Spanish Flu to COVID-19: Healthcare Challenges And Evolution

Pooja Sachdeva[1], Rohit[2]

[1]Consultant, Department of General Medicine, Sengkang General Hospital, Singapore,
[2]AdjProfessor, Department of Diagnostic Radiology, NgTeng Fong General Hospital, Singapore

Abstract

Spanish Flu (1918-1919) is considered the deadliest Pandemic of the twentieth century, with worldwide mortality of about 50 million people. One hundred years after this Pandemic, WHO had released a pandemic preparedness plan in March 2018 and urged all countries to have planned their response to future pandemics threats. This plan is a guide to building the capacity to face healthcare and economic challenges encountered during any pandemic. Today, in 2020, the world is witnessing Pandemic by another virus called COVID-19. This infection originated in China and has traveled globally to affect almost all countries. Healthcare worldwide in this Pandemic faces many challenges as expected, but the response and resilience in meeting these challenges have been exemplary. HealthCare technological and laboratory advancement has enabled full genomic sequencing within two weeks and the manufacture of trial vaccines within eight weeks. From creating makeshift hospitals and community isolation facilities, manufacturing medical equipment to providing accessible, affordable public health and information are depicting strong political will and motivation to fight this pandemic. This pandemic has also highlighted the gaps in pandemic preparedness among countries and provided them the opportunity to reflect on their healthcare needs and policies.

Key Words: - *COVID-19, Spanish Flu, Healthcare Challenges, Pandemic, Healthcare Evolution*

Introduction

COVID -19 isa respiratory illness caused by Coronavirus, also known as SARS -COV 2 that has affected almost 100 million people worldwide with more than 2.5 million deaths [21] since its first origin in Wuhan, China, in December 2019[22]. It has been declared a pandemic by WHO [36]in March 2020 after acknowledging its fast spread globally.

Corresponding Author :
Dr Pooja Sachdeva,
Consultant, Department of General Medicine. Address : Medical centre level 9, SengkangGeneral Hospital, 110 Sengkang East way, Singapore 544886 Tel No.+65 69302907, Email : dr.poojasachdeva@gmail.com; pooja.sachdeva@singhealth.com.sg.

COVID-19 is being compared with Spanish Flu; the deadliest Pandemic witnessed in the early 20th century (1918-1919) that had affected about 500 million people worldwide with estimated at least 50 million deaths[23.] There has not been any pandemic before and after 1918 that had comparable death rate so far [23.]There are similarities in two diseases in terms of their spread, pathogenesis, management, and challenges these have posed to healthcare worldwide. It is almost a century since the world has witnessed devastating Influenza pandemic, and measures are expected to be in place to prevent another such further pandemic.On May 07, 2018, a one-day symposium [1,2,23] was hosted for the 100th anniversary of the 1918 Influenza pandemic by Rollins School of Public Health at Emory University with Centres for Disease Control and Prevention (USA), to discuss future pandemic threats, its prevention,

control, and preparedness. Global experts acknowledged that challenges would be faced by healthcare in future pandemics despite advancement and readiness and the only way forward would be accepting and confronting them with the rest of the world. This article aims to discuss these challenges in pandemics and the strategies worldwide to meet these challenges.The expedited responses by countries worldwide have shown the rapid evolution of healthcare over the last century.

History

The H1N1 Influenzavirus with avian genes[23]virus caused Spanish Flu. It was first detected in the United States in March 1918 in a military camp wherewith flu-like symptoms [23]were reported in 100 soldiers. It spread rampantly in crowded and poorly maintained military fields, and mortality surfaced as reported by Public health reports in their weekly issue in April 1918. The soldiers were deployed toWorld War Iand required to cross Atlantic every month hence leading to the disease spread through the USA, Europe, and Asia over the next six months. A second wave reported in September 1918 in anothercamp was highly fatal and affected 14000 soldiers with 757 deaths. New York City's Board of health made this Flu reportable and required affected patients to isolate at home or hospitals. There was the third wave in Winters in January 1919 when another surge of cases emerged and continued till Summer before subsiding. It is believed that Flu was eradicated in April 1919.[23]

Spanish Flu had spread like COVID -19 through "Nasal droplets." It caused respiratory illness with cough and breathing abnormalities secondary to pneumonia. This Virus notably affected healthy individuals between 15 to 44 years old [23]. By October 1918, Spanish Flu had spread over a significant part of the world, and challenge in front of healthcare was *inadequate nursing and medical staff* to look after patients as former deployed to military camps in-country and abroad. There was a call made to recruit volunteers to look after the ill. After its eradication, a bill was passed to provide a one-year training course to become "practical nurse" to address the shortage of healthcare staff.

