong Kong (24). The pandemic then reached Japan, Singapore, Taiwan and India in ships. In the following years, plague became endemic in many countries around the world (25).

**The plague nowadays**

The disease still exists today in limited areas of the world and is maintained in bat populations. In humans, it manifests as sporademia. Since 1990s plague has been classified by the World Health Organization (WHO) as a re-emerging infectious disease (26). Globally, between 2010 and 2015, the number of plague cases was 3,248 with 584 deaths, most of them in the Democratic Republic of Congo, Madagascar and Peru (27). Plague is seasonal in most endemic countries with well-defined geographic distributions that match those of vectors and rodent reservoirs (28). Nowadays plague is seen as a neglected human threat due to its rapid spread, high mortality without early treatment, and its ability to disrupt social and health systems (29). Y. pestis can be aerosolized and used as a biological hazard. Y. pestis is considered a category A pathogen because it can spread or transmit easily from person to person, cause high mortality rates, and have the potential for major impact on public health (30).

**Malaria**

Malaria is one of the most ancient diseases accompanying humanity and is among the most deadly parasitic diseases in the world today. Throughout recorded human history, fevers have been described, most likely caused by malaria parasites. Epidemics of paroxysmal fevers associated with enlarged spleens (splenomegaly) were reported in China almost 5000 years ago. An Egyptian papyrus from 1500 BC describes similar fevers, heaviness and splenomegaly. Ancient Indian writings from about 3,000 years ago contain descriptions of fevers thought to be malaria (31). In the past, malaria has been widespread in large parts of the globe, causing high morbidity and mortality among non-immune populations. Malaria remains endemic in much regions of the tropics. Global warming and related climate change may lead to re-emerging in malaria-free regions. Social adversity and poverty are closely linked to the severity of morbidity and mortality in the world's poorest communities. This stops economic growth and creates a cycle of poverty that is difficult to overcome (32). Many factors, such as agricultural development and concentration of the population in urban settlements, facilitate the spread of the infection, as do the expansion of the trade routes and the migration of the population caused by conflicts, wars and colonization. The disease is

caused by 5 species of Plasmodium sp.: Plasmodium vivax, P. malariae , P. ovale , P. falciparum and P. knowlesi. P. vivax and P. falciparum pose the greatest threat to public health, because P. falciparum being most prevalent and causing the highest morbidity and mortality. P. vivax can grow mosquitoes at lower temperatures than P. falciparum and survives at higher altitudes. It has a wider geographical distribution and adaptability, which explains why it causes more P. falciparum infections in regions outside Africa. Vectors are certain species of Anopheles sp. Pregnant women and children under the age of five are at greatest risk due to their weaker immune systems. In 2019, children under the age of five accounted for 67% of all malaria deaths worldwide. Malaria is prevalent in more than 80 countries, and they increasingly fall into one of two categories: those progressing towards elimination and those who are deteriorating and experiencing difficulties. The Global Fund is working intensively to accelerate the investments needed to control, prevent and treat malaria. The COVID-19 pandemic has led to postponed malaria control programs, as with other deadly diseases. History shows that the disease will ruthlessly exploit these gaps. Impressive successes can be wiped out during a malaria season, and the failure to maintain effective control can lead to its resurgence. The "ricochet" could make the situation even worse than before the control efforts, as people lose the partial immunity they acquired from repeated exposure to malaria infection. According to WHO, malaria programs have suffered only "moderate" disruptions, but these disruptions could lead to tens of thousands of deaths (33, 34,35).

**Cholera**

Cholera is a disease of the gastrointestinal tract that is acute and often fatal. It is caused by Vibrio cholerae (36) and is an anthroponosis. Sources of infection are sick people and vibrio carriers. The bacterium colonizes the small intestine and produces cholera exotoxin, which plays a leading role in water-salt balance disorders, with rapid and massive loss of body fluids leading to dehydration, electrolyte imbalance, hypovolemic shock, and death. The classic symptom is a large amount of watery diarrhea that persists for several days. (37). Sometimes the patient may have up to 30 liters of intestinal secretions and up to 7 liters of vomit, with cholera vibrios representing 77.8% of the total mass (ie about 23 kg) in the faeces alone. Thus, massive contamination with a huge amount of cholera vibrios is possible. This makes it extremely easy to transmit the infection to healthy persons. V. cholerae is a typical waterborne pathogen. The infection is often oligosymptomatic or asymptomatic, and self-clearance occurs in 1 or 2 weeks. If stayed for a long time in water reservoirs, V. cholerae through a horizontal gene transfer can generate the emergence of new toxigenic clones (38). During outbreaks of V. cholerae epidemics is able to form a three-dimensional biofilm in which bacteria survive (39).

