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Infectious Diseases: Treatments, Testing and Advancements

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Contents

Abstract

Pandemics have a long history, but the detection, treatment and monitoring have yet to be improved. There have been a number of significant pandemics recorded in human history that have caused enormous negative health, economic and social impacts globally. This paper will explore the concept and history of pandemics, its consequences and solutions, and will analyze the COVID-19 crisis.

Introduction

As humans have spread across the world, so have infectious diseases. Even in this modern era, outbreaks are nearly constant, though not every outbreak reaches the same pandemic level as COVID-19.[1]

Different diseases and illnesses infected humanity since the earliest days reaching catastrophic levels within short periods of time in the form of epidemics and pandemics. Bubonic plague, smallpox and influenza pandemics are some of the most brutal killers in human history.[2] In addition, as many as 20 major maladies have emerged in novel, more deadly, or drug-resistant forms in the past three decades.[3]

Despite the persistence of pandemics throughout history, healthcare improvements and an understanding of the factors that incubate pandemics have been powerful tools in mitigating their impacts.[4,5] Within those improvements, the paper will explore two main categories which are treatments and testing. Within the treatments section, the paper will analyze the vaccines and therapies market.[6]

As we continue to learn about the different factors that cause these infectious diseases, we also have to keep in mind that these events are occurring more often, and spreading faster and further than ever, in many different regions of the world. Evidence suggests that the likelihood of pandemics has increased over the past century because of increased global travel and integration, urbanization, changes in land use, and greater exploitation of natural resources.[7] That is why, it is expected that newly discovered diseases will appear and many long-established ones will potentially re-emerge, demanding urgent innovation, investment and preparation by companies and governments around the world.[8]

What is a Pandemic?

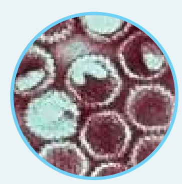
A pandemic is often referred to as an epidemic that has spread over several countries or continents, usually affecting a large number of people and caused by a new pathogen or one that has not circulated among people for a long time.[9] Humans usually have little to no immunity against them so they can spread quickly from person-to-person. Pandemics can cause sudden, widespread morbidity and mortality as well as social, political, and economic disruption.[10]

Because the definition of pandemic is primarily geographic, it groups together multiple types of events and public health threats. The variety of threats is driven by the great diversity of pathogens and their interaction with humans. Pathogens are organisms that cause disease and vary across multiple dimensions, including the way and mechanism they transmit the disease, its severity, and the difference between its associated morbidities.[11] These and other factors determine whether potential pandemic cases will be identified and contained rapidly or whether an outbreak will spread.[12] As a result, pathogens also vary depending on the potential health, economic, and sociopolitical impacts they can cause, as well as the resources, capacities, and strategies required for their mitigation.

Pandemic Pathogens

Within the different categories of pathogens with pandemic potential, there are three main types that have caused several challenges to humanity. The worst of these three are pathogens that have high potential to cause a global severe pandemic such as the influenza viruses. Most experts believe that these pathogens transmit relatively easy between humans (influenza viruses can spread mainly by tiny droplets made when people with flu cough, sneeze or talk)[13], have long asymptomatic infectious periods that prevents the detection of infected people, and cause symptoms that are challenging to differentiate and diagnose, particularly in the early stages of the infection.[14] The second group is composed of pathogens that present a less serious global threat. These agents do not demonstrate a consistent and sustained human-to-human transmission but can become transmitted more efficiently as a result of mutations and adaptation. The third group of pathogens has the potential to cause regional or interregional epidemics, but the risk of a truly global pandemic is limited because of the slow pace of transmission or high probability of detection and containment.

Types of pathogens

	Bacteria Escherichia coli	**Viruses** Herpes simplex	**Fungi** Death Cap Mushroom	**Protozoa** Giardia lamblia
Type of Pathogen				
Description	Single-celled organisms without a nucleous	Non living particles that reproduce by taking over living cells	Simple organisms, including mushrooms and yeasts, that grow as single cells or thread like fillaments.	Single-celled organisms with a nucleous
Human Diseases Caused by Pathogens of This Type	Strep throat, staph infections, tuberculosis, food poisoning, tetanus, pneumonia, syphilis.	Common cold, flu, genital herpes, cold sores, measles, AIDS, genital warts, chicken pox, small pox.	Ringworm, athlete's foot, tineas, candidiasis, histoplasmosis, mushroom poisoning.	Malaria, treveller's diarrhea, giardiasis, typano somiasis (sleeping sickness).

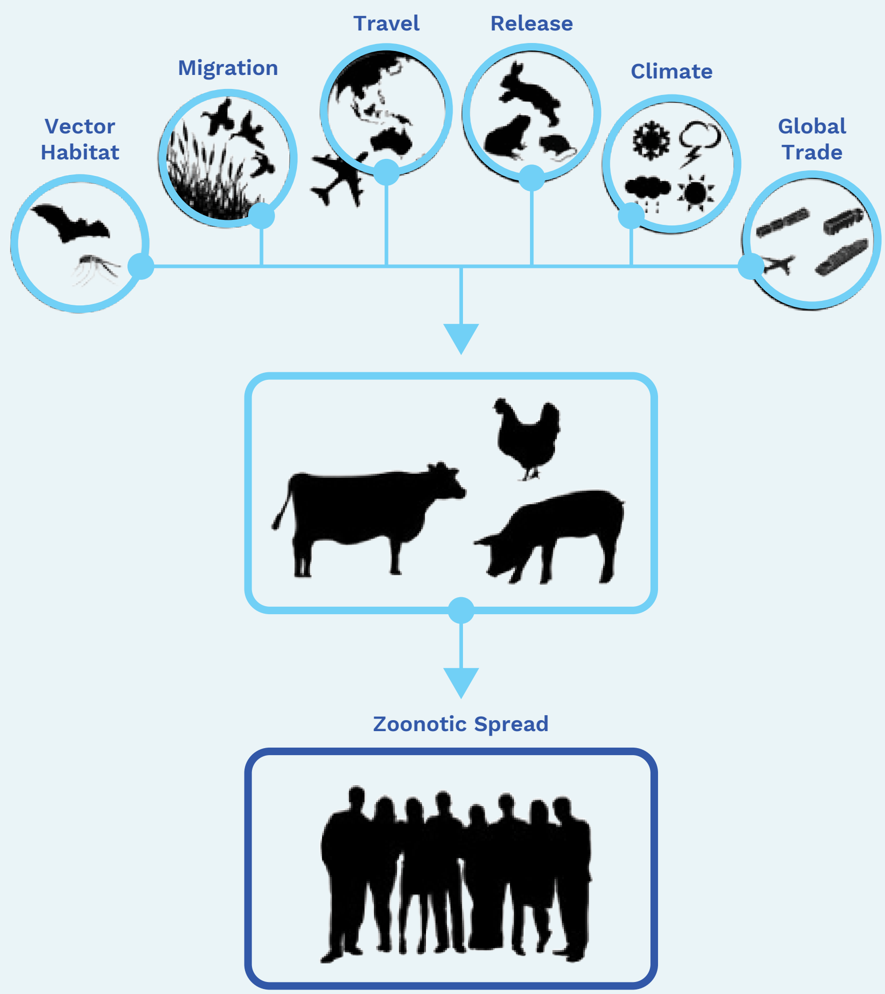
Source: CK-12[15]

Among all known pandemic pathogens, influenza viruses possess the principal threat because of its potential severity and semiregular occurrence since at least the 16th century.[16] This particular disease has a more drastic impact in populations that do not have the health technology to fight it or where there are no antivirals or vaccines available to reduce transmission or mortality. Examples of these populations are low-medium income countries that possess higher levels of malnutrition and comorbid conditions, insufficient access to supportive medical care, and higher rates of disease transmission.

Origin of Pandemics

The majority of all human infectious diseases and pandemics have originated through the transmission of microorganisms from animals to humans called zoonotic transmission.[17] Zoonoses can be transmitted in different ways including transmission through the air, by eating contaminated meat or produce, through close contact with an infected animal, by touching an area or surface that an infected animal touched or through insect bites like mosquitos or ticks.[18]

Zoonotic Spread



Source: Science Direct[19]

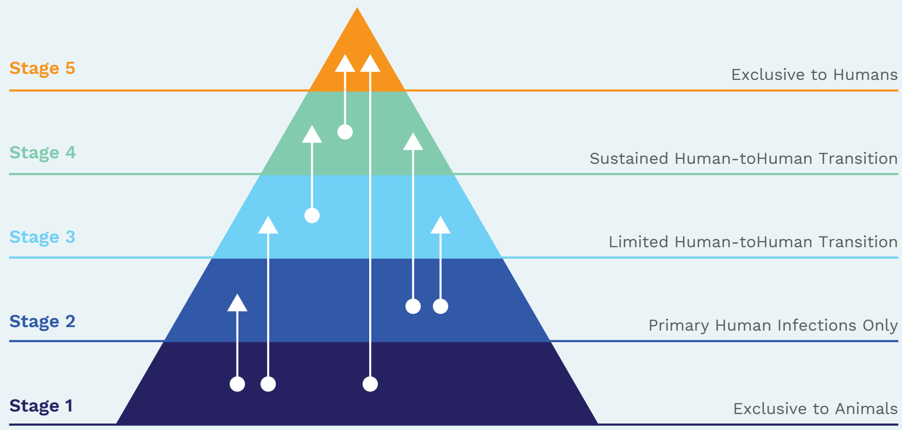
A zoonotic outburst could arise from either domesticated animals or wildlife. Zoonoses from domesticated animals are concentrated in areas with dense livestock production systems, including areas of China, India, Japan, the United States, and Western Europe. Key drivers for outburst risk from domesticated animals include intensive farming and livestock production systems, support of live animal markets, as well as the potential for contact between livestock and wildlife reservoirs.[20] Many historically significant zoonoses were introduced following domestication through increased human-animal interaction, and potentially high-risk zoonoses (including avian influenzas) continue to emerge from livestock production systems.[21]

Wildlife zoonosis risk is distributed far more broadly, with examples found in China, India, West and Central Africa, and the Amazon Basin.[22] Risk drivers include behavioral factors such as use of animal-based traditional medicines, natural resource extraction such as logging, and environmental factors such as the construction of roads within wildlife habitats.[23] Examples such as Ebola have emerged from wildlife reservoirs and entered into human populations through the hunting and consumption of wild species, the wild animal trade, and other contact with wildlife.

Disease Transmission and Spread

The way in which zoonotic pathogens can survive and spread between human hosts varies extensively and not all of them can actually reach human beings. As shown in the table below, the way pathogens are transmitted can go from only within animal populations (stage 1) to transition only within human populations (stage 5). Most zoonotic pathogens are not well adapted to humans (stages 2-3), emerge sporadically, and may lead to localized outbreaks.[24]

Zoonotic disease emergence model outlining the 5 stages of pathogen emergence from animals to humans.



Source: Oxford Academic[25]

Pathogens that are past stage 3 are of the greatest concern, because they are sufficiently adapted to humans to cause high levels of transmission, and their geographic spread is not limited by a specific habitat or place.

