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Pandemics throughout History

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Review Article

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Abstract

Throughout history, the world has faced various diseases, some of which have become pandemics. A pandemic means a disease whose epidemic has spread beyond several continents. For example, the AIDS and Covid-19 pandemics have been the closest pandemics in the past years. Bacteria and viruses often cause these diseases. Some of these diseases that have become pandemics have been transmitted to humans by animals as carriers or mediators and have caused disease. These diseases are called zoonotic. The first disease that became pandemic can be mentioned as the plague disease first occurred during the rule of the Parthians. The battle between the Romans and the Parthians in the Tigris, region caused the Antonine plague pandemic that spread to Europe in 165-180 AD. Plague has always been among the diseases with the highest mortality. After that, other terrible diseases such as smallpox with 56 million deaths, or the Spanish flu with 50 million deaths appeared. The latest pandemic that we have been involved in is the COVID-19 pandemic, which was declared by the WHO as a new pandemic on March 11, 2020. We can study past pandemics and learn from them how to deal with future pandemics in order to have the lowest death rate. Maybe another pandemic is coming. According to the statistical data of the coronavirus family, from 1890 to 2019, they have been the cause of four pandemics, and in the last three pandemics, we have seen the distance between them decrease and they become stronger, the possibility of another epidemic in the next seven years from the family there is a coronavirus. By studying historical, statistical, and medical sources, this article examines and provides complete information regarding the pandemics that have existed in history.

Keywords: COVID-19; Pandemic; Severe Acute Respiratory Syndrome; Smallpox; Influenza; Infectious Diseases; Plague

Abbreviations: HE: Hemagglutinin Esterase; MERS: Middle East Respiratory Syndrome; WIV: Wuhan Institute of Virology; SARS-COV-2: Severe Acute Respiratory Syndrome Coronavirus 2; CT: Computed Tomography; SARS: Severe Acute Respiratory Syndrome; ELISA: Enzyme-Linked Immune Sorbent Assay; WHO: World Health Organization; RT-PCR: Real-Time Polymerase Chain Reaction; RC: Republic of Congo; EVD: Ebola Virus Disease; FDA: Food and Drug Administration; NATs: Nucleic Acid Tests; SIV: Simian Immunodeficiency Virus; CDC: Control and Prevention Disease; AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus.

Introduction

Nowadays, the expansion of trade and travel has increased the chances of infectious diseases becoming pandemic. Also, activities such as raising and keeping farm

animals and pets and related activities such as buying and selling food for animals as well as the exotic animal trade, create a close relationship between humans and different species of animals. Each of these cases plays a huge role in causing zoonotic diseases [1]. The beginning of the great pandemics of history dates back to the time of the Second Peloponnesian War (431–404 BC), and its events were recorded by one of the survivors of the plague and we are currently facing a coronavirus pandemic, which is a zoonotic disease like the plague.

Despite the many advances that have taken place in science since the first pandemic of history (the plague), according to the World Health Organization (WHO), as of January 22, 2022, more than 126 million deaths have been reported in continental Europe, and more than 124 million deaths in the Americas due to the coronavirus pandemic [1-5]. These statistics are a warning to humanity that pandemics are developing faster than science. Statistics show that during the four years of the American Civil War (1861-1865), about 620,000 casualties were reported, indicating that pandemics suffered even more casualties from the wars [6].

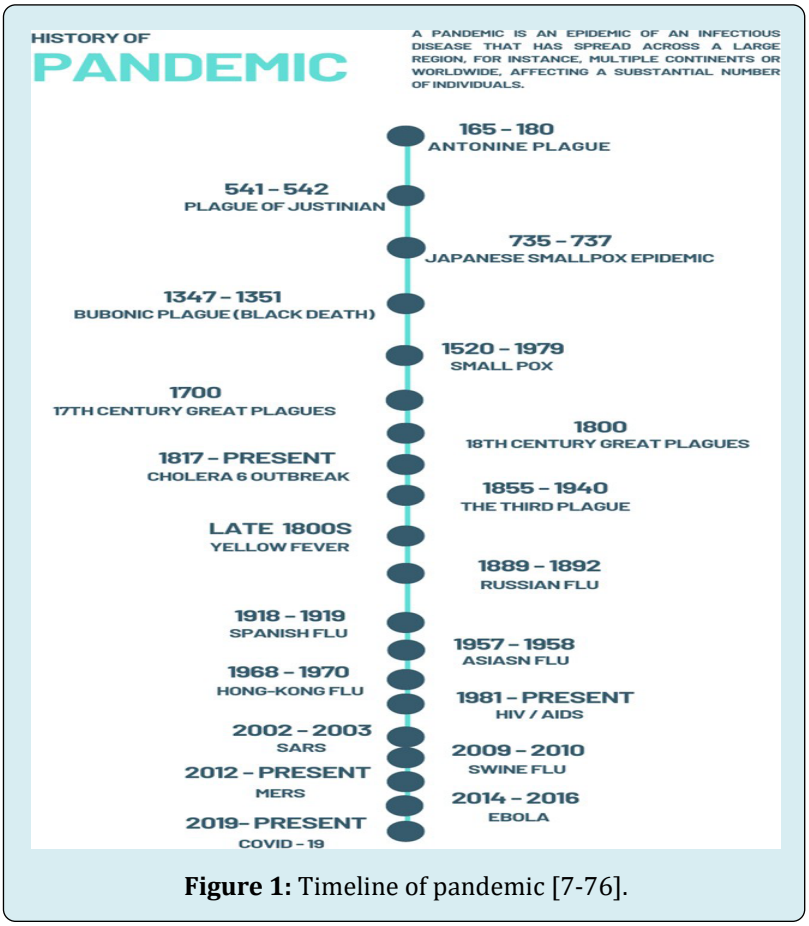

Figure 1: Timeline of pandemic [7-76].

This article provides a brief overview of some of the great pandemics in history to warn that the coronavirus is not the last pandemic in the world and that the current science of the world should be able to predict pandemics like an earthquake or a tsunami. Coronavirus was not an unknown virus and its discovery dates back to 1960, but it was not predicted or researched that it could cause a pandemic in the future [77].

Education Strategy and Infection Susceptibility Models

Public health education strategies change simulator model change, for example in Bahrain Corona, public health education and behavior change was significantly seen. Billboards installed in the city for public health education were to prevent congestion such as reducing Employees' working hours or admission to clients selling drugs safety drugs useful food use useful reduced traffic in the city and shutting down crowded places including behavioral strategies and behavioral changes to control patients. These factors can be used to control future pandemia. Overall, simulator models can be divided into three categories.

These models are defined by the body's response to the disease:

- **Model A:** In which the person is safe from the disease

and is not reinfected with the disease, for example, smallpox or measles are diseases that the person obtains immunity and does not get the disease again.

- **Model B:** In this model, the person is not safe from the disease and can return to the disease. Coronavirus and influenza are diseases that the person may be redeveloped and is not safe from the disease.
- **Model C:** The third factor is the base-based simulator model used as the main unit of the simulator. This model considers the effect of interactions between individuals. This mole contains a set of rules used to control the behavior of agents or diseases, for example. Perez used the base-based factor method to simulate measles expansion [78-82].

There are many effective factors in the prevalence of a pandemic. The most important of these is the population and imprisonment. The population is a factor that has a positive effect on the prevalence of pandemic outbreaks. The increasing population increases the prevalence of the epidemic. Taller, it causes everyone to happen faster, for example, the Coronavirus has a five day latency, so its prevalence increases [79,83-86].

Different Perspectives of a Pandemic

A pandemic from this point of view should be defined as critical and worrying. In the usual definition, a pandemic is a disease that affects many people in the world, but the real meaning is that a large number of innocent people in the world are sacrificed every day and many economic losses are inflicted on different countries. The definition of ordinary people is closer to reality than the scientific definition of a pandemic, for ordinary people, a pandemic means death, poverty, depression and the like effects of pandemics. If we understand pandemics in this sense, then we will understand the importance of research to predict and prepare for possible pandemic factors. There are various fields in science capable of working on predicting pandemics, including bioinformatics, biotechnology and various branches of biology.