**Cholera pandemics**

Cholera was endemic in Asia until 1817. From India it spread to several other regions of the world as the first cholera pandemic (36). The main reason for the spread is increasing globalization as a result of technological advances in transportation. The appearance of steamships and railroads allowed a drastic reduction in the travel time and an increase in the trade exchange. The prevention strategies were like those during the Black Death (15): infected people were isolated in infirmaries; a ban was imposed on the entry into ports of ships arriving from regions where cholera was present; quarantine was imposed on those arriving from places where cholera was circulating, as well as on the contacts of those infected.

During the 19th and 20th centuries five major cholera pandemics developed which originated in India and spread to other continents (36). They were caused by the classical O1 biotype of V. cholerae (40, 41). In 1854 in the British Isles, during the second cholera pandemic, the physician John Snow used epidemiological methods for the first time to trace the source of the outbreak and described the time course of the outbreak in Soho (London) and its geographical spread in the city. He identified the public pumps used to supply water in these areas and understood that water was the source of infection. He suggested effective measures to interrupt the transmission of the infection. John Snow's work did not eradicate cholera overnight, but it eventually led to improved city sanitation and

protection of drinking water from fecal contamination (42). The cholera vibrio was isolated by Robert Koch (1884) in Alexandria, Egypt, during the fifth pandemic, which also affected South America. In 1905, a cholera vibrio called "El Tor" was isolated at the El Tor quarantine station in Africa. At present the mankind is being subjected to the seventh cholera pandemic caused by the cholera vibrio 'El Tor', which began in Indonesia in 1961, continues to the present day and has become endemic in many countries of Asia, Africa, Europe and Latin America. (43, 44). In the absence of favorable environmental conditions for the survival of vibrio, cholera epidemics usually stop. Cholera is a natural inhabitant of aquatic ecosystems, so it cannot be eradicated. V. cholerae serogroups O1 and O139 are responsible for cholera outbreaks in the developing countries. The changes in the environment and the climate may expand the geographical spreading of cholera (45). The emergence of environmental non-O1/O139 vibrios is favored by changes in the ecosystem and climate (46). The persistence of cholera is associated with poor living conditions, including shortages of safe drinking water, compromised sanitation, densely populated housing, and lack of effective sanitation systems. The disease can also occur after natural disasters such as earthquakes, floods, hurricanes, which disrupt access to safe water supply systems.

**Smallpox**

Smallpox occupies a unique place in medicine. One of the deadliest diseases known to man, it has killed between 300-500 million people in its 12,000 years of existence. It is caused by one of the two variants of the virus, Variola major and Variola minor. (47). About 30% of cases end in death, usually in the second week of infection. Most survivors are left with extensive scarring and other deformities such as loss of lip, nose and ear tissue, corneal ulceration and blindness. The origin of smallpox is lost in prehistory. It is thought to have appeared around 10,000 BC, at the time of the first agricultural settlements in northeast Africa (48, 49). From there it spread to India through the Egyptian traders. The earliest evidence of skin lesions resembling those of smallpox was found on the faces of mummies from the time of the 18th and 20th Egyptian dynasties (1570-1085 BC). The mummified head of the Egyptian pharaoh Ramses V (d. 1156 BC) bears the marks of the disease (50). In the ancient Asian cultures smallpox was described as early as 1122 BC in China and is mentioned in ancient Sanskrit texts of India. Smallpox was introduced into Europe between the 5th and 7th century and was a common epidemic in the Middle Ages. The disease strongly influenced the development of the Western civilization. The first stages of the decline of the Roman Empire (108 AD) coincided with the massive Antonine Plague, which caused the deaths of nearly 7 million people (51). The Arabic expansion, the Crusades, and the discovery of the West Indies all contributed to the spread of the disease.