The other challenge that was with *inadequate testing*. The diagnosis was mainly clinical, and the virus was not isolated or cultured in a laboratory. It was postulated that the third wave of Influenza was fuelled by inadequate reporting and management of the cases. There were no available treatments or vaccines; hence the management mainly consisted of nonpharmacological measures such as isolation, quarantines, good personal hygiene, use of disinfectants, and avoidance of public gatherings. Cold storages were used as temporary morgues as corpses waited to be buried for more than a week.

Public health units had issued recommendations of wearing masks in public about six months after the first case and prohibited all public gatherings and closing of schools, movie houses, and theatres. People were encouraged to walk to work and avoid public transport. They businesses were suggested to stagger working hours to avoid overcrowding. There were an estimated 195000 patients were killed by this pandemic in October 1918 alone.[23.] Public health authorities issued education guidance people to dispose of their nasal discharges properly and maintain social distance.

By the end of World War,I, the U.S. military grew from 378,000 soldiers in April 1918 to 4.7 million soldiers. Another challenge was*insufficient fund*s to study about Influenza. Trustees of Boston City hospital had asked Mayor for a special appropriation of $3000 to research treatment of Influenza. There was a question on *political outlook and motivation* on channelizing the funds to healthcare. There was no central or federal government control over measures to prevent spread. There was a substantial economic loss in the War, and not many funds were available for medical research.

Pic 1: Boston Red cross Volunteers Guage assembled influenza masks for use at hard-hit camp Devens at Massachusetts, (taken from CDC image gallery)

Pic 2: -Soldiers from Fort Riley, Kansas, ill with Spanish Flu at a hospital ward at Camp Funston (Otis Historical Archives, National Museum of Health and Medicine)

COVID -19

The first case of COVID-19 was reported on December 31, 2019.[22.] Much has been studied about this Virus since then. It hadoriginated in Wuhan, China [22]and continued to spread globally, resulting from urbanization, tourism, and enhanced world connectivity[4.]The world had been a spectator of strategies that were used by China to diagnose, manage, and contain it in the early months of 2020. As the spread was fast and rampant, it was paramount to diagnose the illness early and isolation of the organism from the tissues. The understanding of human-to-human transmission was the basis of most of the recommended strategies for its containment.[4,5]The disease hastravelledinternationally, and about 213 countries and territories [21]around the world has been affected by COVID -19. It is predicted that disease will continue to spread and will last for few years.

The world and the healthcare have been fighting with this pandemic for almost a year now. The World Health Organization (WHO) has been actively providing necessary unrestricted information including latest statistics, diagnostic policies, guidelines on management on their website and diagnostic kits, and Personal Protective Equipment (PPE) to the underdeveloped and low-income countries. There are challenges faced by healthcare in all the pandemics, however response to this pandemic has been exceptional. The early lockdown and travel ban by all major countries have been the most significant factor to contain the spread internationally. Almost all countries have developed their own local and state strategies to deal with this disease's challenges.

Healthcare challenges during COVID-19 pandemic

1. Viral isolation and testing

Viral isolation in a laboratory is the first step to diagnose the symptomatic patient. Once an infected patient is identified, he can be isolated from the community to contain the disease's spread. Two kinds of tests[25]can identify the infection, viral testing by RT-PCR (Reverse transcriptase -Polymerase chain reaction) in respiratory secretions and blood antibody testing of infected patients. Scientists from China released the information of the COVID -19 genome on January 11, 2020[1]followed by the Malaysian Institute for medical research (IMR), producing the primers specific to SARS-CoV-2[26]China developed the first testing kits and reagents for respiratory samples taken from nasopharyngeal swabs, sputum, or bronchoalveolar lavage of affected patients.