Statistics of Pandemics

Pandemic diseases have always been accompanied by a lot of mortality and often cause fear and fear among people. As we go through the history, we see less more deaths as we have made it easier to control the pandemic with the advancement of modern medical science and equipment, and significant improvement in the diagnosis, confrontation, and construction of the vaccine has achieved significant progress. After the discovery of antibiotics, deaths from bacterial diseases decreased. For example, in the Ebola epidemic in 2014-2016, was successful and reduced, which would have prevented them from being killed if they were taken faster. The pandemics that left many dead, such as the Bubonic Plague, known as the Black Death, killing one -third of the European population, or diseases such as Spanish smallpox and influenza, left a lot of dead in popular journals such as Nature and Center for Disease Control and Prevention (CDC) sites & WHO has been mentioned. SARS, Mers, and Ebola, which are close to the pandemic, have fewer deaths [87]. Some of these pandemics can be seen in (Figure 2) and (Table 1).

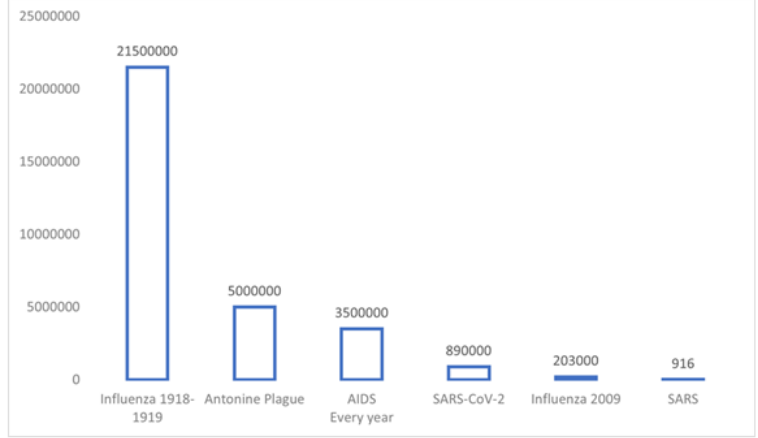

Figure 2: Mortality in major pandemics [88-94].

Reference	Information	Mortality	Year	Area	Sickness
[90]	It is believed to be either smallpox or measles	5 M	165-180	World	Antonine Plague
[95]	In London, England alone, more than 320,000 people have died from smallpox since 1664.	320 K	1664-now	London	smallpox
[96]	A famous example of the almost exclusively infantile nature of smallpox mortality is in the north of England, Manchester, where Percival reported that of 589 smallpox victims in the period 1768-74, only one was 10 years of age or older.	589	1768-1774	Manchester	smallpox
[97,98]	In May 1901, an outbreak of smallpox, initially undetected, was followed by a series of outbreaks in various Boston neighborhoods. From 1901 to 1903, there were 1,596 cases of smallpox (Figure 1), with 270 deaths, in a city with a population of approximately 560,900. The attack rate was 3 cases per 1000 people, with a mortality rate of 17%.	207	1901-1903	Boston	smallpox
[99]	The 675,000 deaths attributed to the influenza epidemic represented 0.64 percent of the total population, a little over six per thousand.	675 K	1918	USA	Spanish Flu
[100]	Estimates of deaths from the 1918 influenza pandemic vary considerably, with recent estimates suggesting that there were 50 million to 100 million deaths worldwide.	50–100 M	1918	World	Influenza
[99]	In Pennsylvania, more than 30,000 people died from the epidemic in October 1918.	30 K	1918	USA	Influenza
[99]	In New York City, more than 16,000 people died of influenza and pneumonia in October 1918.	16 K	1918	USA	Influenza
[89,88]	The 1918-1919 influenza pandemic has been called “the greatest medical holocaust in history” and “the mother of all pandemics.” Preliminary research indicates that the global death toll during the pandemic exceeded 21.5 million	More than 21.5 million	1918-1919	World	Influenza
[99]	However, in drawing these analogies from past epidemics, we must recognize that one of the most commonly reported facts in 1918-19, the death of 675,000 Americans, is based on limited, contradictory, and even speculative reports.	675 K	1918-1919	USA	Influenza
[88]	We estimate mortality from influenza pandemics in India using panel data models and Indian census data. New estimates indicate that for the districts included in the sample, the death rate was a maximum of 13.88 million people.	13 million & 880 thousand	1918-1919	India	Influenza
[99]	When Crosby calculated the death toll from the influenza epidemic, he counted the pneumonia and influenza deaths in the “recorded states” in 1919—approximately 549,000—and then simply added another 25 percent to his “best estimate.” That is, it gained 675,000 deaths.	549 – 675K	1919	USA	Influenza

[101]	That is, approximately 206,037 AIDS-related deaths occurred between 1995 and 2002 (in the HAART era).	206 K	1995-2002	USA	AIDS
[102]	Severe acute respiratory syndrome (SARS) emerged in southern China in November 2002 and was transmitted to Hong Kong in February 2003. From Hong Kong, the disease spread rapidly around the world, but mostly to Asian countries. At the end of the epidemic in June, the global cumulative total was 8,422 cases with 916 deaths (11% case fatality rate).	916	2002-2003	World	SARS
[103,104]	In 2003 alone, an estimated 590,000 to 810,000 children were newly infected with HIV.	590 – 810K	2003	Africa	AIDS
[92]	Assessing the mortality impact of the 2009 H1N1 influenza A virus (H1N1pdm09) is essential to optimize public health responses to future pandemics. The World Health Organization reported 18,631 deaths from the pandemic, but the overall mortality burden of the pandemic was significantly higher.	18631	2005-2009	World	Influenza
[92]	The researchers estimated that between 123,000 and 203,000 respiratory deaths from pandemic influenza occurred worldwide from April 1 to December 31, 2009. Most of these deaths (62- 85%) occurred in people less than 65 years old.	123–203K	2009	World	Influenza
[105]	At all sites, crude mortality rates (19.1–35.4 deaths/1000 person- years) were higher than the expected baseline mortality rate for Haiti (9 deaths/1000 person-years). This finding represents more than 3,406 deaths (a 2.9-fold increase) for 4.4 percent of the Haitian population covered by these surveys, indicating a significantly higher cholera death rate than previously reported.	3406	2010	Haiti	cholera
[106]	More than 3 years have passed since the emergence of pandemic influenza A H1N1 virus in 2009, the associated global mortality remains unclear. Of the 18,500 laboratory-confirmed epidemic- related deaths identified during April 2009 to April 2010, 2010	18.5 K	2009-2010	USA	Influenza
[107,108]	From 2012 to May 31, 2019, Middle East respiratory syndrome coronavirus (MERS-CoV) has infected 2,442 people and killed 842 people worldwide.	842	2012-2013	World	MERS
[109]	As of August 8, WHO reported 1,779 cases of Ebola with 961 deaths.	1779	2013	Africa	Ebola
[91]	In 2013, there were 1.3 million (1.1 million to 1.6 million) AIDS- related deaths in the top 30 countries, accounting for 87% of global AIDS deaths.	1.3 M	2013	World	AIDS
[110]	As of mid-August 2020, more than 170,000 US residents have died from the 2019 coronavirus.	170 K	2019-2020	USA	COVID- 19
[99]	In contrast, the more than 500,000 deaths attributed to Covid-19 represent about 0.15 percent of the total population, or between one and two per thousand people.	500 K	2019-2020	USA	COVID- 19

[111]	First, state-level census extrapolations from seven states indicate more than 3.4 million deaths. Second, using international estimates of age-specific infection- related mortality rates (IFRs) in Indian seroprevalence data suggests an additional loss of about 4 million. Third, our analysis of the Household Consumer Pyramid Survey, a longitudinal panel of more than 800,000 individuals in all states, estimated 4.9 million additional deaths.	3.4–4.9M	2019-2021	India	COVID- 19
[94]	The severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) pandemic continues to evolve, killing at least 890,000 people worldwide and 175,000 in the United States in the 8 months since its identification.	890 K	2020	World	SARS- CoV-2
[99]	As the United States reaches the grim milestone of nearly 550,000 deaths from Covid-19 and growing public recognition that hundreds of thousands of those deaths may have been preventable.	550 K	2021	USA	COVID- 19
[103,104]	Of the 2.5 to 3.5 million AIDS- related deaths worldwide per year, nearly one-sixth occur in children under the age of 15.	2.5 –3.5M	Every year	World	AIDS

Table 1: Important events in pandemics.

Plague

The Bacteria agent, Yersinia pestis, was discovered by Dr. Yersin in 1894. After an incubation period of 3 to 7 days, patients usually experience fever, tremors, headache, and vomiting [112,113]. A Plague is an infection caused by Gram-negative bacteria [114]. It has caused highly contagious and dangerous diseases and epidemics, including the Plague of Justinian and the "Black Death" in the middle Ages, the causative agents of which have been confirmed using modern molecular testing [115-117]. The ability of this microorganism through aerosol transmission and making pneumonic plague to be used as a biological weapon [118].

