CHAPTER

21

Life after COVID-19: Future directions?

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Introduction

The present-day pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel *Betacoronavirus*, originating from Hubei Province in the People's Republic of China, has spread to 213 countries and territories around the world. This virus is a member of the Coronaviridae family, it is a highly virulent pathogenic viral infection having an incubation period between 2 and 12 days, transmitted by inhaling infected droplets or physical contact with disease-ridden droplets. On December 31, 2019, the World Health Organization (WHO) China Country Office was informed of cases of pneumonia of unknown etiology identified in Wuhan City, Hubei Province of China.[1] The virus moved from animals to humans at the Huanan Seafood Wholesale Market in Wuhan, China. The 2019 coronavirus at the whole-genome level is 96% identical to a bat coronavirus.[2] Between December 31, 2019 and January 3, 2020, a total of 44 patients with pneumonia of unknown etiology have been reported by the Chinese authorities to WHO. The Chinese isolated the virus on January 7, 2020 as a new type coronavirus, the novel SARS-CoV-2, and later shared the genetic sequence with the world so as to develop specific diagnostic kit.[3] The first fatality was noted on January 11, 2020. The Chinese New Year enhanced the spread to other provinces in China and neighboring countries like Thailand, Japan, Singapore, Vietnam, and South Korea rapidly due to movement in and out of Wuhan. WHO announced "coronavirus disease 2019 (COVID-19)" as the new name for this novel disease on February 11, 2020. During a press briefing on March 11, 2020, as the virus spread across the globe, WHO categorized COVID-19 to be a pandemic. The number of SARS-CoV-2 remaining asymptomatic has yet to be defined. Among symptomatic patients, the clinical presentation consists of fever, sore throat, anosmia, ageusia, cough, nasal congestion, fatigue, diarrhea, and features of upper respiratory tract infections.[4] In the event of serious disease, the manifestation includes severe chest discomfort with breathlessness and acute respiratory distress syndrome (ARDS). The necessity for intensive care unit admission is indicated to treat ARDS, shock, acute kidney injury, and multiple organ failure. The WHO acknowledged that in the event of mild infection, patients usually recover in about 2 weeks, with generally no complications. However, in severe or critical cases,

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patients may take 3–6 weeks to recover and may have significant morbidity and even mortality. All ages are susceptible to pick up the infection, and health-care workers (HCW) are at a higher risk. The person-to-person transmission of the COVID-19 is estimated by the reproduction number (R_0). The WHO has estimated R_0 to be between 1.4 and 2.5,[5] whereas others have estimated R_0 to be between 2.0 and 3.3.[6] The basic case reproduction rate is probably between 2 and 6.47.[5] The treatment is largely symptomatic and supportive; when patients get hypoxic, oxygen is provided with either nasal prongs, face or venturi mask, or non-rebreathing masks. In patients who are more hypoxic, the high-flow nasal cannula or noninvasive ventilation may be used, and in the critical patients, elective invasive ventilation is indicated. Drugs with antiviral properties such as ribavirin, lopinavir-ritonavir, favipiravir, ivermectin, nitazoxanide combination of azithromycin, and hydroxychloroquine have not yielded very satisfactory results. Remdesivir a broad-spectrum antiviral agent used against Ebola has shown benefits in the treatment of COVID-19.[7] Various immunomodulators such as IL-6 inhibitor (e.g., tocilizumab, sarilumab) have been used when inflammatory markers (e.g., D-dimer, ferritin) and pro-inflammatory cytokines such as interleukin IL-6 are elevated in severe COVID-19.[8] The belief is that by using these immunomodulators, disease progression may be prevented. The use of low-dose dexamethasone in a large trial in the United Kingdom reduced deaths by 35% in ventilated patients.[9] Convalescent plasma may be of benefit if given in the early phase of the mild-to-moderate form of the disease, but this form of therapy currently remains unclear.[10]