Within two months of this pandemic, many countries like United Kingdom, Germany, France, Korea, Japan, and Singapore had developed their local tests to identify the virus and infected individuals[26.] Most of the countries had slowly built up the laboratory capacity to test as many patients and individuals as possible.[26]WHO had urged countries to ramp up the testing capacities to slow down the pandemic advancement in news release in March,2020. Most of the countries had targeted their daily testing from 10,000 to 100,000 per day.[26] Currently, antibody testing is being used to identify asymptomatic carriers and past exposure of the disease under active surveillance [26,27.]CDC,however, has suggested using the antibody test cautiously [25]due to its less specificity and sensitivity.

2. Contact tracing and Active surveillance

The next step to slow down the spread of the virus is to actively identify the contacts of the diagnosed patients to break the chain of transmission. Infectious control departments define the close contacts as any individual within 6 feet of an infected or probable patient for 15 minutes.[27]These contacts need to be tested regardless of their symptoms. Negative tested contacts must stay in quarantine for at least two weeks.[27]. It is a fundamental public health measure for countries to do contact tracing and quarantine actively. WHO had emphasized on that contact tracing and active surveillance as strong elements of response as control measures on 03rd] June 2020. Setting up regional centres to swab high-risk asymptomatic carriers actively utilizes considerable workforce and resources.

The ministries in various countries had developed Task forces to trace positive patients' contact and isolate them early.Staff in task forces helps to discover

the contacts and their symptoms via texts, calls, or videos. Various policies are in place for people and contacts to reduce mobilization and spread. Country wide lockdowns, travel ban are public health measures adopted to mitigate spread of the disease.Digital tools like Bluetooth, GPS-related trackers, Safe entry, Trace Together Apps on the phone can provide the mobility history of patients and help identify unrelated contacts. Smartphones and proximity tracking digital[37]sensors that can detect proximity and exposure to COVID-19 positive patients. These measures help to people to identify themselves if they have been in contact and self-isolate and seek medical attention if they have symptoms.

3. Economic burden, resource allocation, and workforce mobilization

There has been an overwhelming surge in patients with COVID -19 since the pandemic, and it has stretched healthcare resources worldwide. Hospital beds in both general wards and ICU (Intensive Care Unit) are limited andrapidly taken up by patients. Resources and supplies are required to manage both COVID-19 and non-COVID patients. The human-to-human transmission also requires that COVID affected patients areadmitted in isolation rooms or separate wards to prevent transmission to other patients and healthcare workers. It was a challenge for that each hospital in every country faced to allocate manpower in teams to avoidcross transmission at workplace.

Splitting the workforce, extra working hours, opening new wards are just the measures taken during desperate needs in any pandemic. China has been exemplary in opening two hospitals, A 1000 bedded hospital with prefabricated wards and isolation rooms and 1500 beddedLeishenshan hospital to accommodate the rising number of patients within two months of pandemic.[38]Almost every country has opened makeshifthospitals at their sports centres, exhibition halls, and public spaces, including airports[39] or central parks.[40]Guidelines regarding patients' management are being updated as disease pathophysiology, and the spectrum is understood gradually. The resources were allocated to admit patients with moderately severe disease[29]while patients with mild disease are isolated in temporary quarantine and community isolation sites or at their homes. Various firms had taken up building more ventilators and medical equipmentto meet the requirements for sick patients.

Teams of healthcare workers are moved from lower affected regions to higher affected areas in big countries to cover the gaps in human workforce.[41]Retired nurses[41,42]and doctors [43]are resuming practices to meet this demand of healthcare providers. Volunteers[44]are recruited to be trained and work in swab teams to channelize medically trained workforce in clinical areas. The response from community and volunteers showing solidarity has been exceptionally motivating and inspiring for healthcare workers worldwide.