Epidemiology and History of Plague

The Plague is endemic in many countries of America, Asia, and Africa. More than 90% of cases are currently reported from Africa [112,113]. The plague is one of the oldest infectious diseases in Iran, which has had destructive effects on the human population of Iran throughout history [25]. After passing through Italy to Syria, Palestine, and Iraq in 543, the plague reached present-day Iran and infected the Iranian royal army and the people of that time [119]. In 544 CE, plague struck the Roman and Persian armies while they were at war [120].

In 627 CE, a major plague epidemic that killed more than 100,000 people was reported in Ctesiphon, the Sassanian capital, near Baghdad. Shortly after that, Kavad II, the king of Iran, died of the plague [121]. Another plague epidemic occurred from 634 to 642 CE in the region of Yazdegerd III, the "Great King" of Iran [122]. Plague epidemics in Iran usually originate in villages or places with poor sanitation, and rural epidemics have been known to persist for periods of 30 to 40 years without any official cases [123].

Figure 3: Designed by Mohammad Mahdi Bakhshian, a demonstration of doctors' safe clothes during the plague pandemic.

Plague Includes 5 Common Types

- **Bubonic plague (Buboes):** It is caused by a special type of bacteria called Yersinia pestis, and it is named bubonic plague because it causes swelling of the Lymph nodes (bubo). In this disease, the axillary lymph nodes, groin, and neck glands can grow to the size of an egg and secrete pus.
- **Pneumonic plague (pulmonary):** It is caused involvement of the lungs, pneumonic plague is less common than other types of plague, but because it can infect from person to person through very small respiratory droplets, it is considered the most dangerous type of this disease.
- **Septicemic plague (Septicemia):** This plague occurs when the bacteria's pathogenic agent proliferates in the circulatory system.
- **Plague Meningitis:** This plague occurs when bacteria pass the blood-brain barrier and cause inflammation of the meninges.
- **Pharyngeal Plague:** It is an uncommon type of plague and has similar symptoms to tonsillitis (inflammation of the tonsils) [124]. The bubonic form (Buboes) is the most common form, which is caused by the bite of an infected Flea, it is common between humans and animals, but the type of pneumonia (pulmonary) is directly transmitted from human to human through inhalation of infected respiratory droplets [118]. In order, the most dangerous types of plague are pneumonic plague, followed by meningitis plague, septicemic plague, bubonic plague, and finally pharyngeal plague, which is very rare [125].

Treatment and Medicine

Immediate diagnosis and treatment are very important to reduce the risk of complications and death. Streptomycin, Tetracycline, and Sulfonamides are standard therapy but it should be noted that these drugs are not definitive treatments [112,113]. Now a day the medicine Gepotidacin has been discovered as a treatment for pneumonic plague [126].

Vaccine and New Treatment Method: Currently, all vaccine has been un of, but one of the new methods is that the researchers used a mouse model in such a way that they first marked the target mice (created a mark on their tails), then Moore, Barry, and his colleagues transmit the amount of precursors Proteins that caused immunogenetic in mice) It creates immunity against Yersinia pestis. Then blood was taken from the mice every 14 days and their serum was separated and their immunogenicity was checked. Finally, it was found that the mice reached maximum immunity with the F1-V protein, then they used its antibody titer for vaccination in humans [127].

Smallpox

Smallpox is a contagious disease cause by variola virus (Orthopoxvirus). This virus can survive in the form of aerosol in cool dry environments [128,129]. But it is sensitive to ultraviolet radiation and if it is in proximity it goes [130,131]. The risk of mortality in the disease is estimated at 5%. Main sign of smallpox is widespread rashes and sudden fever with severe headache.

Epidemiology and History of Smallpox

Pandemic smallpox was very dangerous and left many victims [132]. It is estimated that smallpox had about 300 to 500 million victims [133,134]. There are theories about the origin of smallpox, but it is said to be in the third century BC and from an Egyptian mummy and from where it originated. it is said that an Egyptian person was infected with the disease which has been prevalent after being mummified. Spread to the world [135]. Celebrities who died of smallpox include Rams Five, a king of ancient Egypt, Edward Sixth King of England Andrew Jackson, a king of the eighth art of other Kings of England [133,134]. The arrival of smallpox in Iran occurred approximately between 1175 and 1304. During the Qajar royallness, smallpox seriously affected the country with its destructive effects. Of course, smallpox continued until after 1304, but it showed itself intermittently. The destructive effects of this disease continued until the Pahlavi period [136]. The oldest written work of third-century smallpox and the book of the treatise is al-Jadri. This book is written by Razi. It is interesting to know that before the vaccine arrives in Iran, the women of the stoning tribes who were from the Bakhtiari tribe dried the patient's discharge. And they combined boiling water and injected in into people with a needle. Over time, this method became popular among the people so the vaccine was injected in public baths and hairdressers. Before the smallpox vaccine arrived in Iran during the Qajar reign, with the widespread support of Amir Kabir, a prominent Iranian minister of history, and Dr. Cromick, who was trusted by Amir Kabir, was controlled by Amir Kabir, the first person to be Launched vaccination against smallpox in Iran.

Cellular Properties and Pathogenesis

Smallpox consists of a variety of chickenpox. Most people are confused chickenpox with smallpox [137]. The disease has its first effects on the patient's respiratory mucosa and initially involves the respiratory tract, then by the invasion of polymer cells virus into the spleen organs of the kidney liver and bone marrow, lesions are caused by lesions on the skin [130,138]. After the respiratory tract involvement, other symptoms of the disease, such as excessive fever, lesions on

the tongue, and oral abdominal pain. In this disease, most of the lesions appear on the back and chest area and their diameter is about 10.7 mm [130,131,138,139]. As a result of the deterioration of the disease, severe skins bleeding of the disorder the abnormalities of the face become a severe pulmonary disorder of deafness. The toxins caused by the virus can lead to the patient's death, the primary effects of which are the patient's blood coagulation, which gradually continues to coagulate and lead the patient to death [130,131,138].

Latency and Laboratory Diagnosis

The incubation period or latency of this disease is between 10 and 14 days. In some cases, the patient will notice the disease after 19 days [140]. One of the most important laboratories to diagnose this disease is the real time-polymerase chain reaction (RT-PCR) test, which is taken from the patient in the early stages. According to this law, all people, especially children under the age of five, had to be vaccinated. According to the death toll, the vaccination was between 0 and 7 percent [141]. The last acquisition of smallpox occurred in the same year that the smallpox virus was legally kept in a high-security laboratory [142]. No effective drug has been identified for the treatment of the disease so far, but the disease is under control in childhood and adulthood. Chickenpox was one of the pandemics that left many victims. In fact, chickenpox is one of the most important types of pox, most of which people are confused with smallpox [133].

Treatment and Vaccination

These drugs can reduce pain and fever somewhat, but increase the recovery period, so taking these drugs increases the time of recovery. Finally, after the discovery of the latest natural sample of the WHO smallpox, he launched a vaccination plan to control the pandemic. The project began on May 14, 2009, and Edward Jenner was the first person to use the cow's vaccine against human smallpox. Three years after this operation Edward Jenner, and Dr. Cromick, also launched a vaccination in Iran [143-148].

Cholera

Cholera is a dangerous and fatal disease that spreads usually in poor health managements. This disease also known as blue death because the infected person loses so much fluid from his/her body through diarrhea which turns his/her skin color to blue-gray [149]. Vibrio cholerae is responsible for this disease. V.cholerae can cause severe watery diarrhea and dehydration. It has an incubation period of approximately twelve hours to five days for the person who has consumed the polluted food or water to show symptoms [150]. Cholera is not only a disease of adults, but it also affects children, and in severe cases that are not treated, it can cause death within a few hours [151,152].

Epidemiology and History of Cholera

The origin of this disease was from India and the Ganges River Delta, where a large-scale epidemic occurred during the 19th century [153]. Cholera has been an epidemic disease 7 times and killed millions of people around the world. The 7th epidemic started in South Asia and reached America by Africa in 1991 [154]. The public health situation in Iran in the Qajar period (1796-1925) was poor. For example, in the 19th century, the infant mortality rate in Iran was more than 50% [155]. Between 1820 and 1903, seven major cholera epidemics with high mortality rates, especially among children, occurred in Iran as part of the global cholera epidemic. In Iran, this was generally due to the lack of an efficient health authority before 1904 to control the spread of deadly epidemics, and therefore effective preventive and quarantine measures were not used. Pilgrimage to Mecca and Iraqi shrines played a significant role in the spread of the disease among Iranian pilgrims during the epidemic [156].