Earlier pandemics

Three of the deadliest pandemics as recorded in history were caused by a bacterium, *Yersinia pestis*, leading to a fatal infection otherwise known as the plague. The Plague of Justinian arrived in Constantinople, the capital of the Byzantine Empire (541–549 CE). It was carried over by ships across the Mediterranean Sea from Egypt by grain and plague-ridden fleas on black rats. The plague annihilated Constantinople and spread all across Europe, Asia, North Africa, and the Arab killing approximately 30–50 million people, nearly half of the world's population. The plague really never left, and when it came back about 800 years later, it caused devastation. When Europe was hit in 1347 by the Black Death, more than 200 million lives were claimed in just 4 years. The etiology was later discovered by Alexandre Yersin from the Institut Pasteur, while investigating the plague epidemic in the year 1894 in Hong Kong.[11] The cholera pandemics occurred all through the 19th century, a minimum of six widespread outbreaks of cholera was documented but may have been much more. It started in India in the Bay of Bengal region and was responsible for tens of thousands of deaths. The Influenza virus was also responsible for large fatalities in various pandemics. The first significant flu pandemic the Russian Flu of 1889 started in Siberia spread to Moscow, from there it spread to the rest of Europe. In the subsequent year, it moved to North America and Africa, over 360,000 died. The Spanish flu of 1918 is likely the worst pandemic of the 20th century, the

1918 flu infected up to one-third of the global population and killed up to 50 million people. At that time, the causative agent was unknown, but the cause was later detected in 1930. Reviewing historical publications indicated the presence of bacterial coinfections which perhaps contributed to the high mortality during that era. On February 1957, a new avian influenza A (H2N2) virus emerged in East Asia, sparking a pandemic the so-called "Asian Flu." A second wave followed in early 1958, causing an approximate 1.1 million deaths globally. The smallpox caused devastation in the 20th century leading to between 300 million and 500 million deaths. The WHO reported till as recent as 1967 that about 15 million people become infected with the disease and that nearly 2 million died that year. The Plague of Athens that occurred in 430 BCE, and the Antonine Plague, which spread to the Roman Empire in 165–180 CE, may have been caused by smallpox. Human immunodeficiency virus (HIV) pandemic was identified in 1981,[12] acquired immunodeficiency syndrome (AIDS) was first observed in American gay communities but is believed to have developed from a chimpanzee virus from West Africa. This disease which spreads through body fluids has affected over 38 million cases of HIV worldwide. Of this, 24 million people are undergoing antiretroviral therapy. About 32 million people have died due to AIDS since the onset of the disease. The first influenza pandemic of the 21st century occurred in 2009–2010 and was caused by an influenza A (H1N1) virus. It was likely that 1,51,700–5,75,400 cardiovascular and respiratory deaths was connected with 2009 influenza A H1N1 pandemic in the first year of the illness in every country in the world. The 21st century saw four epidemics of concern: SARS-CoV, Ebola, Middle East respiratory syndrome (MERS), and Zika. Of these, two SARS and MERS are related to the current pandemic as both these diseases are caused due to coronaviruses. SARS-CoV or SARS-CoV-1 was first identified in 2003, SARS-CoV-1 is believed to have possibly started from bats, spread to cats, and then to humans in China, followed by spreading to 26 other countries, infecting 8096 people, with 774 deaths.[13] MERS or camel flu can be a fatal respiratory illness caused by a betacoronavirus (MERS-CoV). Most cases of MERS have occurred in Saudi Arabia and the United Arab Emirates but has spread to Asia, Europe, and America. Both these diseases have clinical presentations similar to COVID-19. SARS-CoV-2 like SARS-CoV-1 acts on the same human cell receptor, the angiotensin-converting enzyme 2 (ACE-2), while MERS-CoV uses dipeptidyl peptidase-4 to enter into the host cells. The R_0 of COVID-19 is estimated by WHO to range between 2 and 2.5, which is higher than that for SARS-CoV-1 (1.7–1.9) and MERS (<1), clearly indicating that SARS-CoV-2 has a higher potential of pandemic as opposed to SARS-CoV-1 and MERS. The fatality rate of COVID-19 infection is projected to be 2.3%, which is lower than SARS-CoV-1 (9.5%) and clearly much lower than MERS (34.4%).[14] An important experience learnt from the coronaviruses is the high frequency of HCW being affected by infected patients more so during aerosol-generating procedures (AGP), such as sneezing, coughing, cardiopulmonary resuscitation, intubation, and tracheostomy. In Toronto, 13% of HCW involved in intubations acquired SARS during SARS-CoV-1.[15] In the same pandemic in Singapore, 40% of HCW developed nosocomial SARS-CoV-1 and 6% of HCW's died.[16]

Lessons learnt from previous pandemics

In the 1850s, the cities like London, New York, and Paris rebuilt their sewage systems following a century-long global cholera pandemic that killed over 1.5 million people which piloted in a modern urban public health that spread across the world. In 1900 following a typhoid epidemic in the city of Chicago, the city engineers reversed the flow of the river in Chicago, as a result terminating the adulteration of Lake Michigan, which was the principal source of drinking water for the city.