4. Medical Education and Research

COVID-19 is a novel, unknown pathogen, and much research was required to understand its pathogenesis, spread, symptoms presentation, management, and outcome. There have been numerous publications since the pandemic that has educated medical fraternity about this virus. Much of the current knowledge about it is a collective effort of healthcare providers worldwide that have submitted their experiences with this pathogen in various medical journals or forums. It provides necessary crucial information about its clinical presentation, laboratory derangements, and radiological pointers, which helps to detect and diagnose early. There has been much data about disease spectrum and outcome. Many studies are going on to understand risk factors leading to severe disease, including mortality. The challenge is to develop an anti-viral treatment for affected patients and a vaccine to prevent the unaffected. Transfusion of convalescentPlasma [8]from affected patients with antibodies against the virus has shown some evidence of providing passive immunity and early recovery in sick patients. Many drugs have been in trials with positive effects such as Remdesivir[9]Hydroxychrlolquine[10] EIDD- 2801[11], Favipiravir[45,] tocilizumab[46,]lopinavir-ritonavir combination[12](Kaletra)however side effects profile, availability and limited evidencehavebeen

holding their widespread use. In a pandemic, desperate cross-sectional observations provide much of the clinical evidence instead of properly conducted randomized trials. However, many Phase III global, randomized trials are going on for anti-viral drugs, and results are awaited. The viral genome sequencing is complete, and a vaccine has been manufactured[30,31] within two months and currently being administered world-wide. Various vaccines based on different viral components have been developed by pharmaceuticals companies such as Pfizer-BioNtech and Moderna's mRNA vaccines[15], Bharat Biotech's Covaxin (whole killed Virus) [16],Russia's Sputnik V (adenoviral vector vaccine)[18] , China's Sinovac(whole Killed Virus)[17],Oxford-AstraZeneca Covishield (adenovirus vector)[19]and Johnsons and Johnsons one shot vaccine [20] are highly efficacious in preventing the disease spread and studies are underway for their long term effects and efficacies.

5. Healthcare workers wellbeingand leadership

Healthcare workers treating and managing positive patients must be provided with adequate personal protective equipment (PPE)[47]to avoid transmission. The droplet mode of transmission requires patients to be placed in separate wards or isolation rooms to prevent cross-transmission. It requires an impermeable apron, face mask, face shield, spectacles, gloves, shoe covers, and headcovers for one visit in a patient room. The demand for these PPE has risen with a surge in affected patients. Almost all the countries faceda shortage of adequate PPE for healthcare staff and the public. On February 27, 2020, WHO[48,49] issued guidance suggesting the "rational "use of PPE citing the disruption of global supply and the insufficient stockpile of PPE that resulted fromgrowing number of patients, misinformation and panic buying. WHO also called upon industries and governments to increase local manufacturing at least by 40 percent to meet therising demand. Nonetheless, there have been hundreds of medical doctors and nurses who have acquired the disease from their patients and have lost lives to this deadly virus[50]Countries since the beginning of pandemic have been manufacturing,securing, and exporting PPE to other countries. Many manufacturing firms[51], fashion firms, and skincare firms have been building up the PPE supply to meet the requirement.

Like in a war situation, there must be the constant motivation of healthcare workers and the public. Prolonged work and exposure, uncertainties about disease do affect mental health apart from causing physical exhaustion. The limited human interaction and scarcity of support systems during the lockdown period have surfaced many mental health conditions such as anxiety, insomnia, and Major depression [32,33]in healthcare workers and public. The psychiatry departments in hospitals have opened many local helplines [32,33]to provide support and counselling. Ministers and leaders must be transparent about the disease to the public to allay apprehension and to clear misinformation. Many leaders worldwide have been seen speaking to their countrymen about this pandemic on various media channels. Likewise, the hospital administration is actively involved in setting up policies for a smooth workflow, getting feedback from workers, and encourage and inspire them for continued hard work and efforts.

6. Political motivation and support

In any pandemic management, political involvement in healthcare is essential and crucial. Obtaining diagnostic test kits and reagents, running, and setting up laboratories, new hospitals, or placement areas, procuring and manufacturing PPE, recruiting workforce to swab and trace results, contact tracing, active surveillance, and Medical research requires a substantial healthcare budget. While hospitals play their part in healthcare human workforcemobilization, political will and strategies are needed to tackle a pandemic at the state and national levels. Travel & tourism ban, nationwide lockdowns have imposed a substantial financial challenge on economy affecting jobs and small businesses. It requires strong political will and budget from finance ministries to continue providing needed support during this lockdown for its success. Leadership in countries like New Zealand, Taiwan, and Germany have been praised and considered as role models for their responses to this pandemic.