Unknown to the New World, smallpox was introduced by the Spanish and Portuguese conquistadors. Within 60 years, the disease wiped out 90% of the indigenous population and led to the fall of the Aztec and Inca empires. The devastating effects of smallpox are one of the first examples of biological war (52-54). During the French and Indian War (1754-1767), Sir Jeffrey Amherst, commander of the British forces in North America, proposed the deliberate use of smallpox to reduce the Indian population hostile to the invaders. Another contributing factor to the spread of smallpox in America was the slave trade from regions in Africa where it was endemic.

Smallpox affects all layers of society. In 18th century in Europe 400,000 people died from the disease every year, and a third of the survivors became blind (55). The symptoms of smallpox, or the 'spotted monster' as it was known in 18th century England, appear suddenly and the consequences are devastating. Smallpox is estimated to have killed about 300 million people in the twentieth century (56, 57) and about 500 million people in the last 100 years of its existence (58). In 1967 15 million cases were recorded annually (59). The last known case of wild smallpox was in 1977 in Somalia.

In 1796 Edward Jenner, thanks to his observation and determination, successfully vaccinated an 8-year-old boy against smallpox and thus began the eradication of the only human infectious disease through vaccination (60).

**HIV pandemic**

HIV/AIDS is a slowly progressing global pandemic. The first cases were registered in the early 1980s in the United States. HIV inevitably evolves into AIDS and ends in death. At the beginning of the HIV epidemic, it spread mainly to gay communities, with high mortality rates leading to marked social isolation and stigma. Since 1981, HIV has affected about 40 million people worldwide and killed almost the same number. (61). Globally, it causes about one million deaths per year (compared with almost two million in 2005) (62). The HIV epidemic is particularly worrying in some countries of sub-Saharan Africa (Botswana, Lesotho and Swaziland), where about 25% of the population is infected (63). In the United States, about 1.2 million people are living with HIV and about 12,000 die each year (compared to over 40,000 annually in the late 1990s). In the USA HIV disproportionately affects gay communities, transgender women, and African Americans (64). The advances in treatment (protease inhibitors and anti-retrovirals) have made HIV a chronic condition that can be treated medically.

**Influenza**

Influenza viruses belong to the family Orthomyxoviridae. Their genome consists of 7 or 8 RNA segments encoding at least 10 structural and non-structural proteins. Structural proteins include a haemagglutinin (HA), a neuraminidase (NA), two matrix proteins and a nucleoprotein. Influenza viruses can be distinguished in types A, B, C, and D. Influenza A and B are responsible for outbreaks in tropical regions and seasonal epidemics in temperate regions as influenza A viruses have pandemic potential (65). Influenza A virus is endemic for a number of species, including humans, birds and swine (66). Annual influenza epidemics are maintained in the human population by mutations occurring particularly in HA and NA viral surface glycoproteins. Occasionally, antigenic change resulting from resorting between human and animal viruses leads to the emergence of a new viral subtype (67, 68). This antigenically distinct virus may have the ability to infect humans and achieve sustained human-to-human transmission and may cause a pandemic among non-immune populations or among those with insufficient vaccine coverage (66).

**Influenza pandemics**

It is not possible to determine the exact time at which the influenza virus began to infect humans, but many historians believe that the first influenza pandemic probably occurred in 1510 (69). Russian influenza that occurred between 1889 and 1893, was the first well-described pandemic (70). Then, for 3 years, the pandemic virus appeared every year and caused approximately 1 million deaths worldwide. Mortality varies from 0.10 to 0.28%, with the highest levels in infants and people over 20 years of age (71).