Nonpharmaceutical interventions

During the Spanish Flu, numerous nonpharmaceutical approaches were commissioned to limit the spread of virus and to treat patients. Some of these measures are important and applicable in current and future outbreaks, epidemics, and even pandemics.

Quarantine

The exercise of implementing quarantine, began in the 14th century to safeguard coastal towns from plague epidemics. The dockyards in Venice required ships to set anchor for 40 days before being allowed to dock. This was termed quarantine and was derived from two Italian words "*quaranta giorni*" which stands for 40 days. The concept of quarantine may have preceded the Black Death, as the practice of isolating the sick, dates back to earlier times, and is referred to in the Bible with respect to segregating people with leprosy. Australia enacted maritime quarantine both in the first and initial part of second wave. This initial quarantine safeguarded Australia from the second wave of the pandemic till December 1918, this was when quarantine was infringed.[17] Air travel has revolutionized global travel as opposed to earlier maritime transport in the last century. This is in fact why there is rapid spread across international borders in the influenza pandemics in 1957, 1968, and 2009.[18] However, in 2009, airport authorities used modern techniques to screen passengers arriving from potential areas of the outbreak. This method of screening on arrival of international passengers is not likely to prevent the spread of airborne or droplet infections.

Large gatherings

In most cities during the 1918 pandemic, simple nonpharmaceutical methods were implemented to prevent person-to-person spread of the flu. This would involve closing down auditoriums, places of worship, schools, funerals, processions, weddings, and large gatherings so as to prevent crowds and build the concept of social distancing.[19] In Hong Kong during the 2009 influenza pandemic, a 25% reduction transmission of the flu was noted after schools were closed for a month.[20]

Lockdown

The efficacy of a lockdown to counter the pandemic of COVID-19 has mixed views, the political argument seems to have negative impact by tanking the national economy. The skeptics would question a compromise between protecting a society's health or damage the economy. Countries like Taiwan controlled the outbreak without imposing a lockdown, whereas China implemented a strict lockdown and was able to contain the spread of the virus. Sweden on the other hand did not implement a lockdown but put into action a reverse quarantine by protecting the elderly and highly susceptible individuals with comorbidities, The United States of America implemented a lockdown in areas with high contagion but lifted it very early. The United Kingdom like Sweden opted for the concept of herd immunity but quickly implemented lockdown as numbers started to soar. India like many other Asian countries implemented a preemptive lockdown when the numbers of COVID-19 was low; however, after nearly 40 days of lockdown under severe economic crisis, the government reluctantly lifted the lockdown prematurely and continued regional lockdown based on district-wise resurgence of the contagion. In a cross-country analysis, of lockdown measures more so with the European model, its effectiveness begins in about 3 weeks after implementing the lockdown and number of COVID-19 infections keeps on reducing for as much as 20 days.

Hygiene

Handwashing with soap and water has been advocated from time immemorial and has been documented in studies by Ignaz Semmelweis in Vienna in the mid-1800s to reduce infections. Frequent handwashing has been known to limit the spread of the influenza virus during the 1918 pandemic, this was primarily due to influenza viruses being transmitted because of hand-to-face contact. In influenza pandemics, comparing the frequency of handwashing with laboratory-confirmed influenza found a significant protective effect while analyzing the available data.[21] Handwashing with antibacterial solutions did not extend any benefit over soap and water. In Hong Kong during the SARS-CoV-1 outbreak in a case–control study, handwashing over ten times in a day and disinfecting fomites in a multivariate analysis was shown to be protective.[22] The concepts of respiratory hygiene and cough etiquette involve using source control measures to prevent patients with respiratory infections from transmitting their infections to others. Persons with respiratory symptoms should cover nose and mouth with a disposable tissue while coughing or sneezing followed by hand hygiene. Alternatively, cover the nose and mouth with one's elbow during the process of sneezing and coughing. People with respiratory symptoms should maintain a distance of over 3 ft from other people and should be encouraged to wear a mask.