Discussion

CDC talked about 1918'sDeadliest Flu[23]discovery and researchas JohanHultin, a Swedish microbiologist in 1951, requested permission to excavate Brevig Mission, a small oceanside village in Alaska.[23.] A mass grave site marked only by white crosses was created near this village during the 1918 pandemic.Hultin could successfully obtain the samples of the virus from buried bodies' lungs but could not culture them in chicken eggs. In 1997, Dr.Taubenberger, a molecular pathologist working for the Armed Forces Institute of Pathology in Washington, D.C., could do a partial genomic sequencing of this virus by studying a preserved lung tissue sample of a soldier from South Carolina who had died in the pandemic. The Brevig Mission was re excavated to obtain samples of this virus and only in 1999, the scientists succeeded in full sequencing of Spanish flu[13],The Deadly Influenza virus.

Since 1918, the world has witnessed three flu pandemics in 1957 with Asian Flu (H2N2 Influenza), 1968 with Influenza A (H3N2 Influenza) Virus and 2009 with Swine Flu (H1N1 Influenza) virus with much lesser mortalities.[43,44]We are currently amid pandemic, and it is hard to estimate the total burden of disease and its mortalities. However, WHO has mentioned in their news release that COVID -19 is almost ten times deadlier than Swine flu. It has been accelerating extremely fast with slow deceleration. Data suggest about 4 to 11% Case Fatality Rate but vary according to age, geographical location, and healthcare resources. There is enough evidence to suggest that the virus is highly transmissible and has higher mortality than Influenza but lesser than Middle East Respiratory Syndrome (MERS), virus.[14]

Spanish Flu had high genetic virulence, yet there were additional environmental factors that had led to its spread and consequent mortality[23]. During World War I, the movement of troops across the countries placed soldiers in overcrowded closed living spaces. Healthcare services were limited in bothhealthcare workers as they deployed in militaries and medical technology and countermeasures. There were no antibiotics, anti-viral drugs, or Influenza vaccines that could prevent mortality. Mechanical ventilation and ICU support were not available either; hence physicians had options of mainly supportive care [23]for affected patients.

The laboratory services were not developed enough to culture the Spanish flu virus until 80 years of the pandemic.[23]For the longest time, the 1918 pandemic was thought to be caused by a bacteria Pfeiffer bacillus[23]but having full genomic sequencing of COVID -19 within a month of this pandemic is a result of successful modernization of laboratories and healthcare evolution. This exceptional achievement of genomic sequencing has not only permitted the manufacture of rapid diagnostic kits but also opened the doors for trials for anti-viral drugs and vaccines. Setting up temporary labs, recruiting workforce to swab the patients and their contacts actively, and reducing turnaround time for the investigation has been the definite steptowards controlling the transmission of the disease.

New hospitals, isolation, and quarantine facilities are made available to house patients, contacts, and suspected cases. Healthcare workers from various paraclinical specialties, community hospitals, primary care clinics, and nursing homes are getting adequate training to involve them in a bigger workforce pool for allocation at clinical care centres. There is funding made available to research laboratories to work on anti-viral drugs and vaccine manufacturing. Most remarkable in this pandemic has been a timeline for developing the vaccine. It took 42 days[24] for Moderna therapeutics to manufacture a vaccine for human trials from time Viral Genome sequencing on January 11,2020. This timeline is much shorter than the latest H1N1 pandemic(2009), where the vaccine was available 26 weeks after the manufacture.[23]The pharmaceutical companies are prepared to manufacture and distribute the drugs and vaccines to meet the global demand.