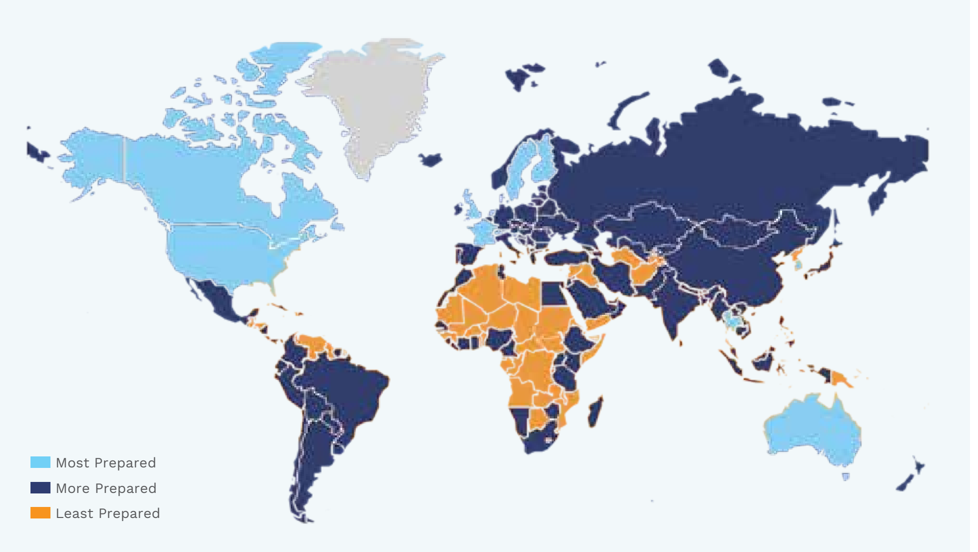
When pathogens are transmitted, the risk that the pathogen will spread within a population is influenced by two main factors which are pathogen specific and human-population specific. Within the former ones, examples include genetic adaptation of the pathogen as well as mode of transmission. Within the human factors, examples are: density of the population and the susceptibility of getting infected; patterns of movement such as travel, trade, and migration; and speed and effectiveness of public health surveillance and response measures.[26]

Disease transmission can increase in speed when there are dense concentrations of population such as urban centers and overcrowded informal settlements.[27] In addition, social inequality and poverty can increase individual susceptibility to infection significantly.[28] This happens because those populations usually suffer from comorbidities, malnutrition and caloric deficits which ultimately weaken the individuals' immune systems. Moreover, environmental factors such as lack of clean water and adequate sanitation amplify transmission rates and increase morbidity and mortality.[29]

Global Pandemic Preparedness

Effective public institutions, strong economies, and adequate investment in the health sector are factors that separate countries that are well prepared for pandemics to those that are not. They usually have specific competencies critical for detecting and managing disease outbreaks, including surveillance, mass vaccination, and risk communications. Poorly prepared countries may suffer from political instability, gaps in fundamental outbreak detection and response systems, inadequate resources for public health, and weak public administration.[30]

Preparedness Rank



Source: GHS Index[31]

The map above shows a global distribution of epidemic preparedness as of 2019, with countries grouped into three different colors. A geographic analysis of preparedness shows that some areas of high outburst risk are also the least prepared. Geographic areas with high outburst risk from domesticated animals include China, North America, and Western Europe. Even though their risk is elevated compared to other countries, they have relatively higher levels of preparedness, although China lags behind its counterparts.[32] However, geographic areas with high outburst risk from wildlife species, including Central and West Africa, have some of the lowest preparedness scores globally, indicating a potentially dangerous overlap of outburst risk and spread risk.

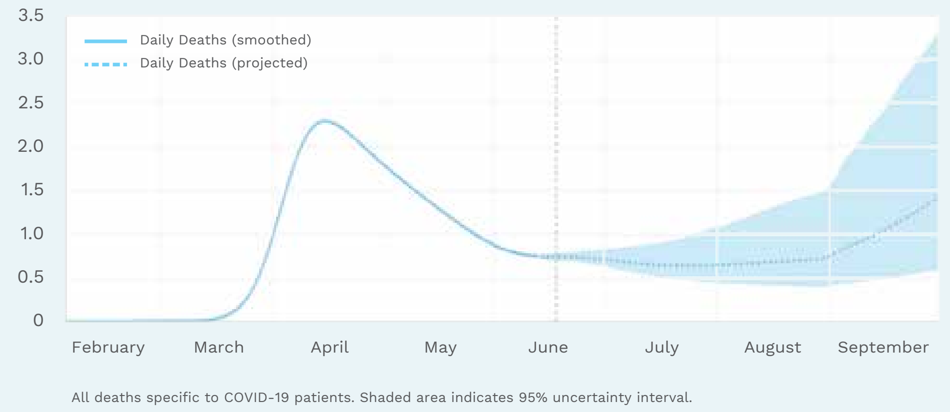
Pandemic Modeling

Quantifying the morbidity and mortality burden from pandemics can be achieved through estimates available from historical events or through probabilistic modeling techniques. These can augment the historical record with an ample index of hypothetical and simulated pandemics that represent a wide range of possible scenarios. Modeling can also better account for changes that have occurred since historical times, such as medical advances, changing demographics, and shifting travel patterns.[33]

Basic models allow researchers to forecast the progression of diseases and understand the effects of interventions within a certain population.[34] More complex scenario models of epidemics and pandemics achieved through large-scale computer simulations can help forecast the expected global spread, dynamics, and illness outcomes of a disease.[35] These models permit to be specific about the different parameters adopted such as the location and frequency of an outburst, as well as the determinants of severity like the transmissibility and virulence. The models then simulate at a daily time step the spread of disease from person to person via disease transmission dynamics and from place to place via incorporation of long-range and short-range population movements. The models also can incorporate mitigation measures, seasonality, stochastic processes, and other factors that can vary during an epidemic. Millions of these simulations can be run with wide variation in the initial conditions and final outcomes.[36]

During the COVID-19 crisis, healthcare institutions as well as universities, public institutions and private researchers developed, and continue to develop, different models to estimate the degree of mortality and morbidity around the world. The following chart from The Institute for Health Metrics and Evaluation (IHME)[37], which is an independent global health research center at the University of Washington, shows the total daily deaths reported in the U.S. as of May 6th, 2020 caused COVID-19 and the expected number of daily deaths in the next coming months.

Deaths Per Day (thousands)



Source: IHME[38]

This model uses data reported by a volunteering organization called "The COVID Tracking Project" which collects data on COVID-19 testing and patient outcomes from all 50 U.S. states, 5 territories, and the District of Columbia.[39] The shaded area shows the level of uncertainty which is the range of values that is likely to include the correct projected estimate for a given data category. Larger uncertainty intervals can result from limited data availability, small studies, and conflicting data, while smaller uncertainty intervals can result from extensive data availability, large studies, and data that are consistent across sources.[40]

Consequences of Pandemics

To be able to assess the consequences of pandemics, researchers, economists, sociologists, and people who have studied these events have relied on data from past pandemics. Direct measures based on data from past episodes are usually hard to find and most of the information has typically focused on one event in one country or region and have traced local outcomes for up to a decade at most.[41] Even then, consequences can be grouped into three main categories which are: health impacts, economic impacts, and social and political impacts.

Health Impacts

The direct health impacts of pandemics have historically been catastrophic. For example, in 14th century, the Black Death plague killed half of the European population.[42] In the 20th century, there were three major pandemics: the Spanish flu in 1919-1920 which caused 20-40 million deaths[43]; the Asian flu in 1957-1958 which caused about 2 million deaths; and the Hong Kong flu in 1968-1969 which caused 1 million deaths.[44,45] More recently, HIV/AIDS has killed between 25-35 million people since 1981.[46]

Depending on the type of disease that gets transmitted, pandemics can have disproportionate effects among different age groups. Some researchers argue that during past influenza pandemics, as opposed to seasonal outbreaks of influenza, it was the younger and more economically active segment of the population that got affected the most. This was the case with the 2009 H1N1 pandemic were the mean age of dead people was 37 years old.[47] However, as it is the case with the COVID-19 pandemic, it is the older and more vulnerable age group that has suffered the most fatalities. This virus has caused more severe health issues to adults over the age of 60, with particularly fatal results for those 80 years and older. These consequences have been exacerbated by underlying health conditions characteristic of older populations such as diabetes, heart disease, and other chronic illnesses. In other words, as people age, their immune system gradually loses its resiliency, meaning that they are more susceptible to infections of any kind, especially a new one like COVID-19.[48]

Many infectious diseases can have chronic effects, which can become more common or widespread in the case of a pandemic. However, the indirect health impacts of pandemics can increase morbidity and mortality even further. Among the different indirect health impacts, the most important ones include depletion and waste of healthcare resources; decreased access to routine care due to an inability to travel, fear, or other factors; and lack of healthcare workers available to treat patients. Additionally, fear can make healthy individuals seek unnecessary care, further burdening the healthcare system.[49]

During the 2014 West Africa Ebola epidemic, lack of routine care for malaria, HIV/AIDS, and tuberculosis led to an estimated 10,600 additional deaths in Guinea, Liberia, and Sierra Leone.[50] This indirect death toll nearly equaled the 11,300 deaths directly caused by Ebola in those countries.[51] Additionally, diversion of funds, medical resources, and personnel led to a 30% decrease in routine childhood immunization rates in affected countries.[52] Facility closures as a result of understaffing and fear of contracting the disease prevented people from routine health care. One study of 45 public facilities in Guinea found that the Ebola outbreak in 2014 led to a 31% decrease in outpatient visits for routine maternal and child health services.[53] Among children of 5 years and younger, hospitals witnessed a 60% decrease in visits for diarrhea and a 58% decrease in visits for acute respiratory illness (ARI), while health centers saw a 25% decrease in visits for diarrhea and a 23% decrease in visits for ARI. In Sierra Leone, visits to public facilities for reproductive health care fell by as much as 40% during the outbreak.[54]

The availability of healthcare workers also decreases during a pandemic because of illness, deaths, and fear-driven absenteeism. Viral hemorrhagic fevers such as Ebola take an especially severe toll on health care workers, who face significant exposure to infectious material. During the 2014 West Africa Ebola epidemic, health care workers experienced high mortality rates: 8% of doctors, nurses, and midwives succumbed to Ebola in Liberia, 7% in Sierra Leone, and 1% in Guinea.[55] Even if health care workers do not die, their ability to provide care may be reduced. At the peak of a severe influenza pandemic, up to 40% of health care workers might be unable to report for duty because they are ill themselves, need to care for ill family members, need to care for children because of school closures, or are afraid.[56,57]

Economic Impacts

Pandemics represent a serious threat not only to the world population, but also to the economies of each country or region. The impact of economic loss can result in instability of the economy through short-term and long-term burden, and direct and indirect costs. During a severe pandemic, all sectors of the economy including agriculture, manufacturing and services face disruptions such as shortages, rapid price increases for staple goods, and economic stresses for households, private firms, and governments.[58]

Pandemics can cause sharp, short-term fiscal and monetary shocks as well long-term damage to economic growth.[59] When pandemics develop, early social measures such as tracing contacts, implementing quarantine and social distancing, and isolating infectious cases can have significant human resources and healthcare costs.[60] As the pandemic grows, hospital capacity decreases very rapidly causing a shortage of available rooms and beds so new facilities may need to be constructed to manage potential infectious cases. In addition, healthcare expenditures in medical supplies, protective equipment and drugs increase, causing more economic hardship.[61] During the COVID-19 crisis, some studies state that healthcare costs could go as high as U$D 654 billion in the United States alone if a majority of the population gets infected, due to hospitalizations, ventilators, and other health resources that patients would require.[62]

Diminished tax revenues may exacerbate fiscal stresses caused by increased expenditures, especially in lower-medium income countries where tax systems are weaker and government fiscal constraints are more severe.[63] However, today even developed countries are expecting a sharp decrease in GDP growth due to the COVID-19 crisis with countries like Canada, France and Germany expected to experience more than 5% annual reduction in GDP growth, and Italy expecting almost 10% growth decline for the value of goods and services produced during 2020.[64] During mild pandemics, developed countries can serve as lenders of last resort to affected countries through direct budgetary support. However, during a severe pandemic where developed countries suffer the same fiscal and monetary stresses, the chances of aiding lower-medium income countries are significantly reduced. This could turn into larger budget shortfalls for undeveloped countries, potentially leading to weakened public health responses or cuts in other government spending.[65,66]