Face masks

Before the year 1910, the usage of face protection was infrequent during any surgical procedure in hospitals. The use of surgical mask in operating rooms in the United States and Germany started around the 1920s. In the year 1940s, both washable and sterilizable masks came into vogue. In the mid-1960s, disposable masks were introduced across the globe. A surgical mask also known as a medical mask, it is essentially a loosely fitting disposable mask that protects the individual's mouth and nose from splashes, sprays, and droplets that may include microorganisms. A surgical mask may protect others in the vicinity by diminishing the spread of respiratory secretions of the person wearing the mask. A N95 mask offers more protection than a surgical mask does as it can filter out both large and small particles. The N95 mask must meet standards set by National Institute for Occupational Safety and Health, implying it needs to filter at least 95% of the particles. Some of the N95 masks have valves, this makes breathing easier. All healthcare workers (HCW) should be trained to conduct a fit test so as to ascertain a proper seal before using an N95 respirator in an infected zone. All surgical masks and N95 masks are proposed to be disposable. However, as there may be a short supply during a pandemic, some of these masks may be reused after subjecting them to sterilization. The free flight phase 2 respirators of the European Union and KN95 respirators of China are considered equivalent to N95 respirators. The evidence if N95 respirators are more effective than medical masks in preventing viral respiratory infection in HCW, is uncertain but has been shown to be protective under laboratory conditions. Some studies and systemic reviews have asserted its efficacy, while some have not.[23–25] The P100 mask protects people from particles 0.3 μm or larger and filters out all odors, making it undetectable to the human nose. A N95 mask keeps out at least 95% of particles but isn't oil resistant, and a P100 mask is oil proof while protecting the wearer from at least 99.8% of particles. P100 or high-efficiency particulate air (HEPA) filters are considered much safer than the N95 masks. While surgical and N95 masks may be in short supply and should be set aside for HCW's, cloth masks are easier to get, can be washed, and reused. This may be used by citizens in countries where wearing masks is mandatory.

Powered air purifying respirators

The powered air purifying respirators (PAPRs) have a battery that uses a blower to drive air through filter cartridges or canisters under pressure to a hood or face piece or a helmet, providing a higher assigned protection factor. The high positive pressure inside the facepiece reduces leakage in, from the external contaminated air. PAPRs have a higher protection more so during intubation and tracheostomy. They filter 99.97% of 0.3 μm sized particle and is oil proof.[26]

Personal protective equipment

The recommended personal protective equipment (PPE) for HCW caring for critically ill COVID-19 patients includes fluid-resistant gown or a hazmat suit, two pairs of long gloves, eye protection goggles, which should include side shields. Face shields can offer both eye protection and will prevent infectivity of both face and mask. Disposable shoe covers may be needed before putting on the leggings of

PPE or even the hazmat suit. Shoes should be waterproof and be capable of being disinfected. All HCW should wear scrub suits under the PPE. The PPE should be so designed for easy removal so as to avoid any blemish during removal. Hand hygiene should be carried out both during and after removing the PPE. The process of donning and doffing of PPE should be done in a stepwise fashion and ideally under the supervision of a colleague to avoid errors.

Air handling units with negative pressure

An isolation facility aims to control the airflow in the room so that the number of airborne infectious particles is reduced to a level that there is no cross infection to other people within a health-care facility. Heating, ventilation, and air-conditioning system maintain good air quality within the intensive care unit. This is an important nonpharmacological strategy to prevent nosocomial infections. WHO suggests in COVID-19 patients to be isolated in an adequately ventilated negative pressure rooms with a minimum of 12 air changes per hour, specially if AGP is intended.[27] If the air is recirculated, then the incoming air should be filtered. High-efficiency filters like HEPA filters improve the efficiency but are very expensive to maintain. HEPA filters are 99.97% efficient for removing particles with a size of $\geq 0.3\,\mu m$ in diameter.

Most of these nonpharmaceutical interventions are lessons learnt from previous outbreaks and are pearls of wisdom acquired across generations. The more recent interventions improvised during recent pandemics help in limiting and suppressing an ongoing contagion.