In COVID -19 pandemic, various National and state-level policies are set up early. The central governments in the respective countries have been actively planning and initiating interventions such as isolation, quarantine, and stay at home (SAH) orders. Chinese authorities stopped the movement in and out of Wuhan and Hubei Provinces by suspending trains and flights and blocking roads[4,5]

in late Jan 2020 to reduce the spread. Many countries, including India, Singapore, Korea, China, Germany, Spain, France, UK, USA, Australia, New Zealand and Canada, have implemented community mitigation measures such as early nationwide lockdowns to prevent public gatherings and spread. The international and domestic travel ban, and advisories are issued to avoid movement of the virus

There is increased communication and networking in the digital world. Information is made available and accessible for medical professionals, as many esteemed medical journals have provided their free of charge access during this pandemic. Many websites, including WHO, CDC, local Ministry of Health sites, are providing the statistics with numbers of patients diagnosed, quarantined, recovered & discharged, or demised. These are the portals of authentic information about measures to prevent the disease, seek medical attention, contact numbers of involved public health authorities, helplines to reach out. The COVID -19 pandemic has united the world. Numerous international collaborations with teams of doctors and nurses are working together to learn more about the disease and its management. Scientists and researchers worldwide havecollaborated to makesuccessful vaccines and anti-viral drugs. Previous pandemics have prepared nations with medical and societal advancements for an expedited and early response to current and future outbreaks.

Conclusion

There is much to learn about COVID -19 for the medical fraternity. Only the future will tell how this pandemic would be controlled with its final statistics. Nonetheless, this will be a historical landmark in medical history that had embarked upon the best of medical technology and public health. It has provided the world with an opportunity to reflect upon its healthcare, its shortcomings, and needed improvement. Healthcare should be a priority for any country. The author has tried to highlight challenges in healthcare that are faced during any pandemic and have assured that it is being dealt with a much better response compared to a century ago.

Funding : No funding is provided for this article

Conflicts of Interest: Nil

Ethical Clearance: Taken from Institutional Research Committee.

References

1. Barbara Jester et al. Readiness for Responding to a Severe Pandemic 100 Years After 1918. Am J Epidemiol. July 2018. 187(12): 2596-2602. DOI: 10.1093/aje/kwy165.external icon
2. Barbara Jester et al 100 Years of Medical Countermeasures and Pandemic Influenza Preparedness.Am J Public Health. 2018; 108: 1469-1472. DOI: 10.2105/AJPH.2018.304586
3. K. Taubenberger, Ann Reid, Amy Krafft et al. Initial Genetic Characterization of the 1998 "Spanish' Influenza Virus. Science. Mar 1997; Vol 275, Issue 5307, pp 1793-1796
4. David Cyranoski. What China's Coronavirus response can teach the rest of the world, Nature, March 2020
5. The Huayiu Tian et al. TheImpact of transmission control measures during the first 50 days of Covid-19 epidemic in China,BMJ, March 2020, https://doi.org/10.1101/2020.01.30.20019844
6. R. Lu et al. Genomic 231 characterization and epidemiology of 2019 novel Coronavirus: implications for virus origins and receptor binding. The Lancet, DOI: 233 https://doi.org/10.1016/S0140-6736(1020)30251-30258 (2020).
7. F. Wu, S. Zhao, B. Yu, Y.-M. Chen, W. Wang, Z.-G. Song, Y. Hu, Z.-W. Tao, J.-H. Tian 235 Pei. A new coronavirus associated with human respiratory disease in China.Nature, 1-8 (2020).
8. Long Chen, et al; Convalescent plasma as a potential therapy for COVID-19, The Lancet; February 27, 2020, DOI: https://doi.org/10.1016/S1473-3099(20)30141-9
9. Yeming Wang et al Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial,The Lancet, April 29, 2020, DOI: https://doi.org/10.1016/S0140-6736(20)31022-9
10. Wei Tang et al; Hydroxychloroquine in patients

with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial; BMJ 2020; 369 DOI: https://doi.org/10.1136/bmj.m1849