The long-term burden can also be severe. One of the main issues is the loss of earnings from those who have died. An analysis made by Prager, Wei Et Al in 2016 estimated that economic losses from a mild pandemic influenza in the USA could be between U$D 90-220 billion, and of that, 80% would come from the value of expected future lifetime earnings of those who died.[67] McKibben and Sidorenko estimated in 2006 that the economic costs of an influenza pandemic range from U$D 374 billion for a mild pandemic to U$D 7.3 trillion for a severe one.[68] These results align with country-specific estimates: an analysis of pandemic influenza's impact on the United Kingdom in 2009 found that a mild pandemic could reduce GDP by up to 1%, whereas a severe event could reduce GDP by 3-4%.[69] The World Bank's estimates from the 2014 West Africa Ebola epidemic argued that economic disruption in low income countries could be greater.[70] For example, the 2015 economic growth estimate for Liberia was 3%, as compared to a pre-Ebola estimate of 6.8%; for Sierra Leone, it was -2%, as compared to a pre-Ebola estimate of nearly 9%.[71] Nowadays, estimates for Peru's GDP growth pre-COVID-19 were around 3%, as compared to a 0% estimate as of May 2020; for Argentina, GDP growth for 2020 was expected to be -2%, and as of May 2020 it is expected to be close to -7%.[72,73]

The direct costs of dealing with the disease outbreak can be very high. The Ebola outbreak in 2014 seriously deteriorated the economies of the region, with direct costs amounting to U$D 6 billion in Sierra Leone including hospitals, staff and medication. That alone amounted to 3 years of funding for the World Health Organization (WHO) and was over 20 times the cost of WHO's emergency response cuts in its 2014-2015 budget.[74] Negative economic growth shocks are also driven by labor force reductions caused by sickness and mortality and indirectly by fear, which manifests itself through multiple behavioral changes.[75] Fear of contagion can cause many businesses to close their doors, the labor force to reduce its participation, as well as restrictions of entry of citizens from other countries causing a total disruption in trade, travel and commerce.[76] As a matter of fact, on April 2020 in the United States president Donald Trump ordered the suspension of the entire U.S. immigration system to reduce the potential of contagion and prevent cross-border transmission of the virus causing COVID-19.[77] In addition to that, indirect impacts of a pandemic can have effects on the financial system. The financial and corporate sectors can suffer large scale deteriorations through market meltdowns, high levels of unemployment, balance sheet pressure, and potential likelihood of large-scale bankruptcies. During the COVID-19 crisis, rapidly increased risk aversion among investors also led to a sudden stop in capital flows to emerging markets.[78]

Social and Political Impacts

Pandemics can have both positive and negative social and political consequences which include: tensions between countries, states and citizens; population displacements and travel bans; schools and store closures; cancellation of sporting events and music concerts; and an increasing reliability on technologies to better work and communicate.

There have been many cases during past pandemics where existing political tensions, particularly in fragile states with histories of violence and weak institutions, caused an even greater unrest within its citizens. During the 2014 West Africa Ebola epidemic, steps taken by the government to mitigate disease transmission, such as quarantines and military controls, were viewed as suspicious by the public and opposing political leaders which led to riots and violent clashes with security forces.[79] In addition, outbreaks of infectious disease can cause vulnerable social groups (such as ethnic minority populations) and/or competitor countries (such as China for a vast group of countries) to be stigmatized and blamed for the disease and its consequences. During the Black Death, Jewish communities in Europe faced discrimination, including expulsion and communal violence, because of stigma and blame for disease outbreaks.[80] During the COVID-19 crisis, at least six lawsuits have been filed against China in U.S. federal courts seeking damages for deaths, injuries and economic losses. In addition, other countries such as Australia, Germany and Britain are asking China for an inquiry into the origin of the virus.[81,82]

Another social consequence during a pandemic is related to social mobility. While public panic during a disease can cause rapid population migrations, air travel is usually restricted to avoid cross-border transmission. When airplane travel is not cancelled early during a pandemic, many people would try to leave crowded cities and travel to other states or countries to look for safer places to stay. That is what happened in the 1994 outbreak in Surat, India where even though a small number of people got infected, more than 500,000 people, or roughly 20% of the city's population, fled from their homes.[83] Those movements caused elevated health risks due to poor sanitation, poor nutrition, and faulty social distancing measures.[84] However, once the pandemic starts to accelerate and the amount of people infected increases exponentially, it is a safe measure to restrict international and local travel and the use of airplanes to move. This measure can have positive consequences preventing more people from getting infected but has dire economic consequences for the travel and leisure industry in general, as well as disruptions in supply chains. This was the case during the SARS pandemic originated in southern China in 2003 where the closure of airports and cancellation of flights affected many people's travel, livelihood, and family life and also harmed the economy of the affected regions.[85]

School closures, cancellation of public events, and closure of stores are usually considered the first social distancing measures to prevent the transmission of a disease. Timely school closures and cancellation of public gatherings significantly reduced mortality during the influenza epidemic of 1918 in the United States.[86] During the 2009 Swine Influenza Flu pandemic, more than 1,300 public and private schools in 240 communities across the United States were closed.[87] However, school closures also raised ethical and social issues, particularly since families from disadvantaged backgrounds suffered more due to the closures.[88] Closure of non-essential stores, factories and business offices are other measures taken to prevent contagion. During the Asian Influenza diseases of 1997 (H5N1) and 2013 (H7N9) wholesale and retail live poultry markets associated with the zoonotic outbreaks were closed.[89] This caused a disruption of food supply in the cities and the citizenry were not able to find necessary food and household necessities. This also caused a long-lasting change in people's diet. After the influenza was finally controlled, the consumption of poultry products fell by more than 80% on average in the market of Jilin province in China and affected the income of many farm workers.[90]

One of the positive developments caused by the COVID-19 crisis is the use of technology to allow people to continue with their jobs and to better support governments to deploy effective measures to contain the outbreak. With lockdowns and other social distancing measures in effect in many countries, governments and private companies have designed new apps to facilitate services such as delivering food and other essential items to people in need by optimizing the entire supply chain via digital government services.[91] Technology and internet allowed governments to include information and guidance about COVID-19 related issues in their portals. According to the United Nations, a review of the national portals of the 193 United Nations Member States showed that by March 25th, 2020, 57% (110 countries) had posted some kind of information on COVID-19. But by April 8th, 2020, around 86% (167 countries) updated their portals.[92] In addition, people have started to work from their homes thanks to the advancements of internet capacity and have also started to use mobile apps to communicate and have meetings, shaping the way they interact.[93]

Pandemics Throughout History

Throughout history, disease outbreaks have threatened humanity, sometimes changing the course of history and, at times, signaling the end of entire civilizations. There is no doubt that nothing has killed more human beings than infectious diseases.[94] Below is a list of the 20 worst epidemics and pandemics, dating from the 1st century to modern times.

Name	Time Period	Geographic Extent	Type/Pre-human Host	Death Toll
Antonine Plague	165-180	Eurasia	Believed to be either smallpox or measles	5M
Japanese smallpox epidemic	735-737	Japan	Variola major virus	1M
Plague of Justinian	541-542	Eurasia / North Africa	Yersinia pestis bacteria / Rats, fleas	30-50M
Black Death	1347-1351	Eurasia / North Africa	Yersinia pestis bacteria / Rats, fleas	200M
New World Smallpox Outbreak	1520 – onwards	Global	Variola major virus	56M
Great Plague of London	1665	Italy	Yersinia pestis bacteria / Rats, fleas	100,000
Italian plague	1629-1631	England	Yersinia pestis bacteria / Rats, fleas	1M
Cholera Pandemics 1-6	1817-1923	Global	V. cholerae bacteria	1M+
Third Plague	1885	Global	Yersinia pestis bacteria / Rats, fleas	12M (China and India)
Yellow Fever	Late 1800s	Africa / Americas	Virus / Mosquitoes	100,000-150,000 (U.S.)
Russian Flu	1889-1890	Global	Believed to be H2N2 (avian origin)	1M
Spanish Flu	1918-1919	Global	H1N1 virus / Pigs	40-50M
Asian Flu	1957-1958	Global	H2N2 virus	1.1M
Hong Kong Flu	1968-1970	Global	H3N2 virus	1M
HIV/AIDS	1981-present	Global	Virus / Chimpanzees	25-35M
Swine Flu	2009-2010	Global	H1N1 virus / Pigs	200,000
SARS	2002-2003	4 Continents, 37 Countries	Coronavirus / Bats, Civets	770
Ebola	2014-2016	10 Countries	Ebolavirus / Wild animals	11,000
MERS	2015-Present	22 Countries	Coronavirus / Bats, camels	850
COVID-19	2019-Present	Global	Coronavirus – Unknown	444.9K*

* Johns Hopkins University estimate as of 8:33am PT, June 17, 2020)

Source: Visual Capitalist[95] and NCBI[96]

Most of these pandemics and epidemics have been spread over different periods of time and do not follow a certain pattern as to when they develop. However, it is clear that huge population growth (especially since the 1900s)[97], together with urbanizations and rising global connections, have caused the number of pandemics and epidemics to be more frequent during the last decades.[98]

The Black Death (Death Toll: 200M)

The following is a description of the five most deadly pandemics of all times including the Black Death, the New World Smallpox outbreak, Spanish Flu of 1918, Plague of Justinian and HIV/AIDS; and the four most recent outbreaks which include SARS, Swine Flu, Ebola and MERS.

The Black Death was an outbreak of bubonic plague that occurred from 1347 to 1351 and ravaged Europe, Africa, and Asia, with an estimated death toll between 75 and 200 million people. It is believed the pandemic originated in Asia and most likely jumped to other continents via the fleas living on the rats. The transmission was possible because infected rats lived aboard merchant ships and they were transported to different cities by those ships. Ports being major urban centers at the time, were the perfect breeding ground for the rats and fleas, and thus the bacteria flourished, devastating three continents in its wake.[99] The practice of quarantine began during this pandemic, in an effort to protect coastal cities from this disease. The origin of the word quarantine from the Italian "quaranta giorni", or 40 days, was first used by cautious port authorities which required ships arriving in Venice from infected ports to sit at anchor for 40 days before landing.[100]

New World Smallpox Outbreak (Death Toll: 56M)

In the Old World, the most common form of smallpox killed perhaps 30% of its victims while blinding and disfiguring many others. However, the effects caused in the Americas were unprecedented, which had no exposure to the virus prior to the arrival of Spanish and Portuguese conquistadors.[101] After Columbus arrived at the Americas in 1492, epidemics soon became a common consequence of contact. Tearing through the Incas populations, outbreaks of smallpox made the empire unstable and ripe for conquest. It also devastated the Aztecs, killing, among others, the second most important of their rulers.[102] Historians believe that smallpox and other European diseases reduced the indigenous population of North and South America by up to 90%, a death toll greater than any war ever fought by those empires.[103] That facilitated the hegemony of European countries in the Americas.[104]

Spanish Flu of 1918 (Death Toll: 40-50M)

The Spanish Flu occurred between 1918 and 1919 and is considered the deadliest outbreak of influenza of the last century. The disease spread across the globe, infecting over a third of the world's population and ending the lives of 40-50 million people. The flu's spread and lethality was enhanced by the cramped conditions of soldiers and insufficient wartime nutrition that many people were experiencing during World War I. Despite the name Spanish Flu, the disease likely did not start in Spain. Spain was a neutral nation during the war and did not enforce strict censorship of its press, which could therefore freely publish early accounts of the illness. As a result, people falsely believed the illness was specific to Spain, and the name Spanish Flu stuck.[105]

Of the 500 million people infected in the 1918 pandemic, the mortality rate was estimated at 10% to 20%, with up to 25 million deaths in the first 25 weeks alone. What separated the 1918 flu pandemic from other influenza outbreaks was the victims. Past influenzas usually killed juveniles and the elderly or already weakened patients, however, the new flu stroke down completely healthy young adults, while leaving children and those with weaker immune systems alive.[106]

Plague of Justinian (Death Toll: 30-50M)

The Plague of Justinian was an outbreak of the bubonic plague during 541 and 542 that afflicted the Byzantine Empire and Mediterranean port cities, killing between 30-50 million people.[107] The plague is named after the Byzantine Emperor Justinian who reigned from A.D. 527 until 565. When the Byzantine Empire was impacted by the bubonic plague, it marked the start of its decline and outbreaks reoccurred periodically afterward.[108] Some estimates suggest that up to 10% of the world's population died. It is regarded as the first recorded incident of the bubonic plague, and ended up devastating the city of Constantinople, where at its height it was killing an estimated 5,000 people per day and eventually resulting in the deaths of 40% of the city's population.[109]