Public unsanitary conditions, serious lack of safe water supply, ignorance, and poverty all played a major role in the emergence and spread of infectious epidemics in Iran during the nineteenth and early twentieth centuries. The first outbreak of cholera started in 1821 in Bushehr through the Persian Gulf and gradually appeared in Kazerun, Shiraz, Abadeh (Fars province), Isfahan, and central parts of Iran, after two years it spread to Russia through the Caspian coast [155,157,158].

Treatment and Transmission

Patients with mild consumption of cholera can recover and be treated using oral rehydration solution (ORS), but in people with more severe symptoms, you should refer to serum therapy and drug treatment centers [159,160]. In terms of O blood type, Cholera is the most dangerous, while AB blood type is the least dangerous [161,162]. In addition to spreading and causing disease through infected food and water, the *V.cholerae* bacterium can be spread by a sick person who has no symptoms in the environment [163]. Currently, the disease is very endemic [164].

Yellow Fever

Yellow fever, a disease that caused public panic in tropical regions of South America and Africa among 18 to 20th century for the first time officially reported in the

cities of Yucatan and Guadeloupe in 1846. A Proper subset of flaviviruses that contain 10,500 to 11,000 nucleotides provides more than 70 types of Flaviviruses that cause a common disease between non-human mammals and blood-sucking mosquitoes (ticks) and humans [165-168]. A pathogenic virus known as yellow fever due to the skin color change to yellow, referring symptoms are abdominal pain, vomiting, nausea and bleeding, anorexia, severe hepatitis, kidney failure, shock, and heart failure [165,167-171]. Because of the similarities of the symptoms between this disease and malaria, it is difficult to have the right diagnosis in the beginning steps [171].

Transmission and Pathogenesis

According to new research, a specific type of yellow fever known as sylvatic yellow fever was transmitted to the human body by mosquitoes that bite infected monkeys and then bit young men who were working in the forest, and through the trade of African slaves entered the American continent by ship and quickly spread in North America and Europe the ships in which the disease was seen quarantined themselves and used a yellow flag to announce their infection to others [170,172]. It is noteworthy that this disease is seldom found in Asia [165,166,168,171]. Yellow fever is not limited to the sylvatic "forest" type, other types such as moderate yellow fever which occurs in humid and semi-humid areas of Africa, and urban and also yellow fever which is seen in crowd populated areas are other strains of this disease [171]. It is estimated that the mortality rate of yellow fever patients is about 15% to 30% [168,171].

Treatment and Vaccination

Vaccination, which was officially and successfully introduced in 1937, deforestation, urbanization, population movement, and climate changes in the last two decades are the factors in decreasing number of people suffering from this dangerous disease [166,170-172].

Influenza

Influenza is a fever disease that attacks the respiratory tract [173]. The first influenza virus was separated from the chicken with fowl plague in 1901 [174]. In 1997, the influenza virus (H5N1) was transmitted directly from chickens to humans [175,176]. The influenza viruses were first separated in the 1930s [177].

Classification

In terms of ontogeny, influenza is divided into 4 categories A, B, C, and D [178,179]. Pandemics are only caused by type A viruses [180]. Influenza epidemics occur seasonally in temperate climates and lead to significant morbidity and mortality [181]. Major influenza epidemics do not show any predictable course or pattern and are all different from each other [182]. In the 20th century alone, there were three pandemics in 1918, 1957, and 1968 caused by H1N1 (Spanish flu), H2N2 (Asian flu), and H3N2 (Hong Kong flu), respectively [183].

Epidemiology and History of Influenza

The first verified evidence of influenza in Iran dates back to the summer of 1833 when influenza occurred with great severity in Tehran. It's said that this pandemic arrived via trade routes from Syria and Constantinople, part of a larger global epidemic that affected thousands of people in Asia and Europe. Every day, dozens of people lost their lives among the citizens of the capital, and bodies were found on the corners of the streets [184]. Dr.Cyril Elgood wrote in his book about this happening: "In the summer of 1833, a strange epidemic, probably influenza, broke out in Tehran. Even Fath-Ali Shah was attacked. His doctors reported that he had a high fever and ague [185].

Disease caused by the 1918 influenza pandemic, also known as the Spanish flu, spread rapidly. This was due to the influenza A (H1N1) virus [186]. Iran was one of the regions that suffered the most from this epidemic and the death rate was significantly higher than in other regions of the world. Although worldwide flu victims mostly lived in urban areas, it was the rural areas of Iran that suffered the most casualties [187]. The influenza epidemic come to Iran through the western border from Baghdad to Kermanshah and finally reached Tehran. Ashair tribes, especially healthy males, died of influenza. The reported mortality rate in the Qashqai nomadic tribe was up to 30%. At that time, the city of Shiraz had a population of 50,000, of which 5,000 died due to the Spanish flu [188].

Diagnosis and Treatment

Influenza is still an important disease in humans and animals [189]. Symptoms of flu include fever over 37.8 degrees, headache, myalgia, cough, or sore throat [190]. Vaccines, the most cost-effective primary prevention for influenza, are effective and readily available, but they have their limitations [191,192]. Two antiviral agents with similar activity, amantadine hydrochloride, and rimantadine hydrochloride, have been available for many years to prevent and treat influenza [192-196]. However, both of these agents are only active against influenza type A and not influenza type B, and resistance of influenza A viruses to these drugs can be problematic [190].

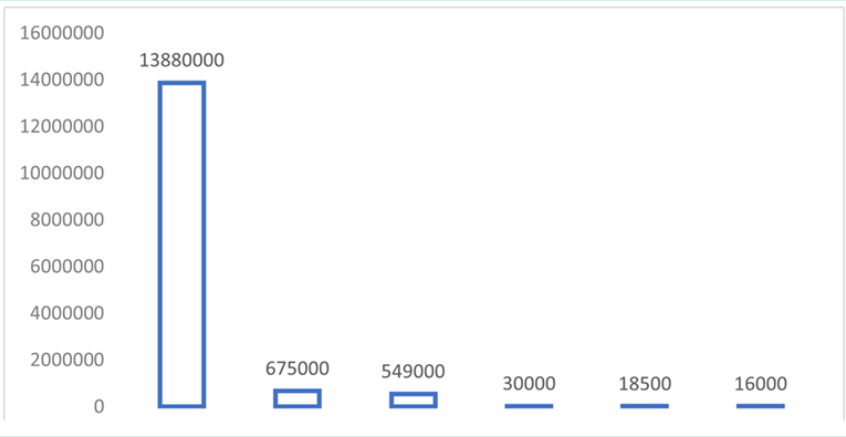

Figure 4: Designed by Mohammad Mahdi Bakhshian with permission [88,94,106].

AIDS

Human Immunodeficiency Virus (HIV) has infected more than 75 million people in the world, and currently, about 34 million people are asymptomatic [197], whose disease is known as Acquired Immunodeficiency Syndrome (AIDS) [198,199]. This disease is an immunodeficiency syndrome, it reduces the immune system of people against other diseases [200-203].

History of AIDS

The ancient Egyptians identified AIDS contagious feature in 2300 BC but they didn't figure out the nature of disease and couldn't describe it. they investigated the ways of transmission and infection and realized that this disease could transmit through the sexual mucosal tract between partners [204,205].

Therefore, they invented one of the first human surgeries. The ancient Egyptians performed male circumcision surgery to prevent the transmission of the disease [204,206,207]. The results show that circumcision can prevent the transmission and growth of the HIV virus in humans. They also made chemical condoms for prevention that were used by women. [204] Circumcision can be clearly seen in the images of papyrus and tablets extracted from Egypt [205,208,209].

Also, they frequently used AIDS in four papyri as follows: 28 times in Ebers, 12 times in Berlin papyrus, and 9 times in Hearst. In the London papyrus, they mentioned the disease directly and introduced it with the names: AAA, uxedu, and uha [205, 210,211].

From the beginning, Egyptian doctors realized that AIDS is transmitted through semen, that's why they called it semen. They hypothesized AIDS is a genetic disorder, but they observed it in infected women who have sexual relations with infected men, so named AIDS as semen in means of "poison" [205,208].

Evidence has shown that HIV was transmitted from nonhuman mammals to humans during the 1900s [212,213]. However, in the 1980s did the virus come to the world's attention, in two homosexual men [214].