Sequela from COVID-19

Survivors from the current pandemic may have specific organ dysfunction following infection, leading to long-term morbidity and mortality. During the SARS-CoV-1 epidemic, observational studies demonstrated that some survivors developed pulmonary fibrosis, restrictive lung anomalies, associated with impaired effort tolerance, and poor quality of life. The computed tomography scan images showed pulmonary fibrosis with air trapping and the evidence of bronchiectasis.[28] Since there are several parallels linking SARS-CoV-2 and SARS-CoV-1 infections, it is possible that lung fibrosis may be seen as long-term outcome in COVID-19 pneumonia. Pulmonary fibrotic disease has been observed in COVID-19, following pneumonia and severe ARDS. On autopsy of fatal cases, COVID-19 have demonstrated pulmonary fibrosis with evidence of severe fibrotic organizing pneumonia.[29] There is thus justification for using antifibrotic therapy and is being currently investigated.[29] During the SARS-CoV-1 epidemic, cardiac manifestations were hypotension, arrhythmias, myocarditis, and sudden cardiac arrests. MERS too was coupled with heart failure and myocarditis. COVID-19 infection may have similar cardiac signs may also be due to a direct cardiac infection by SARS-CoV-2. ACE-2 is bound to the membrane of the cell in the lungs, immune, and cardiovascular systems. ACE-2 has been identified as a functional receptor for coronaviruses. The SARS-CoV-2 infection is initiated by the spike protein of the virus attaching to ACE2, which then more so in the heart and lungs manifest its clinical presentation.[30] During the SARS-CoV-1 epidemic often ended up having hyperlipidemia, cardiovascular disease or diabetes mellitus on long-term follow-up.[31] As the coronaviruses are similar, patients recovering from COVID-19 too need to be followed up for these conditions. In COVID-19, liver injury may be due to the direct invasion of the virus into the liver cells or due to drug-induced liver injury and or from the cytokine storm or even due to severe hypoxic injury.[32] However, long-term manifestations will need to be monitored. In the central nervous system, altered mental status due to encephalopathy or encephalitis and primary psychiatric presentation is usually seen in younger patients.[33] Clinical presentations vary from headache, seizure, encephalitis, strokes with vascular events, and even Guillain-Barré syndrome.[34] Long-term manifestations are yet to be reported.

Economic impact

The COVID-19 pandemic is bringing huge economic, social, and health-care challenges. As per the international monetary fund (IMF), the global economy is projected to decline by over 4.9% at the end of 2020. There will be a precipitous slowdown ever since the Great Depression in the 1930s. The COVID-19 pandemic has thrust the economy around the globe into a tail spin, leading to the financial system shrinking with cessation of growth. In the United States, ever since COVID-19 pandemic surfaced in the month of April, over 20.5 million have lost their jobs. The IMF has said the global economy will take a $12 trillion hit from the COVID-19 pandemic, it would take 2 years for world output to return to levels at the end of 2019. The COVID-19 pandemic thrusted economies into a great lockdown, which hindered the spread of the virus and saved lives but additionally sparked the worst recession since the Great Depression. The manufacturing productivity has dipped considerably in many countries, essentially due to a decrease in demand. China's gross domestic product (GDP) plummeted by 36.6% in the first quarter of 2020, but South Korea, which did not impose a lockdown but followed a strategy of aggressive testing, contact tracing, and quarantining, had a drop in output of 5.5%. World's topmost economies such as the USA, China, UK, Germany, France, Italy, Japan, and many others are at the verge of collapse. The travel, tourism, hospitality, and industry has been decimated by the pandemic. Oil prices have fallen to an all-time low, and the transport sector, which consumes 60% of the oil utilization, has been affected as numerous countries imposed lockdowns. During the lockdown, prices of foodstuff and grocery had increased affecting common people. Extending lockdowns has huge economic impacts on people in the low-income and at-risk categories. High income countries have rolled out finance packages. While India's economic stimulus package was 10% of its GDP, Japan's economic package was 21.1%, the USA 13%, Sweden 12%, Germany 10.7%, France 9.3%, Spain 7.3%, and Italy 5.7%. South Korea and Taiwan economies were hardly affected as they did not stop their businesses during the outbreak in their countries. China, which lifted its lockdown after controlling the contagion, has been gradually reopening its economy without encountering a second wave of infection. Lockdowns have led to cleaner cities and a reduction in greenhouse gas emissions.[35]