HIV/AIDS (Death Toll: 25-35M)

First identified in the Democratic Republic of Congo in 1976, HIV/AIDS has killed between 25-35 million people since 1981. Currently there are between 31 and 35 million people living with the disease, with the vast majority of those in Sub-Saharan Africa where 5% of the population is infected, or roughly 21 million people. For decades, the disease had no known cure, but medication developed since the 1990s now make HIV far more manageable, and many of those infected go on to lead productive lives. Between 2005 and 2012 the annual global deaths from HIV/AIDS dropped from 2.2 million to 1.6 million.[110]

SARS (Death Toll: 770)

Severe Acute Respiratory Syndrome (SARS) is a viral disease caused by a coronavirus (SARS-CoV) that infected humans for the first time in the Guangdong province of southern China in 2002. It is believed that the virus came from an animal reservoir and was perhaps transmitted by bats, that then spread the disease to other animals like civet cats.[111] The epidemic affected 37 countries and spread through 4 continents, killing a little less than 800 people.[112]

According to the World Health Organization, there are currently no areas of the world reporting transmission of SARS. Since the end of the global epidemic in July 2003, SARS has reappeared four times, of which three were laboratory accidents (Singapore and Chinese Taipei), and the other one in southern China where the source of infection remains undetermined although there is circumstantial evidence of zoonotic transmission.[113]

Swine Flu (Death Toll: 200,000)

The 2009 swine flu pandemic was caused by a new strain of H1N1 that originated in Mexico in the spring of 2009 before spreading to the rest of the world. In one year, the virus infected as many as 1.4 billion people across the globe and killed around 200,000 people, according to the CDC.[114] Before COVID-19, this was the world's most recent pandemic, infecting as much as 21% of the world's population. Swine flu was the first of several different flu strains that had never been collectively seen together.[115]

The pandemic primarily affected children and young adults, and 80% of the deaths were in people younger than 65.[116] This was unusual since most strains of flu viruses, including those that cause seasonal flu, have the highest impact in people ages 65 and older. But in the case of the swine flu, older people seemed to have already built up enough immunity to the group of viruses that H1N1 belongs to, so weren't affected as much. A vaccine for the H1N1 virus that caused the swine flu is now included in the annual flu vaccine.[117]

Ebola (Death Toll: 11,000)

Ebola ravaged West Africa between 2014 and 2016, with 28,600 reported cases and approximately 11,000 deaths. The first known cases of Ebola occurred in Sudan and the Democratic Republic of Congo in 1976, and the virus may have originated in bats. However, the first case reported during the 2014-2016 outbreak was in Guinea in December 2013. People became infected by Ebola through direct contact with an infected animal such as a bat or a nonhuman primate, or through a sick or infected dead person.[118] The disease then spread to Liberia and Sierra Leone, and the majority of the cases and deaths occurred in those three countries. A smaller number of cases occurred in Nigeria, Mali, Senegal, the United States and Europe, the Centers for Disease Control and Prevention reported. There is no cure for Ebola, although efforts at finding a vaccine are ongoing.

MERS (Death Toll: 850)

Middle East Respiratory Syndrome (MERS) is an illness caused by a coronavirus called MERS-CoV. Most MERS patients developed severe respiratory illness with symptoms of fever, cough and shortness of breath. About 3-4 out of every 10 patients reported with MERS have died. Health officials first reported the disease in Saudi Arabia in September 2012, but after some investigation they later concluded that the first known cases of MERS occurred in Jordan in April 2012. So far, all cases of MERS have been linked through travel to, or residence in, countries in and near the Arabian Peninsula. The largest known outbreak of MERS outside the Arabian Peninsula occurred in the Republic of Korea in 2015 and was associated with a traveler returning from the Arabian Peninsula.[119] The epidemic killed approximately 850 people and caused a US$2 billion loss in the Republic of Korea, triggering US$14 billion in government stimulus spending.[120,121]

Solutions to Pandemics

Pandemics are a huge concern to all countries around the world, and international, national, and subnational institutions, as well as multiple organizations with functional responsibility for specific tasks have studied past pandemics to develop steps to prevent its occurrence and mitigate its outcomes.[122,123] Pandemic preparedness and solutions can be classified depending on the timing with respect to its occurrence: the prepandemic period, the outburst period, and the spread period, as shown in the table below.

Prepandemic Period	Outburst Period	Spread Period
Stockpile Building	Initial Outreak Detection	Global Pandemic Declaration + Risk Communications
Continuity Planning	Pathogen Characterization or Library Confirmation	Contact Tracing, Quarantine, Isolation
Public Health Worforce Training	Risk Communicaton and Community Engagement	Social Distancing
Simulation Excercises	Animal Disease Control	Stockpile Deployment
Risk Transfer Mechanism Set-up	Contact Tracing, Quarantine, Isolation	Vaccines
Situational Awareness	Testing	Therapies
	Situational Awareness	Testing
		Situational Awareness

Source: NCBI[124]

Whereas some interventions fall under more than one period, the paper pays close attention to two main categories of solutions which are treatments and testing. Within the treatments category, the paper will analyze the vaccines and therapies market. Pandemics

Vaccines

Vaccines are the most powerful and cost-effective way to protect a population, and its development has the potential to transform health by almost eliminating the burden of infectious diseases among people.[125] According to the Centers for Disease Control and Prevention (CDC), vaccination of children born between 1994 and 2018 has saved the U.S. nearly U$D 406 billion in direct medical costs and U$D 1.88 trillion in total society costs.[126] In addition, the World Health Organization (WHO) states that immunization awareness and government initiatives help in preventing 2-3 million deaths annually.[127]

According to a study done in 2006, vaccines could cost around $800 million dollars to develop.[128] However, the costs to produce them can change dramatically due to the different variables involved. More recently in 2018, The Washington Post reported that vaccine costs could range from U$D 521 million to U$D 2.1 billion depending on the manufacturer and vaccine.[129] In terms of market outlook, investments coupled with merging and partnerships of companies are boosting the production and sales of vaccines all over the world and the global vaccine market is projected to exceed U$D 77.5 billion by 2024, at a CAGR of 10.3% according to a report by Grand View Research, Inc.[130]

Due to the current vaccine research, development and production timelines, a quick response to create a new vaccine for a novel pathogen is hard to achieve. Most influenza vaccines are produced through vaccine platforms that rely on animal trials and can take several months to be produced.[131] Additionally, vaccines that are in development usually take decades until they are safe to use.[132] For example, Ebola vaccines were in development for more than a decade, with the first vaccine approved for clinical use only in 2015.[133] On April 2020, government officials commented that the vaccine for COVID-19 could take 12-18 months to be produced, the fastest scientists have ever created a new vaccine for mass distribution.[134]

Types of Vaccines

Vaccines can be divided into four main types, which are live attenuated, inactivated or whole killed, subunit/conjugate/recombinant and toxoid vaccines. In addition to those, there are also two relatively new vaccine designs called DNA and RNA vaccines.

Live attenuated vaccines contain whole bacteria or viruses which have been "weakened" so that they create a protective immune response but do not cause disease in healthy people. Live vaccines tend to create a strong and lasting immune response and are some of the best vaccines; however, live vaccines are not suitable for people whose immune system does not work, either due to drug treatment or underlying illness. This is because the weakened viruses or bacteria can multiply too much and might cause disease in these people.[135] According to Fortune Business Insight, live attenuated vaccines occupy the third position in terms of market share as compared to other vaccine types. This segment is expected to witness a low growth rate when compared to other vaccine categories from 2020-2026.[136] The usual drivers behind live attenuated vaccines are awareness of vaccines, rise in government funds for vaccination programs, prevalence of livestock diseases, improvements in healthcare infrastructure, presence of veterinarians in rural areas, and efforts for prevention of infectious diseases.[137]

Inactivated or whole killed vaccines contain whole bacteria or viruses which have been killed, or small parts of bacteria or viruses, such as proteins or sugars, which cannot cause disease. Because inactivated vaccines do not contain any live bacteria or viruses, they cannot cause the diseases against which they protect, even in people with severely weakened immune systems. However, inactivated vaccines do not always create such a strong or long-lasting immune response as live vaccines do and they usually require repeated doses and/or booster doses. From a market share perspective, this segment shows the second position in the vaccines market due to the surge in demand for influenza and hepatitis A & B vaccines during recent years.[138] In addition, according to Fortune Business Insight, inactivated vaccines demand will continue to increase due to the prevalence of seasonal influenza in emerging countries as well as the competitive advantage of being safer and more stable than live attenuated vaccines.[139]

Both subunit and conjugate vaccines contain only pieces of the pathogens they protect against. Subunit vaccines use only part of a target pathogen to provoke a response from the immune system. This is done by generating antigens from isolated specific proteins of a pathogen. Recombinant vaccines are similar to subunit vaccines but are created via genetic engineering. A gene coding for a vaccine protein is inserted into another virus, or into producer cells in culture. When the carrier virus reproduces, or when the producer cell metabolizes, the vaccine protein is also created. This way the immune system recognizes the expressed protein and provides future protection against the target virus. Conjugate vaccines are somewhat similar to recombinant vaccines since they are made using a combination of two different components. Conjugate vaccines, however, are made using pieces from the coats of bacteria. These coats are chemically linked to a carrier protein, and the combination is used as a vaccine. Typically, the piece of bacteria would not generate a strong immune response on its own, while the carrier protein would. So conjugate vaccines are used to create a more powerful, combined immune response. The piece of bacteria cannot cause illness, but combined with a carrier protein, it can generate immunity against future infection.[140] The recombinant, conjugate and subunit vaccines occupy the first position in terms of market share according to Fortune Business Insight, and are anticipated to have the highest CAGR from 2020-2026 as compared to other vaccine types due to the efficacy of immune response, their long-term protection, simplified large scale manufacturing and the lack of pathogenicity risk.

Immunizations created using inactivated toxins are called toxoids. Toxoids can actually be considered killed or inactivated vaccines but are sometimes given their own category to highlight the fact that they contain an inactivated toxin, and not an inactivated form of bacteria. Some bacterial diseases are not directly caused by a bacterium itself, but by a toxin produced by the bacterium. Immunizations for this type of pathogen can be made by inactivating the toxin that causes disease symptoms. As with organisms or viruses used in killed or inactivated vaccines, this can be done via treatment with a chemical such as formalin, or by using heat or other methods.[141]

Two relatively new vaccine types that were introduced decades ago but have been widely used in infectious and malignant diseases are DNA and RNA vaccines. The COVID-19 pandemic has caused many companies to start researching and developing these two types of vaccines which created excitement in the scientific world. The reason why is because if any of those two methods succeed, it will be much faster to get a vaccine ready to produce it and distribute it around the world. Many companies and scientist claim that these are the vaccines of the future, which has provided the base for biotech companies to start producing RNA and DNA vaccines as the ideal technologies for rapidly fighting new pathogens such as the novel coronavirus causing COVID-19.[142]

Nucleic acid vaccination is a technique for protecting against disease by injection with genetically engineered DNA (as a plasmid) or RNA (as mRNA). In contrast to recombinant bacteria or virus vaccines, nucleic acid vaccines consist only of DNA or RNA, which is uptake by cells and transformed into protein. In other words, rather than injecting a pathogen's antigen into the patient's body, vaccines instead give the body the genetic code needed to produce that antigen itself. Unlike viruses, naked nucleic acids lack the help of essential proteins, lipids, and sugars, which are important to viral infection. One way to enter cells is that cells spontaneously take up nucleic acids. For example, it has been shown that myocytes can take up DNA, transcribe and translate to produce proteins. Another way is to increase uptake by adding cationic lipids that bind to DNA. Scientists also tried to use the "gene gun" to physically blast DNA into cells. However, the most commonly used administration method for nucleic acid vaccines is still needle injection into skin or muscle. After entering the cell, nucleic acid vaccines employ the host's transcriptional and translational machinery to produce the desired gene product. This resulting product can then be recognized by the immune system.[143,144]

Among the advantages, DNA and RNA vaccines are relatively inexpensive and easy to manufacture and use. In contrast to recombinant bacteria or viruses, the composition is simple enough and has immunological benefits. Nucleic acid vaccines consist only of DNA or RNA, which is taken up and translated into protein by host cells. Their immunogenicity and efficacy have been analyzed in a large number of systems, and the results of preclinical studies have supported human clinical trials.