Spanish influenza is caused by an A/H1N1 virus that has probably originated through genetic adaptation of an existing avian influenza virus to a new human host (72). Its region of origin cannot be determined. Analysis of laboratory-fixed samples as well as frozen carcasses from that time confirmed the strain to be influenza A/H1N1virus (73). Typical attack rates were 25-33% and the Ro was estimated at 2-3 (74). The 1918-1919 pandemic spread in at least 3 distinct waves within a9-month interval. The first wave occurred in the spring-summer of 1918 and caused high morbidity and low mortality. Both the second and third waves in the summer-autumn of 1918 and the winter of 1918-1919 caused high mortality. The 1918-1919 influenza pandemic had an estimated 500 million infections and 50 million deaths worldwide (75). The 1918-1919 pandemic showed high mortality in many young and elderly people, as well as in healthy young people aged 20-40 years (76). In most cases death occurred within a few days to weeks (average 7-10 days) of symptom onset (77). In major Western cities, health authorities have implemented strategies to control the epidemic, such as closing schools, churches and theaters and stopping many people from attending public events. Health authorities require the use of individual measures such as respiratory hygiene (face masks) and social distancing. But due to military maneuvers during the First World War, these measures were implemented uncoordinated and too late. The conduct of trench warfare in Europe, the poor living conditions of soldiers, the movement of troops facilitate the spread of the disease. As a consequence of the Spanish flu, the modern passport system came into being. There were many reasons for the introduction of passports,

not the least of which was the disease and the supply of protective equipment, including masks, to the armies and the rear.

Over the past century, the descendants of the 1918 pandemic virus have been responsible for nearly all seasonal influenza A epidemics worldwide. The influenza A viruses responsible for the pandemics of 1957, 1968, and 2009 were all descended from the founding 1918 virus through gene redistribution between human, avian, and swine influenza viruses (78). The new A/H2N2 subtype that caused the 1957-1959 pandemic (Asian flu) was derived from the 1918 virus by acquiring 3 new gene segments from birds. Transmission of the 1957-1959 pandemic virus began in December 1957 with repeated waves occurring over several years (79). Morbidity was highest in children, and mortality was highest in old age, with a lethality rate of approximately 0.13% (80). Global mortality from the 1957-1959 influenza pandemic was estimated at 1-2 million.

The global death rate from the 1968-1970 pandemic (Hong Kong flu) is estimated at 0.5-2 million (81). The mean age at death was62-65 years. The first pandemic season was more severe than the second in North America, while the opposite is observed in Europe and Asia (82). The influenza pandemic of 1968-1970 was relatively mild in all countries and was comparable to seasonal influenza epidemics. No specific containment measures were applied during the pandemic.

The 2009 A/H1N1 pandemic began in Mexico and almost simultaneously in the southern parts of the United States (83). Within 6 weeks the virus spread globally. WHO reported 18 631 laboratory-confirmed deaths. However, it is estimated that the death rate is between 148,000 and 249,000 cases based on the excessive mortality in several countries due to respiratory illness (84). The mortality rate based on confirmed cases is 0.5% (85). Mortality rates in younger populations, such as children, adolescents and pregnant women, are higher than those in a typical influenza season. The mean age of those who died with laboratory-confirmed influenza was 37 years (86). The 2009 pandemic was the first to combine vaccine use and antiviral therapy.

**Bird flu and the risks of a new pandemic**

The gene exchange between influenza viruses in different species, including between animals and humans and constant adaptation is still a critical challenge for the emergence of pandemic viruses nowadays. A series of avian influenza A viruses have caused sporadic cases and outbreaks of severe diseases and death in humans. The first human outbreak was in 1997 in Hong Kong and caused by the A/H5N1 virus. Were reported 18 positive cases and 6 deaths (87). This virus continues to spread among poultry and in a large number of wild bird species on several continents (87). It causes severe and fatal infections when introduced into the human population and rarely results in human-to-human transmission (88). It has been detected in 17 countries and resulted in 861 human cases with a mortality rate of 53% as of 23 October 2020 (89).

**Coronaviruses**

Coronaviruses belong to the family Coronaviridae and include four genera - alpha-, beta-, gamma-, and delta-coronaviruses (90). Coronaviruses are single-stranded RNA viruses that infect a wide range of animals and humans. Human coronaviruses cause seasonal respiratory illnesses and, to a lesser extent, gastroenteritis, common cold and more severe, though rarely fatal, infections of the upper and lower respiratory tract (91). Beta-coronaviruses also include three highly pathogenic viruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 (COVID-19)], which cause severe pneumonia in humans (92).