Climate change and pandemics

There are clear connections between COVID-19 and the climate crisis. Though the virus is believed to have originated with the horseshoe bat, they have been living in the forests of the globe for 40 million years and flourishes in the remote jungles of south China. Researcher have shown that pollution worsens the outcome of COVID-19 patients as seen in New York and Milan, two very densely populated cities. COVID-19 could well be nature's warning against climate change as 2019 observed shocking heat waves in Europe, record wildfires in Australia, large number of deaths due to cyclones, and a large number of severe weather conditions. The last 5 years were the warmest on record, and the frequency and intensity of natural disasters are on the rise. The question is, Did these climate changes trigger the pandemic? Though this may not be proven to be so, but history indicates that certain outbreaks are directly or indirectly linked to climate change. It is noteworthy that over the last 15 years, climate change has increased the outbreaks of malaria, dengue, Zika, West Nile virus, Nipah valley virus, and Ebola. Deforestation is linked to 31% of disease outbreaks such as the Ebola, Zika, and Nipah viruses. Roughly 70% of new pathogens come from animals and about 30% of these is ascribed to deforestation, establishing farming near these forests, utilization of natural resource. One study estimates that more than 3200 strains of coronaviruses already exist among bats, awaiting an opportunity to jump to people.[36] Researchers at the Tibetan Plateau in China demonstrated that since thousands of years, they have demonstrated in the glacier viruses, most of these are unknown in the virology dataset. The researchers showed 33 groups of these virus species in the ice glaciers, of these some are potentially pathogenic.

Medications in a pandemic

In general, most cases of COVID-19, there is clearly no need for antiviral therapy and most patients can be managed by supportive care. The SARS-CoV-1 pandemic which appeared unexpectedly in 2003 quickly spread to other countries leaving the medical world in significant distress. Potential therapies were explored based on in vitro studies, without adequate randomized trials, these drugs were fast-tracked into therapy for these sick patients. Some sense was found later from observational cohort studies and case reports. Yet, this data was beneficial in offering clinical guidelines and giving future direction to research in case similar outbreaks reappears. Early in the SARS-CoV-1 pandemic, a combination of ribavirin and corticosteroids were used, so lopinavir/ritonavir too was used. Interferon-alpha, an antiviral used to treat a broad spectrum of viruses, seemed to work against SARS in cell culture tests and was tried in some patients. Like seasonal flu, most people recovered from the H1N1 2009 pandemic usually within a week, without any antiviral medications. Antiviral agents prevent, shorten, and reduce the severity of flu. Antiviral agents used for the treatment and prevention of H1N1 are oseltamivir and zanamivir, but amantadine and rimantadine were ineffective, in severe cases steroids were used. In the Ebola epidemic in 2014, a large number of people developed Ebola viral infection in western Africa; several therapies were administered against the virus, this included chloroquine and its derivative hydroxychloroquine, favipiravir, monoclonal antibodies, and convalescent plasma. In general, most cases of COVID-19, there is clearly no need for antiviral therapy, and most patients can be managed by supportive care. Frequently used antiviral drugs against the current virus in this pandemic are listed in Table 1. Other agents like immunomodulating agents that prevent hyperinflammation due to cytokine storm has been used. Interleukin inhibitors like tocilizumab may prevent severe damage to lung parenchyma due to the cytokine release in cases of severe COVID-19 infections.[8] The use of 10 days of dexamethasone in COVID-19 patients had an excellent outcome both in survival and limiting duration on ventilators.[9] Currently, there are no highly effective broad-spectrum antiviral

Table 1 Drugs with potential antiviral properties tried in cases of Covid-19.

Drug groups	Drugs	Dose
Viral entry inhibitors	Hydroxychloroquine Chloroquine	Days 1–5: 2 × 200 mg/day, orally
Inhibitors of viral protein synthesis	Lopinavir/ritonavir	Days 1–10 (or 14): 400 mg/100 mg × 2/day, orally
Inhibitors of viral RNA polymerase/RNA synthesis	Remdesivir	Day 1: 200 mg, IV Days 2–5 (or 10): 100 mg/day, IV
	Favipiravir	Day 1: 2 × 1600 mg Days 2–7 (or 10): 2 × 600 mg/day
Immunomodulators	Nitazoxanide	Nitazoxanide 500 mg twice daily orally with meal for 6 days
	Ivermectin	Ivermectin 200 μg/kg once orally on an empty stomach
Immune Interferon	IFN-α	IFN-α is vapor inhalation at a dose of 5 million U for adults, 2 times/day
Guanosine analogue inhibits synthesis of viral mRNA	Ribavirin	IV infusion at a dose of 500 mg for adults, 2–3 times/day
Dual-acting direct antiviral/host-targeting agent	Arbidol	200 mg, 3 times/day
Antirhinoviral macrolides of antiviral gene mRNA and protein	Azithromycin	500 mg OD × 5 days

agents, or specific agents capable of interrupting viral life cycle, or destroying receptor proteins on the virus. Theoretically, monoclonal antibodies generally bind to specific proteins. These antibodies provide passive immunization against specific portion of the virus so as to reduce the multiplication of the virus and limit the severity of the illness. In the ideal world, neutralize the virus with the monoclonal antibody till an appropriate vaccine is generated against the contagion.[37]