Among the main disadvantages, DNA vaccination in humans is tempered by the fact that naked nucleic acid is relatively inefficient, particularly in larger animals. Thus, various strategies are being developed to improve immune responses induced by nucleic acid vaccines. The main players involved in those changes are biotech companies that are focusing on mRNA vaccines that translate the static genes of DNA into more dynamic proteins.[145]

Route of Administration

Regarding the route of administration, the vaccines market is segmented into parenteral and oral.

Parenteral route is any route that is not enteral (oral, rectal and sublingual).[146] Even though the elimination of needles in the vaccination process is currently underway, vaccines administered via parenteral route have experienced a bigger demand and higher sales across the globe contributing to larger revenue streams during recent years. This is due to the fact that oral vaccines still have complications in their development and they are not as effective as parenteral vaccines. According to Fortune Business Insight, higher procurement volume by governmental organizations will be one of the main drivers of revenue growth from 2020-2026.[147]

The oral vaccines segment is predicted to witness a comparatively slower growth rate due to complications related to their development. Oral delivery is challenging because it requires formulations to overcome the harsh gastrointestinal environment and avoid tolerance induction to achieve effective protection. This is the current pharmaceutical challenge for all the companies attempting to launch oral vaccines into the market.[148] However, development of vaccines administered orally might become preferable to traditional injection-based vaccines for reasons such as improved safety and compliance, and easier manufacturing and administration.[149]

Type of Disease

On the basis of disease indication, the global market can be segmented into viral and bacterial diseases. Viral diseases include hepatitis, influenza, human papillomavirus (HPV), measles/mumps/rubella (MMR), rotavirus, herpes zoster, and others; bacterial diseases include meningococcal disease, pneumococcal disease, diphtheria/tetanus/pertussis (DTP), among others.

Bacterial diseases segment holds the dominant position in the vaccine market revenue owing to higher sales of pneumococcal, meningitis and DTP vaccines across the globe. These vaccines are the first-line immunization for a newborn as well as booster doses for pediatrics. However, even though the revenue share is smaller, the viral diseases segment is forecasted to have the highest CAGR from 2020-2026 due to the upcoming launch of viral vaccines and an increase in demand for sales of HPV vaccines and influenza vaccines, according to Fortune Business Insight.[150]

Age Group

Based on the age group, vaccines can be created for children (pediatric) or for adults. Pediatric vaccines hold the highest market share in terms of value. The potential size of the pediatric vaccines market is mainly dependent on worldwide growing birth cohort and increasing pediatric vaccination doses. Adult vaccines, however, are anticipated to register a high CAGR from 2020-2026 due to a rise in research and development, and a strong pipeline of new vaccines.[151]

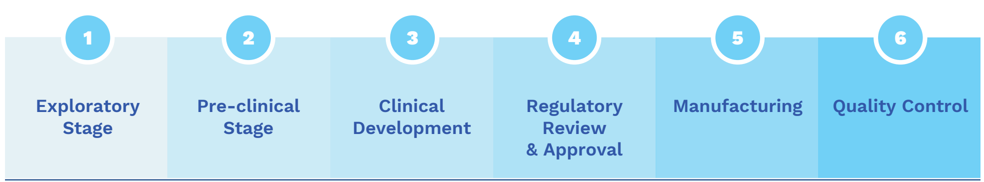
Timeline

Vaccine development is a long and complex process, often lasting between 10-15 years, and which involves a combination of both public and private investments. In general, vaccines are more thoroughly tested than non-vaccine drugs because the number of human clinical trials is usually greater. In addition, post-licensure monitoring of vaccines is closely examined by the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA).[152]

Vaccines take long to develop because they need to be safe for human use and effective at fighting the disease. Safety means that they should not have major side effects when applied to human beings; efficacy means they need to be able to protect humans from getting sick. Although 100% efficacy should be the aim of every vaccine, most of the vaccines in the market have lower efficacy and still do their job at protecting individuals. For example, the annual flu vaccine is around 45% effective.[153]

To test for safety and efficacy and eventually get manufactured, every vaccine goes through several stages, which are:

General Stages Of The Development Cycle Of New Vaccines



Source: CDC[154]

Within the clinical development stage, there are three important phases of trials. During phase one, or the safety trial, a small group of healthy volunteers gets the vaccine candidate and different dosages are tried to check for the immune response. In phase two, the clinical study is expanded and the vaccine is given to people who have characteristics, such as age and physical health, similar to those for whom the new vaccine is intended. During this phase, hundreds of people get the vaccine. Finally, in phase three, the vaccine is given to thousands of people and tested if the vaccine reduces the number of people that get sick.[155,156] After the vaccine passes all three trial phases, it gets submitted to the WHO and various government agencies for approval.

As mentioned before, the COVID-19 pandemic has caused researchers worldwide to work incessantly to find the vaccine against the virus causing the pandemic. Even though vaccines usually take a decade or so to be developed, the fastest a vaccine for a new disease was ever developed took 5 years.[157] Nowadays, experts estimate that a fast-tracked vaccine development process could speed a successful candidate to market in approximately 12-18 months, as long as the process goes smoothly from conception to market availability.[158]

How Soon Will A Vaccine be Ready?

Source: NEJM as cited in GatesNotes[159]

In the traditional process, the steps are sequential to address key questions and unknowns. This can help mitigate financial risk, since creating a new vaccine is expensive. Considering many candidates fail, companies usually wait to invest in the next step until they know the previous step was successful.

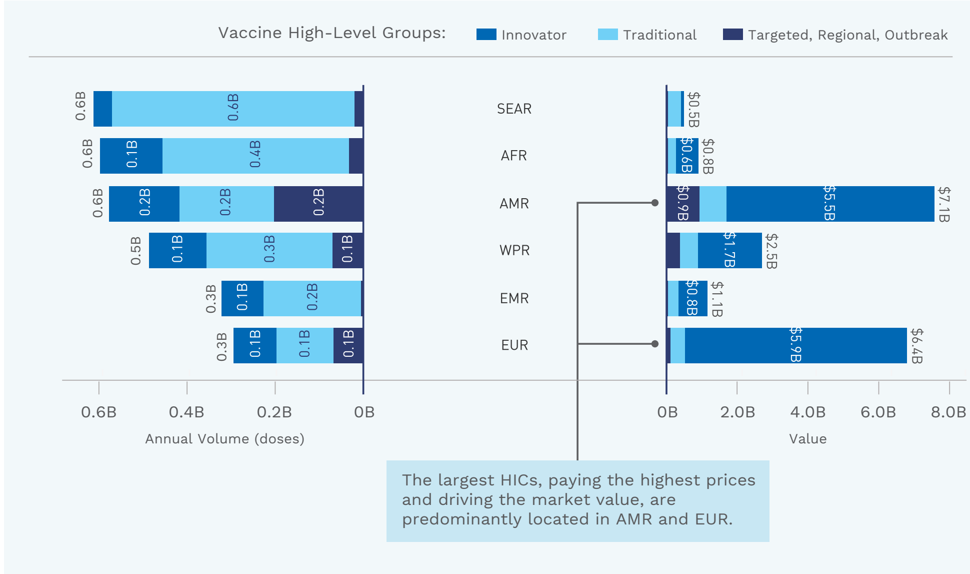
For COVID-19, financing development is not an issue since the urgency to get the cure is extremely high. Governments and other organizations such as the Coalition for Epidemic Preparedness Innovations (CEPI) have committed to find a vaccine as soon as possible. That way, scientists are able to save time by doing several of the development steps at once.

Market Outlook

The global vaccine market size valuation is expected to exceed U$D 77.5 billion by 2024, at a CAGR of 10.3% according to Grand View Research, Inc.[160] The majority of this growth is expected to come from key players that focus on vaccine development to gain an edge over competitors. Furthermore, governments are expected to stimulate the market growth by working to promote the awareness of vaccination benefits through immunization programs with the objective of containing the propagation of communicable diseases that are associated with high morbidity and mortality.[161]

Geographically, North America accounted for the largest share of the vaccines market during the last years, followed by Europe. Factors such as high prevalence of infectious diseases and increasing investments by government and non-government organizations for vaccine development have been driving the vaccines market in North America.

Global market volume and value by region (2017)

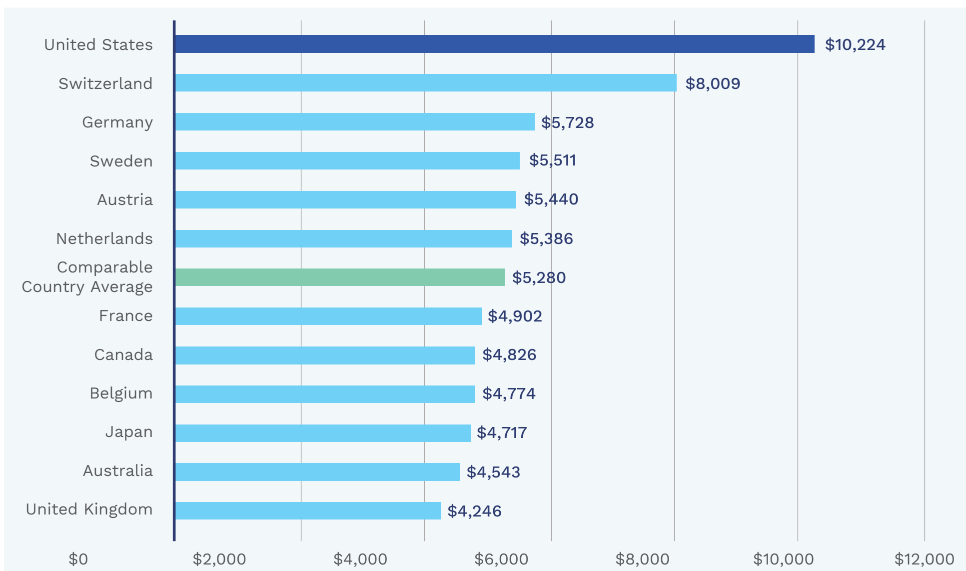


Source: WHO[162]

The analysis of the global market volume and value by region in 2017 shows the annual volume of doses and the total value in U.S. dollars of the vaccine market. Vaccines are grouped as traditional, innovator (new vaccines), and targeted, regional and outbreak. The analysis shows that traditional vaccines drove global market volume while innovator vaccines drove global market value for 2017.[163]

Comparing health spending in the U.S. to other countries is complicated, as each country has unique political, economic, and social attributes that contribute to its spending. However, wealthy countries like the U.S. tend to spend more per person on health care and related expenses than lower income countries. Health spending per person in the U.S. was $10,224 in 2017, which was 28% higher than Switzerland, the next highest per capita spender.[164]

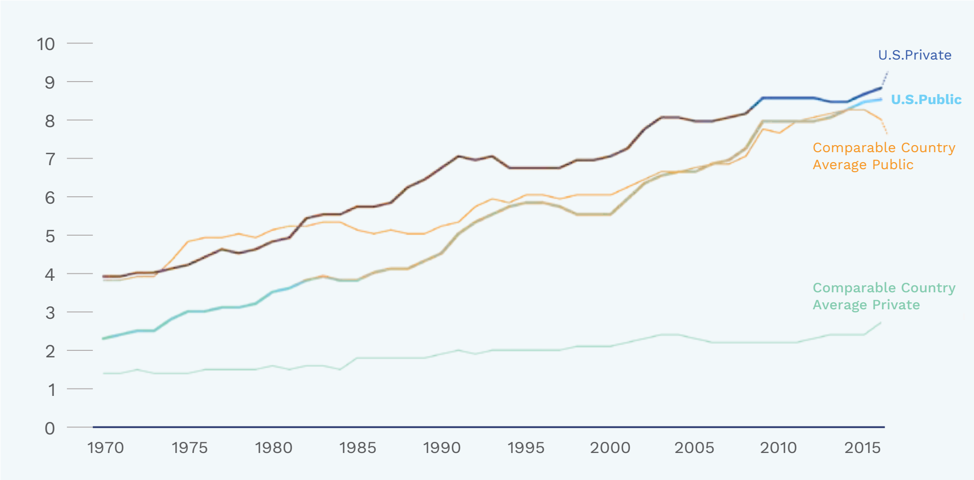
Health consumption expenditures per capita, U.S. dollars, PPP adjusted, 2017



Source: OECD as cited in Health System Tracker[165]

While the U.S. has much higher total spending as a share of its economy, its public expenditures alone are in line with other countries. In 2016, the U.S. spent about 8.5% of its GDP on health out of public funds which is essentially equivalent to the average of other comparable countries. However, private spending in the U.S. has been much higher than any comparable country with 8.8% of GDP in the U.S., as compared to 2.7% on average for other nations during the same period.[166]

Total health expenditures as % of GDP, 1970 - 2016



Source: OECD as cited in Health System Tracker[167]

Over the last three decades, the U.S. has seen increased spending by both the public and private sectors. Comparable countries increased private sector spending from 1.4% to 2.7% of GDP from 1970 to 2016, while the U.S. increased private sector spending from 3.9% to 8.8% during the same period.