Epidemiology

This disease is most common in sub-Saharan Africa [215]. Currently, approximately 34 million people are living with HIV, with a total of 24 million AIDS-related deaths. With an estimated 6.1 million people living with HIV in South of Africa, South Africa's epidemic remains the largest in the world [216,217]. Over the past few decades, HIV has slowly spread throughout Africa and then to other parts of the world [218].

Transmission

In 2005, the Centers for Control and Prevention Disease (CDC) published data about AIDS, many cases of infection were caused by sexual transmission between infected people [219-221]. Also, the use of drugs with a common needle, transmission through blood (especially plasma), mucosal transmission or from mother to child during pregnancy, childbirth or breastfeeding are effective in the transmission of infection [222-224]. HIV infection in humans came from a type of chimpanzee in Central Africa. Studies show that HIV has been transmitted from chimpanzees to humans since the 1800s [218]. The chimpanzee version of the virus is called simian immunodeficiency virus (SIV). Probably, when humans hunted these chimpanzees, HIV came into contact with their infected blood, and this is how it spread to humans [45].

Laboratory Diagnosis

Antibody tests look for HIV antibodies in a person's blood or oral fluid. Antibody tests can be used 23 to 90 days after exposure to the virus [225]. Most rapid tests and the only FDA- approved are antibody tests. In general, antibody tests that use blood from vessels can detect HIV soon after infection [226-228]. Antigen/antibody tests look for both HIV antibodies and antigens. Antibodies are produced by person's immune system when they're exposed to microorganisms. Antigens are virus cell surface proteins that activate the body's immune system [227-229]. An antigen/antibody test on blood from a vessel can usually detect HIV 18 to 45 days after exposure. There is also a rapid antigen/antibody test available that is done with a finger stick. Tests done with blood from a finger stick can take 18 to 90 days after exposure [230-232]. Nucleic Acid Tests (NATs) look for the virus in the blood. This test should be considered for people who have had a recent exposure. A NAT can usually detect HIV 10 to 33 days after exposure [233].

Sign and Symptoms

Most people will have flu-like symptoms within 2 to 4 weeks of infection. These symptoms may last for days or weeks after infection [218]. HIV has three stages: Stage 1 (acute HIV infection): People have a large amount of HIV in their blood and are highly transmissible. At this stage, the symptoms are like the flu. Stage 2 (chronic HIV infection): This stage of infection is asymptomatic. The virus is still active and continues to multiply in the body. People at this stage either have no symptoms or become ill but can transmit HIV. Stage 3 (AIDS): People with AIDS have high amounts of the virus in their blood and easily transmit the virus to others. People with AIDS have a severely damaged immune system. Opportunistic infections occur strongly in their bodies [218,234,235].

Classification and Taxonomy

The HIV belongs to the genus Lentivirus in the family of Retroviridae, subfamily Orthoretrovirinae [236]. On the basis of genetic characteristics and differences in the antigens, HIV is classified into the types 1 and 2 (HIV-1, HIV-2). The HIV of non-human mammals (SIV) are also belong to the genus Lentivirus [45,237].

Cellular Changes and Immunogenesis

HIV replication causes progressive loss of CD4+ T cells and immune abnormalities, leading to increased infectious complications. HIV primarily targets CD4+ T cells. After transmission in the body, HIV penetrates the mucous tissues and reaches the lymphatic organs within a few days [238]. During the primarily phase of HIV infection, specific CD4 T lymphocytes that respond best to HIV may be killed by the virus, permanently impairing the immune system's ability to control HIV [239,240].

Treatment and Vaccination

Currently, there is no vaccine approved by the US Food and Drug Administration (FDA) to treat and prevent HIV, but research is ongoing. Several unapproved vaccines have been introduced to health organizations, the most important of them are InnaVirVax – (a spin-off of INSERM, Evry, France) is developing VAC-3S, a vaccine designed to induce a humoral immune response against a highly conserved region. HIV-1 gp41 envelope protein called 3S has been made [241-243]. Genetic Immunity (Budapest, Hungary) is developing DermaVir, a DNA vaccine encoding 15 HIV proteins administrated by skin patches [244]. So far, there is no effective treatment for HIV infection or AIDS [218]. There are several drugs targeting HIV infection that are used to slow down the disease and strengthen the immune system. One of the key treatment strategies is highly active antiretroviral therapy, or "cocktail AIDS," which is a combination of several antiretroviral drugs designed to combat HIV. Since the beginning of this treatment, the life expectancy of patients has improved over two decades [245].

Ebola

Ebola is a viral disease that has attracted the world's attention after its outbreak in West Africa [246,247]. Ebola Virus Disease (EVD) is a hemorrhagic fever and caused by the Ebolavirus [248-250].

Epidemiology and History of Ebola

In 430 BC, Thucydides, a Roman historian, described the symptoms of the disease during the war between the two states of Athens and Sparta [251,252]. The disease he told included symptoms such as fever, headache, pain, vomiting, and diarrhea. He also reported hands and feet necrosis probably due to gangrene. Identifying viral diseases before 1976 was impossible due to the lack of technics in science and it was not possible to discover the difference between diseases [253,254]. Thucydides describes a terrible summer during the Peloponnesian War between two rival governments in ancient Greece [252,255,256]. The symptoms and duration of treatment or death which he describes, are the same as the symptoms of Ebola nowadays. But before Ebola was discovered as a virus, this disease was called Thucydides syndrome [251,252,257].

The first cases of EVD were reported in 1967 in South Sudan and the Republic of Congo (RC) [248]. For the first

time, it was observed near the Ebola river in RC, Ebola took its name from this river [258]. Since the first EVD outbreak in Congo, at least 17 outbreaks of the virus have been reported in Gabon, Guinea, Zaire, and RC. until 2020, there have been 33,604 cases of infection and 14,742 deaths due to Ebola in the world [246,259,260]. The death rate of Ebola is about 40 to 90 percent [250,261].

Reservoirs and Transmission

The main reservoir of the Ebolavirus is unknown, but it is believed that the virus is transmitted to other communities through carrier animals (e.g., fruit bats, chimpanzees, gorillas, monkeys, forest antelopes or porcupines) [262-264]. The transmission of Ebolavirus infection in human communities is through direct skin contact with the infection, blood transmission, body fluids transmission, and sexual transmission [265-267].

Sign and Symptoms

During the affliction of EVD, a sudden onset period of 2-21 days occurs [261,268,269]. Its clinical symptoms are non-specific, and it is generally diagnosed with fever, internal bleeding, diarrhea, and hematemesis (vomiting blood), and damage to organs or organ failure due to infection (e.g., liver, kidney and lung necrosis) [270,271].

Classification and Taxonomy

Ebolavirus belongs to the Filoviridae family of Monjiviricetes class of viruses. So far, 12 genus of the Filoviridae family has been discovered, that 7 genus of them directly affects humans [246,248]. Filoviridae which affects humans, belong to the Ebolavirus genus, which includes Bundibugyo virus (BDBV), Zaire ebolavirus (ZEBOV), Reston virus (RESTV), Sudan virus (SUDV), and Tai jungle virus (TAFV); or the genus Marburg virus (Marburg virus (MARV) and Raven virus (RAVV)) [247,248,272].

Laboratory Diagnosis

To make a correct diagnosis, the World Health Organization (WHO) has suggested blood sampling and swabs from the mucus of infected patients [273]. Real-time polymerase chain reaction (RT-PCR), and checking the level of immunoglobulin M (IgM) antibodies by using the enzyme-linked immune sorbent assay (ELISA) are effective for diagnosing the disease [249,272,274].

Cellular pathways and Pathogenesis

Ebolavirus creates the colony by surface receptors and mediators between the virus and the host's body. After the molecular investigation, it was found that these receptors are membrane phospholipids and proteins [275]. Protein receptors bind with higher affinity to the surface glycoprotein of the Ebola virus. The virus uses attachment factors such as vitamin B9 and cell surface proteins to be recognized by receptors [276,277]. On the other hand Ebola virus can release proteins that cause clots in bloodstream [278].

Treatment and Vaccination

There is no licensed treatment and vaccine to prevent EVD. However, attempts for production of a vaccine to lead found a vaccine in 2019 developed by Merck company in the united states for ZEBOV [279,280]. The Center for Disease Control and Prevention (CDC) has suggested Inmazeb TM and Ebanga TM for control and treatment of ZEBOV [281].