**SARS-CoV epidemic**

SARS-CoV emerged in 2003 in Guangdong province (China). Bats are a possible natural reservoir of SARS-CoV (93), and palm civets could be intermediate hosts before their spreading to humans (94). The causative agent was identified within a few weeks (95, 96). During the 2002-2003 outbreak, SARS-CoV infection was reported in 29 countries in North America, South America, Europe and Asia. Overall, 8437 probable cases with 813 SARS-related deaths were reported (97). The case fatality rate was 9.7%. Transmission of SARS-CoV is mainly nosocomial, 33-42%, while between family members, 22-39% (98). SARS-CoV infection

usually causes a flu-like syndrome. In 20-30% of the infected patients, the disease progresses to atypical pneumonia, which rapidly progresses to hypoxemic respiratory failure, with the need for treatment in an intensive care unit or mechanical ventilation, subsequent polyorgan failure and subsequent lethality. Many of these patients also develop watery diarrhea with active virus shedding. The main routes of SARS-CoV transmission are droplets, aerosols and fomites (99). SARS-CoV has rapidly become a global threat due to its rapid transmission and high mortality. There was a lack of protective immunity against this virus as well as effective antiviral drugs and vaccines. The low infectivity and long incubation period (peak viral load at 6-11 days after onset of symptoms) of SARS-CoV provided time to implement a series of containment measures to prevent transmission (100). Case identification and isolation, followed by contact tracing and surveillance, proved effective in containing the global threat and eradicating the virus in almost 7 months. However, it has been proven that some SARS-CoV-like viruses found in bats can infect human cells without prior adaptation, indicating that SARS may re-emerge in the future (101).

**MERS-CoV epidemic**

The first appearance of MERS-CoV was in 2012, in Jeddah, Saudi Arabia. Potential reservoirs of MERS-CoV are bats, and dromedary camels have been proposed as intermediate hosts (102). The virus was identified within weeks of global spread by molecular diagnostic methods (103). Between 2012 and 2020, 2519laboratory-confirmed cases of MERS-CoV have been reported with at least 866 deaths in 27 countries (104). All cases involved persons on the Arabian Peninsula or persons who had returned from travel in MERS-CoV endemic areas. Almost 50% of MERS-CoV cases were due to intra-hospital transmission to patients, hospital workers and visitors (105). Transmission between family members occurred in only 13-21% of cases (106). People with MERS-CoV have a wide range of clinical characteristics (107). Those with a severe course of infection are often older than 65 with accompanying diseases and may develop symptoms later. Asymptomatic to mild infection has been reported in 25-50% of cases. MERS-CoV is still circulating these days. The outbreak in South Korea highlights the potential for MERS-CoV to spread worldwide and be a threat to global health (108). WHO has issued recommendations not to consume unpasteurized camel milk and undercooked animal products and to be careful in cases of close contact with dromedary camels. Contact tracing to rapidly diagnose suspected MERS-CoV cases and isolate individuals to break the chain of infection in the community is also essential.

**SARS-CoV-2 pandemic**

In early December 2019, atypical pneumonia was reported in a group of patients in Wuhan (China) and was proven to be caused by a novel coronavirus called SARS-CoV-2 (109), and the disease was referred to as COVID-19. The reservoirs are probably bats (110). It has been suggested that pangolins may be the animal hosts that transmit the virus to humans (111), but the intermediate host, if any, has not yet been identified. SARS-CoV-2 infection can be asymptomatic (up to 40% of the cases) or cause a wide range of manifestations, from mild symptoms to life-threatening illnesses (112). Clinically, the disease most commonly presents with fever, dry cough, shortness of breath, fatigue, myalgia, nausea/vomiting or diarrhoea, headache, weakness, rhinorrhoea, anemia and ageusia. Common complications among hospitalized patients include pneumonia, ARDS, acute liver disorder, cardiac disturbances, prothrombin coagulopathy, acute kidney disturbance, and neurologic manifestations. Critically ill patients may also develop cytokine storm and macrophage activation syndrome. Comorbidities such as hypertension, diabetes, cardiovascular disease, chronic lung disease, chronic kidney disease, malignancy, and chronic liver disease are present in 60-90% of the hospitalized patients (113). Mild symptoms occur in 80% of laboratory-confirmed cases. Approximately 14-19%of patients are hospitalized and 3-5%of cases require transfer to an intensive care unit, most commonly due to hypoxemic respiratory failure. Among these, 29-91%require invasive mechanical ventilation. Overall, the mortality of hospitalized patients with COVID-19 is approximately15-20%, while it reaches up to40% in patients requiring intensive care. The global estimated case fatality