Research and Development

Research and vaccine development are supported by many different players within the healthcare industry. The World Health Organization's Global Action Plan for Influenza Vaccines is a plan that aims to increase the capacity to produce vaccines for global influenza pandemics, quicken the production of vaccines, and research a universal influenza vaccine.[168]

In addition, the public-private Coalition for Epidemic Preparedness Innovations (CEPI) is building a bank of potential vaccines for viral diseases, such as SARS and MERS, that are not currently of commercial interest. CEPI's goal is to focus on the development or licensure and manufacturing of high-potential viral vaccines through early-stage human trials and to purchase small stockpiles to mitigate the next pandemic.[169]

Moreover, many private companies focus on eradicating complex diseases through vaccination by having strong product portfolios and the capability of strategic decisions. These companies specialize in the continued development of vaccines and vaccine doses for viral as well as bacterial diseases.[170]

Therapies

During pandemics, different therapies and patient care measures can be adopted to help decrease the likelihood of severe outcomes such as hospitalizations and deaths. Therapies can range from nonspecific, supportive care to disease-specific drugs. Maintaining supportive care during an epidemic or pandemic can improve mortality rates by alleviating the symptoms of disease.[171] Even if the availability of drugs or vaccines is scarce or does not exist, efforts to engage communities with added medical supplies and trained clinicians can help decrease mortality rate moderately as more patients feel more comfortable receiving clinical care.[172] Medical supplies that may be needed for supportive care during a pandemic include hospital beds, disinfectants, ICU supplies (such as ventilators), and personal protective equipment.[173] Medical interventions for pandemic influenza include antiviral drugs and antibiotics to treat bacterial infections. Antivirals can reduce mortality in as little as 48 hours when given after symptoms start developing.[174]

Considering the COVID-19 crisis, several companies have approved products on the market that could potentially mitigate the effects of the virus. Some are trying to develop new therapies that can kill the virus causing COVID-19, while others have been using experimental drugs that have been included in testing for other viruses.[175] One potential therapy that does not fit the normal definition of a drug involves collecting blood from patients who have recovered from COVID-19, making sure it is not harmful, and giving the plasma to people who are sick. A variant of this approach is to take the plasma and concentrate it into a compound called hyperimmune globulin, which is much easier and faster to give a patient than unconcentrated plasma.[176]

Another type of potential therapy against COVID-19 involves identifying the antibodies produced by the human immune system that are most effective against the novel coronavirus. Once those antibodies have been found, they can be manufactured and used as a treatment or as a way to prevent the disease. Antivirals are also being tested against COVID-19, with some drug candidates being authorized by the FDA for emergency use.[177] Immunosuppressive drugs and anti-parasite, such as hydroxychloroquine, are other classes of drugs that works by changing how the human body reacts to the novel coronavirus. It is believed though that these drugs can be most helpful for late-stage serious disease.[178]

Testing

When dealing with pandemics, there are different ways people can get tested that depend on the type of pathogen that is causing the disease as well as the method to detect it. Using the COVID-19 pandemic as an example, the two ways people can get tested to check if they currently have or had the disease are through diagnostic tests and serology tests. The main difference between them is that diagnostic tests can check for the presence of viral genetic material, while serology tests are blood tests that are designed to detect antibodies produced in response to the coronavirus.[179]

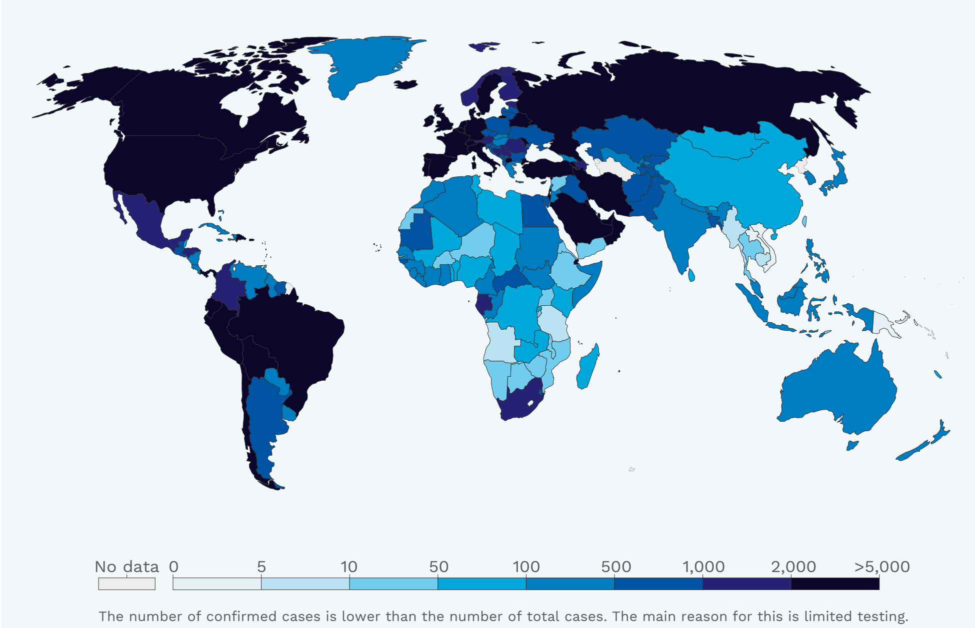
The most pressing immediate need against the COVID-19 pandemic is the availability of diagnostic tests to be able to test as many people as possible and determine if they are infected. Companies, as well as public organizations, have been developing such tests, with several receiving emergency use authorization from the FDA to market them.[180] The diagnostic test is done by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab.[181] rRT-PCR is a laboratory technique of molecular biology that is used to detect the presence and quantity of viral genetic material in case of a positive result.[182] There are two types of PCR machines: high-volume batch processing machines and low-volume machines. The high-volume machines provide most of the capacity and testing, while the low volume machines are better when getting a result in less than an hour is needed.[183]

Another type of diagnostic test that is being developed is called Rapid Diagnostic Test (RDT). This is similar to an in-home pregnancy test where people swab their noses the same way as for the PCR test, but instead of sending it into a processing center, they would put it in a liquid container and then pour that liquid onto a strip of paper that would change color if it detects the virus.[184] Finally, chest CT imaging may also be helpful for diagnosis in individuals where there is a high suspicion of infection based on symptoms and risk factors but it is not the most recommended testing method.

Analysis of the COVID-19 Crisis

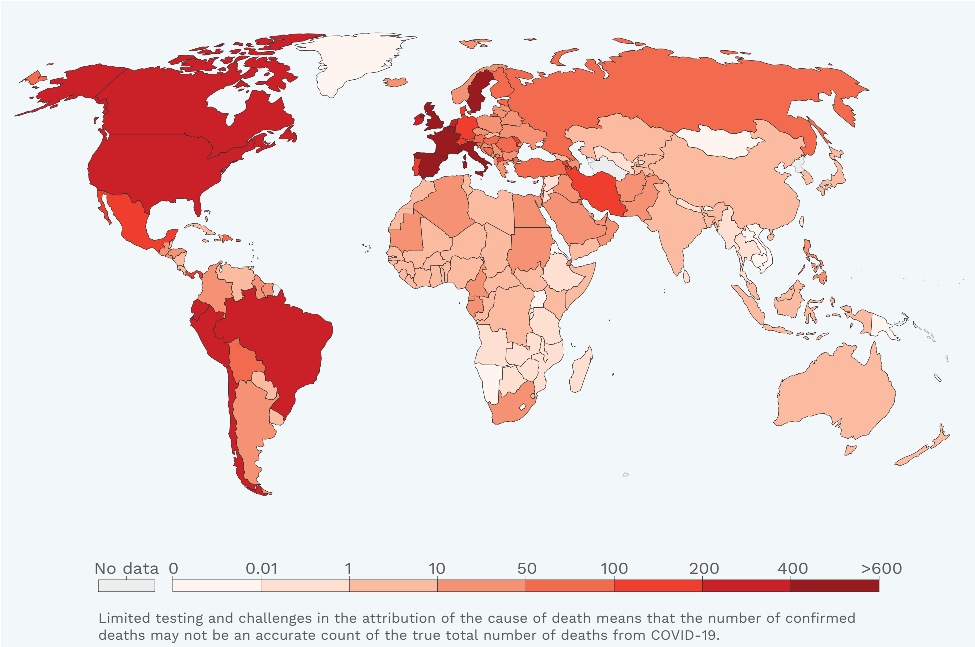
The latest threat to global health is the outbreak named as Coronavirus Disease 2019, or simply COVID-19. COVID-19 was first recognized in December 2019 in the city of Wuhan, China and was rapidly discovered to be caused by a novel coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is structurally similar to the virus that caused SARS.[185] As in two preceding instances of emergence of coronavirus disease in the past 18 years (SARS in 2002 and 2003, and MERS since 2012) the COVID-19 outbreak has posed critical health, economic and social challenges for communities around the world.[186] As of May 11th, 2020, more than 4.14 million cases have been reported across 187 countries and territories, resulting in more than 284,000 deaths. More than 1.42 million people have recovered.

Total confirmed COVID-19 cases per million people, Jun 22, 2020



Source: European CDC as cited in Our World in Data[187]

Total confirmed COVID-19 deaths per million people, Jun 22, 2020



Source: European CDC as cited in Our World in Data[188]

The World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC) on January 30th, 2020 and a pandemic on March 11th, 2020.[189,190] Local transmission of the disease occurred in most countries across all six WHO regions and spread rapidly around the world.[191] However, the burden was asymmetrically distributed because countries were affected by the pandemic at different stages.