One Family and Four Pandemics (SARS, MERS, CoVid)

In 1890, we saw the OC43 pandemic, and then 113 years later, in 2003, the SARS-CoV-1 pandemic was created, the third pandemic, MERS-CoV, was created with a gap of nine years (2012) compared to the second pandemic, and finally seven years later (2019) we witnessed the last pandemic, SARS-CoV-2 [282]. Considering the decreasing distance between pandemics and their epidemic rate and power of infection, it can be said that in less than seven years, we will see another epidemic of the coronavirus family.

First Afflictions and Spread

Severe acute respiratory syndrome (SARS) A type of acute disease caused by the SARS virus. In spring 2003, Asia was the epicenter of a potentially global health crisis. The advent of a new, deadly disease SARS, disrupted the lives of millions of people in China and its southeast Asian neighbors [283]. SARS disease or acute respiratory syndrome with a surprise appearance is a type of pneumonia with a viral agent from the family of viruses. The virus, which is transmitted by coming in contact with infected people, originated in the southernmost state of China and its final goal was to spread to 30 countries around the world [284].

In 2012, the first case of Middle East respiratory syndrome (MERS) was reported in Jeddah, Saudi Arabia [285,286]. MERS is an endemic disease that has spread in 27 countries of the world by 2022, including Saudi Arabia, UAE, Bahrain, Jordan, Kuwait, Qatar, Oman, South Korea, etc [287,288,285]. The first reported case was a 60-year-old man in Saudi Arabia who had a 7-day history of fever, cough, sputum, and shortness of breath. Due to acute pneumonia and subsequent kidney failure, a coronavirus, which was later named HCoV-EMC, was isolated from his sputum [289,290].

After that, in April 2012, the first outbreak of the disease occurred in the public hospital of Zarqa city in Jordan [291]. In December 2019, a pneumonia outbreak of unknown origin was reported in Wuhan, Hubei Province, China. Pneumonia cases were epidemiologically linked to Huanan Seafood Wholesale Market [292,293]. Genome analysis of the virus showed that it is a new coronavirus related to SARS-CoV and therefore named SARS-CoV-2 (SARS-CoV-2). The global spread of SARS-CoV-2 and the death of thousands of people due to (COVID-19) caused the World Health Organization to declare this disease a pandemic on March 12, 2020. Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, Hubei Province, China, during a recent pneumonia epidemic in January 2020 [292].

Transmission and Reservoirs

Different species of bats are the natural hosts of coronaviruses, which were related to those that caused the SARS outbreak [294]. Therefore, it is said that it is most likely that MERS is a kind of zoonotic disease, which is believed to have originated from bats and then transferred to camels by examining different genomes of the virus. The route of virus transmission from animals to humans is not fully understood, but camels are the main reservoir host of MERS-CoV and the animal source of infection in humans [285,295].

SARS-CoVs

SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats. Studies have shown that some bats are capable of transmitting SARSr-CoV to humans [296]. Genome analysis and comparison with previously known coronavirus genomes show that SARS-CoV-2 has unique characteristics that distinguish it from other coronaviruses, such as optimal affinity for the angiotensin-converting enzyme receptor 2 (ACE2) and a polybasic cleavage site at the S1/S2 spike junction that determines the amount of infectivity and the amount of host contamination. RaGT131 is approximately 96% similar to SARS-CoV-2, with some differences in the spike receptor binding domain (RBD) that could explain the difference in ACE2 affinity between SARS-CoV-2 and SARS-like coronaviruses [282,293,297]. On January 22, 2020, the Chinese Centers for Disease Control and Prevention (China CDC) reported that out of 585 swab samples taken from around the market, 33 were positive for SARS-CoV-2, and these samples were concentrated from the wild animal holding corridor. It is stated in this report that "It is highly doubtful that the current epidemic is related to the wild animal trade [298]. The discovery of possible intermediate hosts of the coronavirus can be crucial for better control of COVID-19. Genomic and evolutionary evidence of the occurrence of the novel coronavirus-like coronavirus-nCoV-2019 (called Pangolin-CoV) was found from dead Malayan pangolins. Pangolin-CoV is 91.02% similar to nCoV-2019 and 90.55% similar to BatCoV RaTG13 at the whole genome level. Pangolin-CoV is the lowest common ancestor of nCoV-2019 and RaTG13. The S1 protein in Pangolin-CoV is closest to RaTG13. ACE2 in Pangolin-CoV was fully compatible with 2019-nCoV. This indicates that Pangolin-CoV has the same virulence ability as 2019-nCoV [299]. So far, several animals have been identified as reservoirs 1- Bat coronavirus of this virus, including camels, pigs, turkeys, mice, dogs, bats, cats, etc., among these animals, bats are the most well-known carriers of human infections [300]. According to the reports, the animal reservoir of SARS-CoV-2 can be considered to be Rhinolophus and Pangolin bats, which have the most genetic similarity [301].

Virus Spread & Epidemiology

We should say In about to the sudden outbreak of this disease that is in China's southern province, an agricultural region of about 75 million people with a tropical climate, had to large start [297]. The unprecedented epidemic of SARS caught people of Hong Kong from March to May 2003. The outbreak in Guangdong was centered in the provincial capital of Guangzhou and its nearby Pearl River Delta area. At the beginning of March 2003, a professor from Guangzhou who had been treating atypical pneumonia cases in a Guangzhou Hospital visited Hong Kong and stayed at a hotel in the Kowloon district in Hong Kong. He was admitted to a local hospital with symptoms of acute respiratory disease. He later died of the disease. Arising from this index case, seven other people who stayed on the same floor of the hotel were affected by SARS. These included three visitors from Singapore, one visitor from Vietnam, two visitors from Canada, and one local person. All of them developed SARS and two people died of the disease. The epidemic in Hong Kong reached its peak at the end of March 2003 [283,302].

The second outbreak in Hong Kong involved another guest visiting the same hotel floor. The index case was admitted to the Prince of Wales Hospital, where he, directly and indirectly, infected 138 hospital staff, patients, and visitors from March 11 to March 25, 2003. But in Vietnam, this severe acute respiratory syndrome was first identified on February 28 by World Health Organization epidemiologist Dr. Carlo Urbani, who later died of the disease in Thailand. On the same floor as the doctor from Guangdong. The Vietnamese government worked closely with the WHO to bring the disease under control very quickly. In Hanoi, the cumulative number of cases was only 63, and it was removed from the list of areas with localized outbreaks on April 28. As a matter of fact in another country like Singapore, the spears of this epidemic look like Hongkong because three guests from M Hotel returned to Singapore in late February. On March 6, 2003, three cases of pneumonia were reported

to the Ministry of Health. These included two of the three passengers. The outbreak in Singapore was caused by hospital transfers from people who were not immediately diagnosed as having SARS. Wholesale market. Quick action by health authorities in contact tracing, implementing isolation, and quarantine limited the outbreak. Toronto was among the first areas where a guest of the M Hotel in Hong Kong returned home in late February. 13 Outbreaks in Toronto occurred early, as did Hong Kong and Singapore when the nature of the disease was unknown. Severe acute respiratory syndrome (SARS) spreads rapidly in hospitals and to the wider community when other patients, hospital visitors, and people close to staff become infected. Toronto had two outbreaks. The city was removed from the "areas of recent local transmission" list on May 14, only to return on May 26 when the virus emerged in another outbreak. The city was finally declared free of local transmission on July 2.13. The mortality rate in Canada is 17% [102].

Also, regarding the spread of the disease from Saudi Arabia to Bahrain, it is said that in 1986, a 25 km long passage was built from Bahrain to eastern Saudi Arabia, which is one of the busiest areas between the two countries, and the traffic statistics of 20 million passengers in 2013 has done This area was also one of the first areas of MERS outbreak [303].

Most cases of MERS outbreaks in other parts of the world are related to the Middle East region, and most of the cases were either in contact with camels or were present in hospital environments. Also, 80% of patients are reported by Saudi Arabia [303-305].

New Year and New Spread: The Chinese Lunar New Year holiday has coincided with the outbreak of Corona, people travel to their hometowns at this time. It is estimated that people will make 3 billion trips during this 40-day trip. About 5 million people will travel before the travel ban begins. On January 23, 2020, they left Wuhan, the capital of Hubei Province, the epicenter of the COVID-19 pandemic. About one-third of this population has traveled outside of Hubei province [306].

Sign and Symptoms

The duration of this disease is reported to be between 2 and 7 days and sometimes 10 days. At first, symptoms such as cold, fever of 38 degrees, muscle pain, and finally dry cough affect the patient, and then these symptoms change. A Lung photo shows unilateral or bilateral pneumonia symptoms in some patients. Laboratory symptoms can include lymphopenia, decreased blood oxygen, and increased CPK and LDH. By identifying the genome of the disease-causing virus, which is a new type of the coronavirus family. New molecular methods of virus detection in clinical samples using RT-PCR in a few hours are acceptable [284].