rate ranges between 0.25 and 3.0% (114). Mortality ranges from 0.02% in patients aged20-49years to 0.5% in patients aged 50-69 years and over 5.4% in patients aged 80 years and older. Children with COVID-19 have milder symptoms, mostly limited to the upper respiratory tract. However, a rare multisystem inflammatory syndrome has been described in some children with COVID-19 (115). Patients with life-threatening COVID-19 have been shown to have an impaired type I interferon response (116, 117). In most countries, multiple public health measures have been implemented. The aim of these measures is to slow and flatten the epidemic curve, prevent a huge burden on the health system, and protect people at highest risk from severe outcomes before safe and effective vaccines and treatments are available (118). On December 2, 2020, the UK's Medicines and Healthcare Regulatory Agency (MHRA) approved the world's first anti-Covid19 vaccine, Pfizer-BioNTech. Free access to safe and effective vaccines is crucial to ending the COVID-19 pandemic. The WHO is actively working to develop, manufacture and implement safe and effective vaccines. Effective vaccines with an acceptable number of side effects are the main tool for reducing mortality rates among infected individuals with a pronounced clinical picture. However, the WHO recommends that we continue to wear masks, clean our hands, provide good indoor aeration, physical distance, and contact control. The vaccines approved for use in Bulgaria are Moderna vaccine, Pfizer / BioNTech vaccine, Janssen vaccine, Oxford / AstraZeneca vaccine (not currently available). As of the end of January 2022, more than 170 different vaccines have been developed and are being tested.

**Ebola outbreak (2014-2016)**

The Ebola virus appeared in December 2013 as an outbreak in a remote village in Guinea. It is endemic in Central and West Africa, with probable fruit reservoirs. Spreading mainly through close contacts, the epidemic reached Sierra Leone and Liberia, where it generated significant outbreaks of more than 28,000 cases and more than 11,000 deaths. A small number of cases have been reported in Nigeria and Mali, but these outbreaks have been quickly controlled (119).

**ZIKA (2015-2016)**

The Zika virus is a little-known, dormant virus found in anthropoid apes in Uganda. It is transmitted by mosquitoes (Aedes aegypti) but can be sexually transmitted. Prior to 2014, the only known outbreak in humans was recorded in 2007 in Micronesia. In 2015, the virus was identified in Brazil in an outbreak of mild disease causing macular rash, conjunctivitis, fever, arthralgia, headache resembling dengue. Despite the mild course that initially made it invisible from a public health perspective, Zika infection can cause Guillain-Barre syndrome in adults and severe microcephaly congenital transmission from an infected mother (risk of about 1%). The Zika outbreak is an illustrative case in the context of global transmission. From Micronesia, across the Pacific it has reached Brazil, where it continues to spread (120). It is also a case of modern media pandemic; it has appeared on a prominent place in the social media. At the beginning of 2016 Zika was mentioned 50 times a minute in Twitter posts. Social media was used to spread information, to educate, or to communicate concerns (121).

As of 2016, Zika continues to spread in South America, Central America, the Caribbeans and several states of the US. This remains a serious public health problem as there is no vaccine and the only reliable way to avoid the risk of congenital transmission is to avoid areas where Zika is circulating. (120).

Infectious diseases have accompanied mankind. Some of them have dramatically changed people's lives. Some have put an end to certain historical processes and phenomena, but others, new and unknown, have flourished. Thus human society has evolved, though for the witnessing victims, survivors or not, it has been about their entire lives. Our contemporary life raises new challenges that inevitably concern each of us. How will we deal with them? We simply have to read history. On its title page, everything is clearly written, but between the lines there are questions whose answers still surprise us today.

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