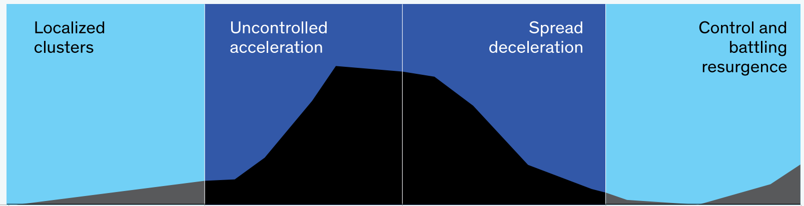
According to the CDC, the way the virus spreads is primarily during close contact between people, usually via small droplets produced by coughing, sneezing and talking.[192,193] Less commonly, people may become infected by touching a contaminated surface and then touching their face.[194] Since infected people can show symptoms or be asymptomatic, it is hard to know when the disease can be more contagious. It is understood, however, that it is most contagious during the first three days after patients start showing signs of having the disease, although the disease may be spread before symptoms appear.[195] The standard method that has been used so far to diagnose the disease is by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab.[196]

Common symptoms of the disease include fever, cough, muscle pain, shortness of breath, and loss of smell and taste.[197] While the majority of cases result in mild symptoms, some progress to acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, and blood clots.[198,199] The time from exposure to development of symptoms is typically around five days but may range from two to fourteen days.[200] Recommended measures to prevent infection include frequent hand washing, maintaining physical distance from others (especially from those with symptoms), social distancing, quarantine, covering coughs, and keeping unwashed hands away from the face.[201] In addition, the use of a face covering is recommended for those who suspect they have the virus.[202]

COVID-19 has motivated many governments, organizations and individual companies to think how they believe the disease can progress. As mentioned previously, these models are based on past pandemics and depend on information that is released daily about COVID-19. The following is an example from McKinsey & Company that shows their opinion about the disease progression and its different phases. Even though this might not be the actual disease progression, it is just an example of how these different entities, both public and private, analyze the consequences that COVID-19 can potentially have.[203]

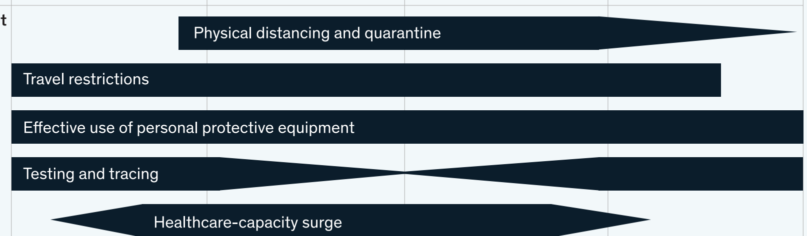
Disease Progression by Phase and Response

Countries will base decisions about which measures to implement on local situations and the progression of the disease.



	Localized clusters	Uncontrolled acceleration	Spread deceleration	Control and battling resurgence
Indicators Transmission	Majority of cases can be linked to known chains of transmission (ie, cases can be managed individually)	Majority of cases involve an unknown source of infection and infection rate is accelerating	Number of new cases has peaked, and infection rate is decreasing	Limited number of new cases, and systems are in place to control spread of infection (eg, track and manage individual cases)
Magnitude	Handful of new cases per day	Significant number of new cases per day	Significant number of new cases per day	Handful of new cases per day, with no significant spikes
Growth	Percentage growth may be high, but absolute number of cases remains within the capacity of public-health systems	Exponential-to-fast linear growth in the number of new cases	Decline in the number of new cases over time (with potential day-to-day variation)	Cases flat or trending down over time
Likely interventions	• Detect and trace all cases without losing control of chains of transmission (contain acceleration)	• Apply distancing measures • Expand healthcare capacity • Build testing capacity	• Maintain distancing measures; prepare to release when feasible • Prepare systems for individual case management	• Detect and trace all cases, without losing control of chains of transmission while restarting activity

Predominant measures



Source: McKinsey & Company[204]

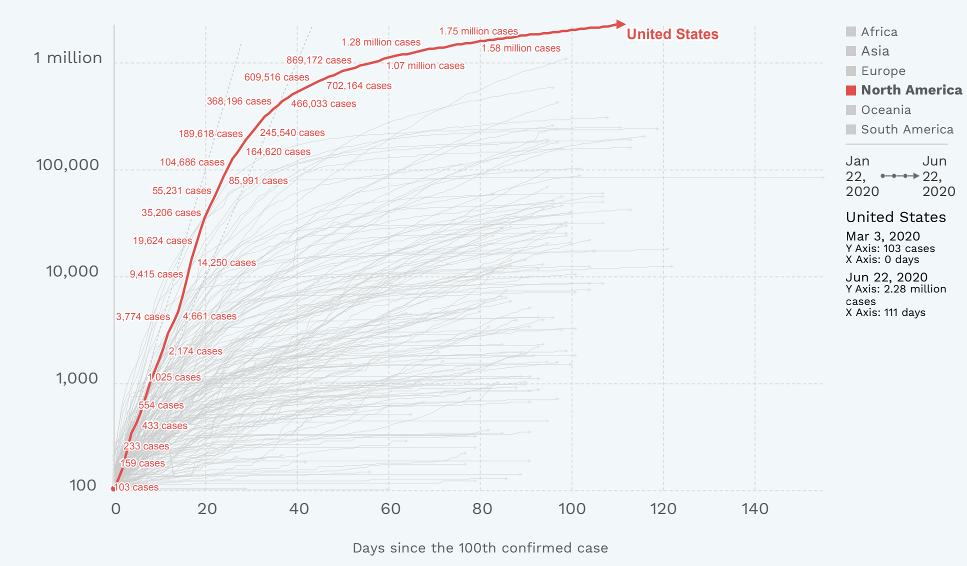
As shown in the chart, it is important to track several indicators such as transmission, magnitude and growth of new cases to develop a reasonable strategy to normalize restrictions and reopen economies. During these phases, governments have to ensure that their citizens are following the right preventive measures and taking as many precautions as possible.

The following is an analysis of the health, economic, and social consequences that COVID-19 has caused in the United States specifically.

Health Impacts

An analysis of the health consequences that the COVID-19 crisis has caused in the United States as of May 11th, 2020, shows that a total of 1.3 million cases have been confirmed, resulting in approximately 81,000 deaths according to John Hopkins University.[205]

Total confirmed COVID-19 cases: How rapidly are they increasing?



The number of confirmed COVID-19 cases is lower than the number of total cases. The main reason for this is limited testing.

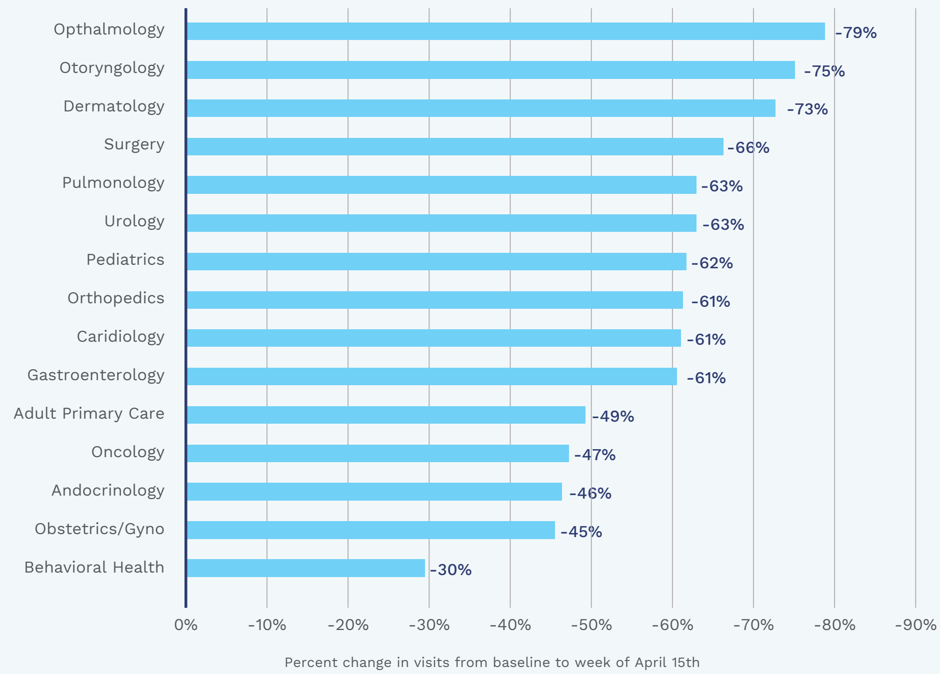
Source: European CDC as cited in Our World in Data[206]

According to Our World in Data, the infection fatality rate, which is the proportion of deaths from a certain disease to the total number of cases diagnosed for a certain time period, cannot be accurately calculated.[207] This happens because numbers vary by region and over time and are influenced by the volume of testing, healthcare system quality, treatment options, time since the initial outbreak, and population characteristics such as age, sex, and overall health.[208] However, according to a researcher from the University of Washington in Seattle, the infection fatality rate in the United States is close to 1.3% as of March 12th, 2020.[209] The 1.3% rate calculation is based on cumulative deaths and detected cases across the United States, but it does not account for undetected cases, where a person is infected but shows few or no symptoms.[210]

In addition, among the indirect health costs caused by the crisis, hospitals nationwide have canceled elective surgeries, visits to primary care doctors and specialists have dropped off precipitously, and millions of people have lost their employer-sponsored health insurance.[211] According to Ellen Nolte, professor of health services and systems research at the London School of Hygiene and Tropical Medicine, one of the key concerns that hospitals and practitioners will have is the increase in backlog of people that need to be treated.[212] Visits to primary care doctors and other outpatient specialists dropped off steeply during the COVID-19 pandemic in the United States. The decline in visits was generally larger among surgical and procedural specialties and milder among specialties such as adult primary care, obstetrics, gynecology, oncology, and behavioral health.[213]

Visits to primary care doctors and other outpatient specialists

The decline in visits was generally larger among surgical and procedural specialties and smaller in other specialties such as adult primary care, obstetrics/gynecology, oncology, and behavioral health.



Relative decline in visits between week of April 5 (last full week of data) and baseline week of March 1. Data only for specialties shown. Decline shown is reflective of all visit types, so increase in telemedicine visits dampen the overall decline. Visits from nurse practitioners and physician assistants are not included.

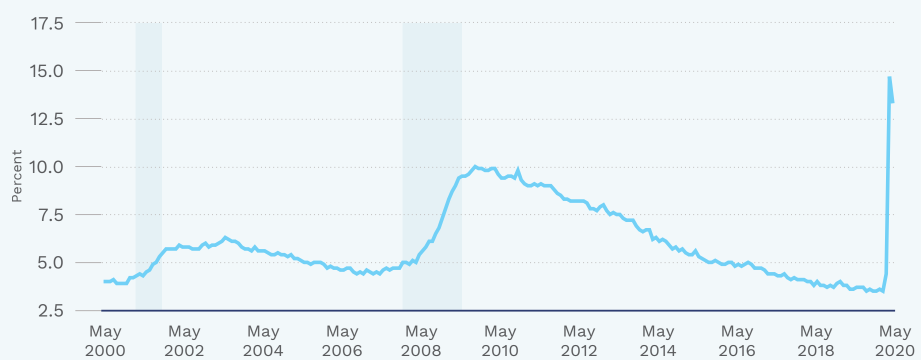
Source: Vox[214]

What this data might suggest is that the backlog in patient treatment could lead to less timely medical care for Americans in the future, which would in turn lead to more adverse health outcomes. The main solutions to stop and reverse the health impacts caused by the virus will be the development of treatments such as vaccines and therapies; continued testing and contact tracing.[215]

Economic Impacts

The economic impacts of the pandemic have so far been unprecedented in the United States. The mandatory quarantines and lockdowns to prevent the spread of the virus have caused many businesses to partially or completely shut down, creating a stampede of unemployment applications never seen before. As of May 12th, 2020, the U.S. economy lost 20.5 million jobs due to the pandemic, pushing the unemployment rate to 14.7% according to data by the U.S. Bureau of Labor Statistics.[216]

Civilian Unemployment Rate, Seasonally Adjusted

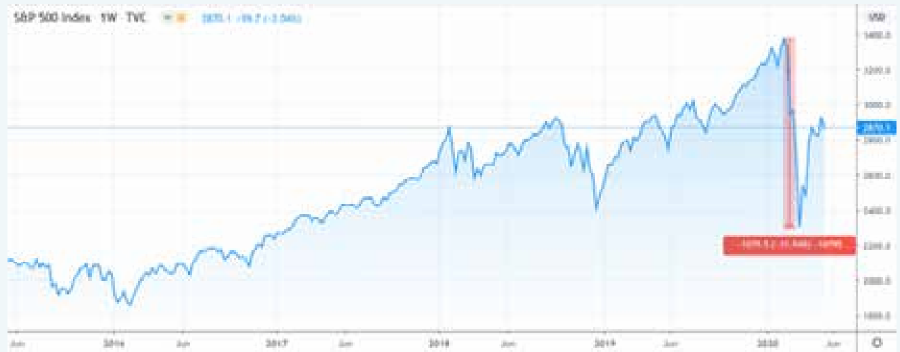


Note: Shaded area represents recession, as determined by the National Bureau of Economic Research.