Based on available data, the CDC defines a suspected SARS case as someone who has a fever (temperature greater than 38 °C [100.4 °F]) and lower respiratory tract symptoms within 10 days of each It starts with them [307].

It has been observed in vivo and in vitro studies that the SARS-CoV-2 virus can cause infection in several organs. Histopathological features such as pulmonary involvement with alveolar diffusion damage with hyaline membrane formation and pulmonary microemboli are the most prominent acute histopathological findings. These features are often associated with elevated inflammatory cytokines and increased angiogenesis, which is fatal in some cases. The hyaline membrane is attributed to increased vascular permeability and the accumulation of hyaluronic acid in the alveolar space, which leads to the trapping of a large volume of water. The initial symptoms of the disease are similar to the flu. The patient can be asymptomatic or with symptoms such as self-limiting syndrome of fever, fatigue, myalgia, arthralgia, rhinorrhea, sore throat, or conjunctivitis. As the disease progresses, symptoms such as persistent fever, cough, hemoptysis, silent hypoxia, discomfort or chest pain, respiratory failure, or even multi-organ failure are mentioned. Also, the disorder in smell (hyposmia, anosmia, and parosmia) or taste (dysgeusia) is an important chemical disorder in COVID-19. Extrapulmonary symptoms include diarrhea, lymphopenia, thrombocytopenia, liver and kidney dysfunction, rhabdomyolysis, meningoencephalitis, stroke, convulsions, Guillain-Barré syndrome, cardiac arrhythmia or heart block, pancreatitis, skin diseases such as rhabdomyolysis or Kawasaki, thromboembolism, and acute thyroiditis. Mild and moderate cases get a partial recovery almost 10 days after the onset of symptoms, which coincides with a decrease in viral load and an increase in antibodies against protein N or S. "post-acute COVID-19 syndrome" are disorders that sufferers of COVID-19, which include fatigue or persistent muscle weakness, sleep problems, anxiety or depression, impaired smell or taste, palpitations, joint pain, dizziness, diarrhea, vomiting, and chest pain [282].

Diagnosis

Diagnosis of SARS-CoV-2 is done through reverse transcription PCR (rt-PCR), which uses nasopharyngeal swabs (NP) and oropharyngeal swabs (OP) for sampling. rt-PCR testing for SARS-CoV-2 may not be appropriate because it may be falsely negative due to early or late sampling or insufficient viral load, or technical errors such as transportation of test results. Cases have been reported of patients who, due to their negative rt-PCR test, doctors faced many suspicions regarding the diagnosis of SARS-

CoV-2 according to classical computed tomography (CT). WHO suggests that if the test result is negative if the clinical suspicion of the patient is still high, the test should be repeated, preferably from a lower respiratory tract. A few studies have suggested serological antibody testing, useful for patients with suspected viral RNA based on negative rt-PCR and those with asymptomatic infections [293].

Molecular Cell Properties

About this epidemic, we can say: that SARS-CoV is an enveloped, single, and positive- stranded RNA virus [308]. People at risk include elderly people, people who live with the patient, and health workers who are responsible for the care and treatment of these patients. Currently, researchers believe that despite the temporary stagnation of the disease, it is possible that with the arrival of the cold season, the re-spread of SARS will lead to a widespread epidemic in the world, therefore, increasing the awareness of the people of the society, especially the health workers, including nurses, can be very significant in preventing this epidemic [309].

Emerging and Concerns

Emerging infectious diseases are always at the forefront of continuous public health concerns. SARS advertisement emphasizes the focus of this concern. Of course, it cannot be denied that the hope of making a new vaccine is very effective in reducing the effect of the disease. However, often about SARS and in the early stages of this epidemic, its transmission should be prevented by minimizing contact with infected persons [310].

During the outbreak of such disease among the people present in the country's population, there was an untimely fear due to its rapid transmission among the health care workers in the hospitals. At the same time, a surprising question arose in the minds of the general public, and that question did not originate from anything other than everyone's fear and panic, and it implied the issue of whether this fear that exists among hospital employees affects their performance. Does it leave or not? It was these people who suffered from the prevailing atmosphere in the society in addition to the spread of disease. According to this question, human society was faced with a vital and at the same time astonishing challenge, which was how to eliminate the fear and panic among the health guardians of human societies. Nowadays with the promising process of vaccine production, the corona epidemic is still in everyone's memory as the biggest challenge that has threatened human health. This situation is also threatening and dangerous for people who have underlying diseases as they are disproportionately affected and experience high morbidity and mortality. In addition, it seems that the increase of liver enzymes is a risk factor for the progression of the disease, even in the absence of underlying liver disease, while during the outbreak of SARS-CoV-2 infection, the mechanism of a large number of liver enzymes to It remains unknown to this day. It is well understood and known that coronavirus disease (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which is an ongoing epidemic. Health care workers play a key role in promoting flu vaccination, which can have a very good result [311]. At that time, the epidemic challenged China's health system and challenged critical frameworks such as lack of emergency preparedness, lack of effective surveillance, poor communication between HDs, and reporting delays [283].

MERS is the helpless child of SARS. That's why I use the word child, because both are descended from the Corona family and have a lot of genetic similarities, and the outbreak of MERS was after SARS. But the helplessness of MERS is that SARS is characterized by efficient human transmission and a relatively low mortality rate. In contrast, MERS is relatively inefficiently transmitted to humans but has a high mortality rate. People who get MERS have a 35% chance of dying, compared to only 1% for the SARS-CoV-2 pandemic that started in 2019. If the rate of transmission of MERS from one person to another was the same as the outbreak of SARS, a disaster worse than the mass killing of the SARS-CoV-2 pandemic would occur, even though according to the laboratory statistics recorded in who, in 27 countries of the world, MERS is only It was transmitted to 1979 people and caused death in 858 people [312-315]. The HCoV-EMC virus, which is easily propagated in cell culture, is a beta-coronavirus [289]. Also, this virus is one of the closest relatives of HKU4 and HKU5 viruses, which were isolated from Tylonycteris pachypus and Pipistrellus abramus bats, respectively [289,316].

Treatment and Vaccination for SARS-MERS

There is still no effective treatment and vaccine for the MERS virus. In the glycoprotein S of this virus, most of which consists of an alpha helix and has no allergic properties, in the RBD region, the S1 region has a high ability to stimulate the host's immune system, and since it can be stable in the host's immune system, It is a suitable candidate for vaccine design [317].

COVID-19

Coronaviruses are round and sometimes polymorph and their diameter is 80 to 120 nm. One of the most obvious characteristics of this virus is the nail-shaped bumps on its surface. These spikes have caused the state of the solar corona, which is also the name of the corona. Coronaviruses are sensitive to ultraviolet rays, heat, and disinfectants

containing chlorine, peracetic acid, and 75% ethanol, which cause their inactivation, but they can be stored at -80 degrees Celsius for years [300,318].

The origin of SARS-CoV-2 is not exactly known, so many theories have been proposed. According to the current evidence, WHO reports that the transmission of SARS-CoV-2 occurs through respiratory droplets and contact. Transmission by respiratory droplets occurs when an infected person with symptoms such as sneezing and coughing is exposed to respiratory droplets at a distance of 1 meter. At this distance, the person is at risk of getting infected through his mucous membranes, including the mouth, nose, and eyes, as well as transmission through indirect contact through fomites on the surfaces around the infected person. Symptoms usually appear between 4-5 days after contact with the virus. However, studies show that the incubation period may last up to 14 days. The asymptomatic infection has also been reported, and most of these patients had mild symptoms and experienced a mild illness. Asymptomatic infection is rare and has been seen in young people aged 18 to 29 years [293].