Vaccines

Edward Jenner invented a method to protect against smallpox in the 18th century. After observing that cowpox infection seemed to protect humans against smallpox, he observed that milkmaids who previously had caught cowpox did not catch smallpox. At the end of late 1940s, large-scale vaccine production was conceived, and disease control was set in motion. The next array of vaccines was discovered and produced in the early part of the 20th century. These were vaccines against pertussis in 1914, diphtheria in 1926, and tetanus in 1938. These set of vaccines were then merged together in 1948 and became the DTP vaccine. Jonas Salk invented the polio vaccine which was then licensed in 1955. In 1963, the measles vaccine was developed, and at the late 1960s, vaccines were also available to protect against mumps in 1967 and rubella in 1969. These three vaccines were then combined into the MMR vaccine in 1971. Vaccine that was developed in the 1980s included hepatitis B and *Haemophilus influenzae* type b. New vaccines developed later include varicella (1996), hepatitis A (2000), pneumococcal vaccine (2001), rotavirus (2008), hepatitis A (2006), human papillomavirus (2011), and meningococcal serogroup B vaccine (2014).

The influenza virus was detected in 1933 leading rapidly to the development of the first-generation live-attenuated vaccines. The first ever monovalent inactivated flu vaccine was of influenza A. After finding the influenza B virus, the bivalent vaccine was available on 1942. The first trivalent vaccine consisted of two types of influenza A strains, and one strain of influenza B was available for administration on 1978. Since 1940, researchers have demonstrated that there has been a successive drift in the strains altering the antigenicity in the virus and hence the vaccine has often been altered to mirror these changes. Future vaccines will need to be modified to adapt to changes in strains. During this illness, there is a rapid research in developing a vaccine for COVID-19, but it may already be too late to impact the outcome of the first wave in this pandemic. There are numerous potential vaccines currently undergoing clinical trials yet to provide many meaningful results. This fight against coronaviruses (SARS-CoV-1 and MERS-CoV) may not be simple as the previous two coronaviruses did not yield favorable results. In 2003–2004, numerous SARS-CoV-1 vaccines made it to phase I clinical trials and did not move up into further phases as eradication of the virus by nonpharmaceutical methods materialized. Inactivated virus vaccine and a spike-based DNA vaccine had proved to be safe and possibly generated neutralizing antibodies.

For Covid-19 currently there are seven distinctive vaccines across three platforms that have been developed and are in use across different countries. The most vulnerable populations in large number of countries have been vaccinated in the early part of 2021. Two messenger RNA (mRNA) vaccines are currently available one developed by Pfizer (BNT162b2) and the other one being by Moderna (mRNA-1273). Once injected, the mRNA is seized by macrophages which then produce spike protein. The spike protein is then presented on the surface of these macrophages, leading to formation of antibodies against the spike proteins and renders protection against the SARS-CoV-2 infection. The enzymes within the body then destroy and dispose of the mRNA. In this vaccine, no live virus is included. There are four nonreplicating vector vaccines. (1) ChAdOx1-S recombinant vaccine is a chimpanzee-derived adenovirus vaccine developed by University of Oxford and AstraZeneca. This "vector" virus is the virus that causes common cold and not COVID-19. This vector virus which is present within the vaccine produces the SARS-CoV-2 spike protein. (2) Ad26.COV2.S, is an Ad26-vector, is a nonreplicating adenoviral vector vaccine against coronavirus disease, the vaccine conceived by Janssen and known as Johnson & Johnson single dose vaccine. (3) Sputnik V developed by Gamaleya, designed from two different adenoviral vectors Ad26 and Ad5 producing antibodies to spike protein. (4) Ad5-nCoV created by CanSino Biologics in China, where an Ad5 vector is used to express the spike protein antibody. There are other inactivated vaccines and nasal vaccines in phase 3 trials currently underway in India and China. More than 60 vaccines are in clinical development, but challenges faced by governments is to build up manufacturing capabilities to fulfil the needs of general population. Vaccines are a critical new tool in the battle against COVID-19 and it is immensely reassuring to see so many vaccines proving to be successful and getting developed.[38]