Source: U.S. Department of Labor[217]

In addition to the unemployment rate numbers, the stock market experienced a shock and sunk more than 30% from its peaks of February 2020. This was caused by investors' fear of the future impacts of the COVID-19 crisis.[218]

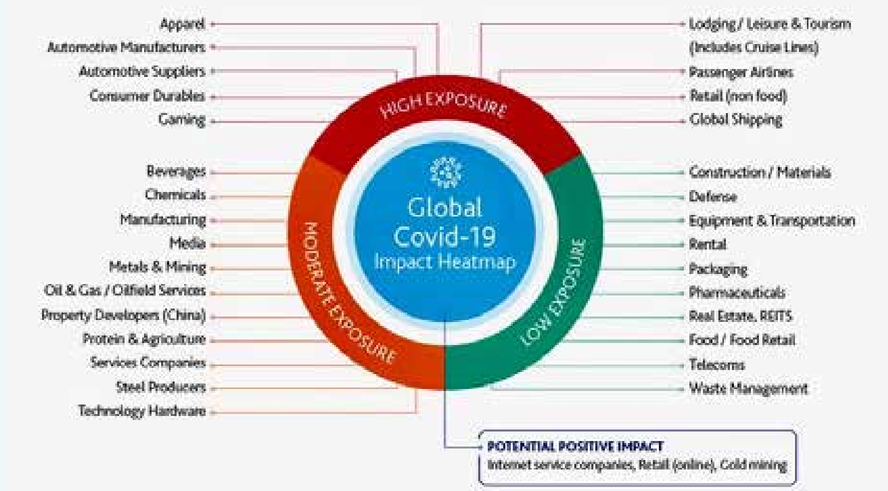
S&P 500 Index



Source: Trading View[219]

The consequences of the pandemic are still being analyzed and it will take time to fully understand the impact to the whole economy. However, what economists and financial analysts are already seeing is a direct impact on production, a disruption of the supply chain, a decrease in consumer demand and financial impacts on company's balance sheets, especially in sectors such as airlines, cruises, hotels, restaurants, entertainment and automotive manufacturers.[220,221]

Heat map shows industries hit hardest and least by the coronavirus crisis.

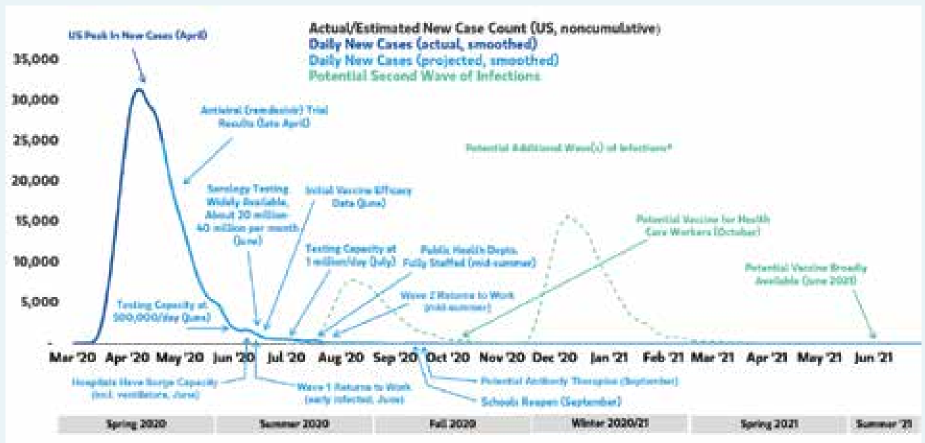


Source: Business Insider[222]

Even though the economic and financial impacts have been unprecedented, the responses from both the Federal Reserve Bank and the U.S. government were also never seen before in terms of magnitude and speed. The U.S. Congress passed a massive stimulus bill that provided for hundreds of billions of dollars in new spending, expanding unemployment insurance and providing a cash handout to low and middle-income Americans. The legislation also provided loans for businesses, targeted at firms with fewer than 500 employees.[223] The Federal Reserve also lowered interest rates as a response to a possible economic slowdown.[224] These measures were taken to ease the pain from having to close businesses and to give people extra income.[225]

According to Morgan Stanley research analysts, three critical criteria must be met prior to resuming activity and letting workers get back to their jobs.[226] The first is peak in mortality; the second is expanded health infrastructure; and the third is testing, both for active infection to find hot spots before they turn into new outbreaks and also for testing blood to understand the outbreak. They also emphasize that people should prepare for reduced levels of activity until there is a vaccine and should expect social distancing to be reenacted as hot spots develop over the next one to two years.[227]

A Projected Timeline and Milestones for a Return to Work in the U.S.



* Timing and size of additional waves are illustrative as they are hard to predict. We would expect the earliest a second wave to occur is four to six weeks after a reopening.

Source: Morgan Stanley Research[228]

The above graph is a projected timeline developed by Morgan Stanley research analysts that estimates the lapse of time until activity in the U.S is resumed. This is another example of analyses made by companies to understand how the pandemic can evolve and develop and how the economy will suffer and recover from it. As shown, they expect further waves of new cases and a potential vaccine coming into market.

Social Impacts

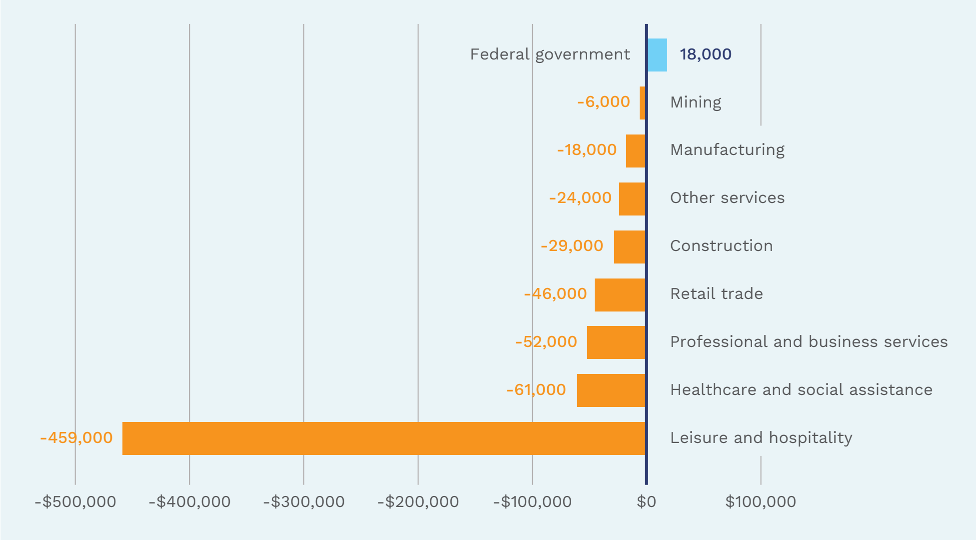
In a response to prevent the spread of the virus, the U.S. government has been adopting different social measures which affect all segments of the population. According to the UN Department of Economic and Social Affairs (UN DESA), the outbreak had a bigger impact on people living in poverty situations, older persons, persons with disabilities and youth.[229] Early evidence has been indicating that the health and economic impacts of the virus were being borne disproportionately by poor people.[230] For example, homeless people, because they may be unable to safely shelter in place, have been highly exposed to the danger of the virus. People without access to running water, refugees, migrants, or displaced persons also suffered disproportionately both from the pandemic and its possible consequences whether due to limited movement, fewer employment opportunities, increased xenophobia, among others.[231]

Measures such as border shutdowns, travel restrictions and quarantines has led many people to become immobilized. The travel industry saw unprecedented waves of cancellations and a significant drop in demand due to strict governmental instructions which has resulted in many travelers being unable to fly back to their homes.[232] Schools were also shut down to prevent further spread of the virus. Even though that decision helped reduce close contact between people, many professionals complained that both students and teachers were not prepared for remote learning and they were not given the resources they needed in order to transition from a classroom setting to online.[233] In addition, other possible impacts related to school closures include lack of free school meals provided to children from low-income families, social isolation, dropout rates with students less likely to return once closures are ended, and increase in childcare costs for families with younger children.[234] If not properly addressed through policy, the aftermaths of the pandemic may also increase inequality, exclusion and discrimination.[235]

The food sector has seen a huge demand due to panic-buying and stock piling of food products. This has led to increased concerns about shortages of certain food products.[236] As a response, the U.S. government has made efforts to provide certain social groups with essential products and free meals to collect and take home.[237] These populations include vulnerable individuals such as the elderly who have no support network, homeless people and school children of low-income families. In addition, the government has also reduced restrictions on delivery hours for retailers in order to allow stores to restock with basic food products.[238] Despite the help from the government, stores have also made drastic changes by restricting the amount of each product that people can buy, and setting special shopping hours for the elderly, vulnerable populations and disabled people.[239]

Independent supermarkets have also been affected by the high demand on food products. Measures implemented by these local stores include free delivery of food products to customers to avoid panic-buying, putting restrictions on the number of customers allowed in at any given time to avoid overcrowding, providing masks and gloves to their employees, installing plexiglass at register areas, and expanding the number of suppliers to whom they buy their products from.[240] Although supermarkets have seen a huge demand on food products, other stores such as restaurants and cafes have been forced to close or to limit their business to takeout and delivery.[241] As a result, many of these food stores have had to close and many of their employees have lost their jobs. Evidence shows that the U.S. restaurants and bars sector (under Leisure & Hospitality) accounted for 60%, or 419,000, of the jobs cut during March 2020.[242]

US job loss by sector, March 2020



Source: Quartz[243]

Future of Pandemics

In recent decades, several trends have affected pandemic probability, preparedness, and mitigation capacity. Different factors such as population growth, increasing urbanization, greater demand for animal protein, greater travel and connectivity between population centers, habitat loss, climate change, and increased interactions between humans and animals have all affected the likelihood of pandemic events. These factors increased either the probability of an outburst event or the potential spread of pathogens.[244] With global population estimated to reach 9.7 billion by 2050 and with travel and trade steadily intensifying, public health systems will have less time to detect and contain a pandemic before it spreads.[245]

For countries with weak institutions and high levels of poverty, building institutional capacity for complex tasks like pandemic mitigation and response is likely to be a slow process.[246] Many of these countries affected by extreme poverty are in areas with high outburst risk, particularly in Central and West Africa, and thus may remain vulnerable and require significant international assistance during a pandemic.[247]

Other environmental and population trends that could increase the severity of pandemics include the persistence of slums, unresponsive health systems, higher prevalence of comorbidities, weaker sanitation, and aging populations.[248,249] The increasing threat posed by antibiotic resistance could also amplify mortality during pandemics of bacterial diseases, such as tuberculosis and cholera, and also viral diseases, such as influenza, in which a significant proportion of deaths is often the result of bacterial pneumonia coinfections.[250,251]

Conclusions

Pandemics continue to be a tremendous threat to human populations, worldwide. Humans have learned from past pandemics what the social, economic and political consequences can be, and a deep analysis into the COVID-19 crisis has helped reinforce those conclusions. These consequences triggered a plethora of innovations and investments by companies and governments around the world. Healthcare improvements and supportive medical care have had the most impact in combating different diseases, with vaccines, therapies and testing being at the forefront of those developments.[252]

Although protective measures and treatments exist to combat the various diseases, containment of outbreaks is not guaranteed. With the mutation of viruses and bacteria, along with their growing resistance to antiviral and antibiotic remedies, outbreaks, epidemics, and pandemics will continue to be a major issue for humans in the years and decades that lie ahead demanding urgent innovation, investment and preparation by companies and governments around the world.[253]

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