Origin of Covid-19 Pandemic: Most scientists think that SARS-CoV-2 has a natural origin and was transferred from an animal to humans, but they do not rule out the possibility of a laboratory leak and suspect that the virus originated from the Wuhan Institute of Virology (WIV) located in the city. Wuhan, China, where the first cases of COVID-19 were reported and emerged. For example, during the acute respiratory syndrome (SARS) epidemic of 2002–2004 and at the onset of the COVID-19 pandemic, Chinese government officials reportedly suppressed important public health data during both epidemics. Scientists do not have enough evidence regarding the origin of SARS-CoV-2, so they are unable to reject the laboratory leak theory or confirm the theory that the virus has a natural origin. Most researchers think that this virus that caused the pandemic can be similar to HIV epidemics, influenza epidemics, Ebola outbreaks, and the coronaviruses that caused the SARS epidemic in 2002 and the Middle East Respiratory Syndrome (MERS) outbreak in 2012 through An animal has been directly transmitted to humans, such as a bat, or it has been transmitted through an intermediary animal. Although laboratory leaks have never caused an epidemic, they have led to small outbreaks, for example in 2004, when two researchers were infected by the virus that causes SARS at a virology laboratory in Beijing studying the disease. They spread the infection to seven more people before the outbreak was contained. Investigations into the origin of outbreaks often take years, and some causes remain unknown. It took 14 years to determine the origin of the SARS epidemic, which began with a virus in bats and most likely spread to humans through civet cats, or the origin of the Ebola epidemics of 2013 and 2016, which remain unknown. Several researchers have investigated whether SARS-CoV-2 is bioengineered. One of the first research teams, led by Mr. Christian Andersen, was carried out, which recognized the theory of laboratory design as (unlikely). After that, some pointed out that furin cleavage is not present in its closest relatives, referring to the location of furin cleavage, which helps the virus to enter the cell. The furin cleavage site is located in the spike virus and is important in infecting the cell. Of course, many coronaviruses have furin cleavage, such as the coronaviruses that cause colds. Stephen Goldstein, a virologist at the University of Utah in Salt Lake City, says viruses with sites are scattered throughout the coronavirus family tree, and not limited to a group of close relatives. Convergent evolution is a process in which unrelated organisms independently evolve similar traits as a result of adaptation to the environment, which is extremely common. WIV researchers identified hundreds of samples of bats living in the mine between 2012 and 2015, which were found because the miners contracted an unknown respiratory disease. Examination of the blood of the infected miners showed no antibodies against SARS-CoV-2, which means that the disease was probably not COVID-19 [319].

Also, the RBD sequence of the spike (S) protein suggests that it arose from a natural evolutionary process. Estimates of the most recent common ancestor of SARS-CoV-2 date the pandemic between late November 2019 and early December 2019, which is consistent with the first reported cases. Thus, human transmission occurred unnoticed after the zoonotic event and before the polybasic furin cleavage site was acquired [292]. The location of polybasic furin with four amino acids (PRRA) in the binding site of spike protein S1/S2 plays a role in virus infectivity, transmission, and host selection and is important [320].

Cellular Gene Structure: Viral gene detection by RT-PCR is the most reliable technique. CoV is positive enveloped single-stranded RNA viruses that have the largest viral RNA genomes, measuring 8.4–12 kDa. The 5' end forms the major part of the genome that encodes the proteins responsible for virus replication. The 3' terminus contains five structural proteins, namely spike protein (S), membrane protein (M), nucleocapsid protein (N), coat protein (E), and hemagglutinin esterase (HE) protein. Protein S is an intermediary protein. N protein is present in RNA complexes and helps in the transcription and assembly of the virus. Protein M also determines the shape and coat of the virus. Protein E is the smallest structural protein that is strongly expressed during the virus replication cycle in the infected cell. The HE protein is responsible for binding the receptor to a specific host [321]. ORF1a and ORF1b encode large polyproteins pp1a and pp1ab, respectively, which are then converted by viral proteases into 16 non-structural proteins (nsp1-nsp16) that play a role in viral RNA transcription and replication [322].

Variants and Recombinants: There are 4 types of coronavirus, alpha type (originally detected in the UK), beta type (originally detected in South Africa), gamma type (originally detected in Brazil), and delta type (originally detected in India) These 4 variants cause concern [323]. Omicron type has more than 50 mutations, of which 26-32 mutations are related to spike protein. Other types of Mojo in Latin America are Lambda (C.37-Peru) and mu (B.1.621-Colombia) which were created by changes in the genome on the characteristics of the virus such as transmissibility, the severity of the disease, and its ability to escape from the system Safety is affected [324]. The types that have been found show evidence that they are more transmissible and cause more severe/reduced disease. Variants are characterized by transmission, disease severity, and ability to evade humoral immunity. In the second quarter of 2021, the alpha type accounted for the most infected cases in the United States and many European countries. Epidemiological studies show that more than 50% of the species in the UK are contagious.

Also, air transmission has increased from 3-fold to 8-fold, and the death rate has increased by 50%. It is estimated that the beta type is about 50% more transmissible than the previous types. As of June 2021, more than 50% of infections in southern African countries are beta type. The gamma type was causing disease in an area of Brazil, and it is believed that those who were previously infected with other types may also be infected with this type. It is estimated that this type is responsible for 1.1-fold to 1.8-fold higher mortality. As of June 2021, Gamma has caused the most infections in South American and Caribbean countries. The delta type, which probably appeared in August and October 2020 and spread to 54 countries due to the high rate of spread, replaced alpha [323].

On November 26, 2021, the WHO announced that it had identified the delta variant of SARS- CoV-2 (B.1.1.529) as a variant of concern and named it Omicron, observations suggest that Omicron has multiple mutations that may are to affect its behavior [325]. The new type of SARS-CoV-2 (B.1.1.529) or Omicron has more than 50 mutations that have been effective in transmitting and escaping from the body's immune system [326].

First spotted in South Africa in April 2022, the BA.4 and BA.5 variants are members of the growing Omicron family. This type causes less death and hospitalization than its previous types. Antibodies stimulated by vaccination have less effect on this type [327].

Treatment and Vaccines: We have used medicine for pandemic diseases in the last few decades, and we want to have an overview of them. The first drug we want to explain about is Tenofovir which we found in the last articles may be useful for corona virus but finally is not confirmed and the treatment is not definitive. Tenofovir has been shown to be effective against HIV, herpes simplex virus- 2, and hepatitis B virus [328].

Another drug is INMAZEB that used for EBOLA and it was effective. INMAZEB reduced mortality by 17% in subjects with EVD when administered at a dose of 3 mL/kg [329].

LEVOFLOXACIN drug is used for plague which In oral and intravenous formulations, levofloxacin is indicated in adults for the treatment of various infections caused by susceptible bacteria, including infections of the upper respiratory tract, lower respiratory tract, skin, skin structures, urinary tract, and prostate But because plague currently has no treatment, these drugs dont have much effect on the patient's recovery process [330]. So far, no definitive treatment that can remove the HIV virus from the body has been discovered or invented, but some articles mention a ATAZNAVIR for AIDS .and the other articles mentioned ATV7's ability to exert antiviral activity may be more beneficial for HIV patients. The analysis of molecular dynamics and binding energy also showed that the drug ATV7 can be more inhibitory ability than the Atazanavir drug [331,332]. Influenza antiviral agents Amantadine or Rimantadine, Zanamivir and Oseltamivir can change the severity of the disease and reduce the duration of the disease by 1.5-2.5 days. Amantadine only inhibits influenza A. The neuraminidase inhibitors Zanamivir and Oseltamivir are effective against both influenza A and B [333]. And about SARS-CoV disease, Interferon β can be important and therapeutic alone or in combination with antiviral drugs [334]. And for MERS disease, treatments have been found, which are mentioned in the last articles, a series of protease inhibitors; Like Plpro, CLpro helicase, Spike And they also use monoclonal antibody and interferon. Echinacea purpurea widely inhibits the corona virus and SARS-CoV-2 only in laboratory conditions. In the treatment of Cholera, it has been suggested that the antibiotic should be selected based on the local antimicrobial resistance pattern [335,336].

Antibiotics such as Tetracycline have been widely reported, and the most important treatment includes water and electrolyte replacement for severe water loss from the body [125].

For yellow fever interferon-α, polyICLC, antibodies, and other immunosuppressants are effective if administered after infection, otherwise, they are ineffective after the infection has developed [170]. The treatment of Smallpox is similar to monkeypox; Monkeypox has two oral medications, Brincidofovir and Tecovirimat, which have been approved and are effective in animals, but there is no virtual medicine for Monkeypox [337].

Conclusion

Considering the pandemics that have occurred throughout history, it can be clearly concluded that humans must acquire the ability to predict and deal with possible factors of future pandemics, and such a method may be a guide:

The first step in predicting epidemics is to identify the causes of common diseases between humans and animals. In the second stage, the pathogenic environment must be identified in terms of mutagenic factors. Now, with this information, we can predict mutations and examine whether these mutations are effective in transmitting these factors? And finally, an answer must be found to a question, what effect does a change in the transmission parameters of the pathogen have on its prevalence?

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