Planning for future pandemics

In the two decades of the 21st century, mankind has faced a number of pandemics (SARS-CoV-1, 2009 H1N1 influenza, 2013 chikungunya, SARS-CoV-2) and epidemics (2006 chikungunya, meningitis, cholera, measles, yellow fever, Zika, and MERS). In every outbreak, the nature of pathogen poses challenges to public health system more so in low- and middle-income countries. Health for all is the basic and fundamental right for all human beings. At times of outbreaks, epidemics, and pandemics, the world looks forward to the WHO to take a leadership role and provides solutions to the ongoing outbreak. Since the WHO was founded back in 1948, it has taken leadership roles in major medical emergencies across the globe. It has done a stellar job over the years but has been found wanting in some situations, more so during the Ebola outbreak.[39] Over the years, there are concerns regarding funding for the WHO, which does come to the fore during budget spending for perceived outbreaks and threats. In major crisis, WHO needs to interact and share strategies with other similar organizations like Centers for Disease Control and Prevention (CDC), Collation for Epidemic Preparedness Innovations, and the Global Research Collaboration for Infectious Disease Preparedness. This coordination between organizations will help in preventing duplication and cutting costs. Most outbreaks and acute public health risks are generally unpredictable and need well-directed strategies. In 2005, the International Health Regulations (IHR) provided a central legal charter that defined countries rights and commitments in dealing with public health incidents and emergencies that can potentially cross international borders. The IHR is legally binding on 196 countries, this includes the 194 WHO Member States. The Joint External Evaluation Tool of the IHR is able to assess a country's capacity to prevent, detect, and rapidly respond to public health threats independently.[40] The greatest tests to achieve control during an outbreak is arranging a trained personnel with the required skill in clinical management, public health, epidemiology, and numerous specialities in the field of medicine. Civic bodies while planning for large epidemics and pandemics delegate teams to meet the mandatory surge capacity encountered following the contagion. This involves trained human HCW's, physical structures able to accommodate hospital beds, and appropriate medical gear and equipment. In the current pandemic, cities across India were able to convert auditoriums, stadiums wedding halls into large medical facilities, but these centres were run with skeletal staff making the logistics truly very trying but did take a load of some of the active medical facilities. In hospitals, elective surgeries were canceled making way for more hospital beds to address the contagion. The financial implications of limiting elective work may have deleterious effects on the financial model of these institutes. Countries which generally do well during outbreaks are those nations which have both robust preventive public health systems and excellent curative health services. During an outbreak, the absolute numbers open doors for potential research and are capable of generating the numbers to get meaningful outcomes in diagnostics and therapeutics. Large information too can be collected prospectively in observational studies to elicit consequential data. Finally, vigorous infection control measures have to be spread to HCW and community too; as in this pandemic, the most susceptible individuals are colleagues at work and immediate family members. In recent times, there has been a surge in global terrorism, the possibility of a contagion being used as a bioterrorism apparatus is a distinct possibility the nations must remain vigilant against this lurking threat. In 1975, a Biological Weapons Convention ensured an embargo on the production and utilization of biological weapons. Over 180 countries participated in the convention and endorsed the proceedings. Terrorist organizations and nation that support them do not follow the established rules and are potentially a huge threat if biological weapons are used against susceptible nations.[41]

Conclusion

This century has already seen numerous outbreaks, epidemics, and pandemic, having a major impact on health care, huge economic impacts affecting the livelihoods of ordinary people increasing mortality in highly susceptible individuals. Organizations like the WHO and CDC have laid down protocols and guidelines to be implemented during outbreaks, these etiquettes need to be implemented in its full propriety to avert and minimize risk to human beings. Across affected countries, the biggest impact has been on large crowded cities leading to lockdowns. Lockdowns lead to prolonged cutbacks in commercial activity from, lockdowns will hit low-income and susceptible factions the hardest. World leaders more so from the developed nations need to address the clear and present danger a pandemic that exposes the free world. These nation-states need to plan for future contagion and the possible impacts it can have on health and the economies of the world. In the current COVID-19 pandemic, Bill Gates quoted "In any crisis leaders have two equally important responsibilities: solve the immediate problem and keep it from happening again." However, well we prepare, some storms will have a significant toll. The final answer in the event of an outbreak happens is to ensure a rapid development of vaccines.

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