11. Timothy P. Sheahan et al. An orally bioavailable broad-spectrum anti-viral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice; Science Translational Medicine April 29, 2020: Vol. 12, Issue 541, eabb5883 DOI: 10.1126/scitranslmed. abb5883
12. Bin Cao et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19,NEJM May 07, 2020; 382:1787-1799 DOI: 10.1056/NEJMoa2001282
13. K. Taubenberger, Ann Reid, Amy Krafft et al. Initial Genetic Characterization of the 1998 "Spanish' Influenza Virus.Science. Mar 1997; Vol 275, Issue 5307, pp 1793-1796.
14. Dimple D Rajgor et al; The many estimates of the COVID-19 case fatality rateThe Lancet Infectious Disease. March 27, 2020 DOI: https://doi.org/10.1016/S1473-3099(20)30244-9
15. Lindsey R. Baden, Hana M. El Sahlyet al, Efficacy and Safety of the mRNA-1273 SARS-CoV-2 VaccineN Engl J Med2021; 384:403-416 DOI: 10.1056/NEJMoa2035389.
16. Raches Ella, Krishna Mohan Vadrevu, PhD Harsh Jogdand, et al Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial.The Lancet Infectious Disease January 21, 2021 DOI: https://doi.org/10.1016/S1473-3099(20)30942-7
17. Yanjun Zhang Gang Zeng Hongxing Pan et al, Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial.The Lancet Infectious Disease. Vol 21, Issue 2, P181-192, Feb 01, 2021
18. Ian Jones, Polly Roy Sputnik V COVID-19 vaccine candidate appears safe and effective. The Lancet February 02 Vol 397, Issue10275, P642-643, 2021 DOI: https://doi.org/10.1016/S0140-6736(21)00191-4
19. Jacqui Wise.Covid-19: New data on Oxford AstraZeneca vaccine backs 12-week dosing interval. BMJ 2021; 372 doi: https://doi.org/10.1136/bmj.n326.
20. Joel Zinberg; The Third Vaccine, Johnson & Johnson's one-shot regimen adds to the Covid-19 arsenal and offers important advantages over the Pfizer and Moderna options. City Journal. February 26, 2021
21. WHO, COVID -19 Dashboard.
22. WHO, Timeline -COVID 19, updated 10th March 2021.
23. History of 1918 Flu Pandemic, The complete story of discovery and reconstruction of the 1918 Virus. Centres for Disease Control and Prevention.
24. https://www.cdc.gov/flu/pandemic-resources/reconstruction-1918-virus.html
25. Testing for COVID-19, Corona Virus disease, CDC
26. https://en.wikipedia.org/wiki/COVID-19_testing#Current_infection, COVID -19 testing, Wikipedia.
27. Coronavirus (COVID-19): Scaling up our testing Programmes, Department of Health and Social Care, April 04, 2020.
28. Corona Disease 2019, Contact Tracing, Centre of Disease Control and Prevention.
29. National Institute of Health: Corona Virus 2019 (COVID-19) Treatment Guidelines.
30. ThedraftlandscapeofCOVID-19candidatevaccines, WHO, June 09, 2020. https://www.who.int/docs/default-source/coronaviruse/novel-coronavirus-landscape-covid-19f65d59aff81049f5a50d37bebf0caf93.pdf?sfvrsn=394d10c9_2&download=true
31. https://www.modernatx.com/modernas-work-potential-vaccine-against-covid-19
32. Guidance for the public on the mental health and wellbeing aspects of Coronavirus (COVID-19); Public Health England. March 31, 2020
33. Coping with Stress. COVID -19, Centre for Disease Control and Prevention (CDC)
34. Pandemic Influenza. World Health Organization
35. Pandemic Influenza, Centre of Disease Control and Prevention (CDC)
36. http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news

37. European expert's ready smartphone technology to help stop Coronavirus, Douglas Busvine; Reuters, Technology News, April 01, 2020.
38. https://www.dailymail.co.uk/news/article-7974641, Xiaoying You and Ryan Fahey, February 06, 2020, for Mail Online.
39. Birmingham airport could become a Coronavirus mortuary for up to 12000 Bodies. News. The Telegraph, March 26, 2020.
40. New York's Central Park now home to a makeshift hospital. News. Fox News. March 30, 2020.
41. Medical assistance teams leave hard-hit Hubei as epidemic wanes. News. XinhuaNet. March 17, 2020.
42. COVID -19: 3000 retired Nurses to return to service. Julia chan; News. Malaymail. March 25, 2020.
43. Retired health workers are urged to return as U.S. coronavirus cases are set to spike. Jessica Glenza. The Guardian. March 25, 2020.
44. Boots wants to recruit hundreds of unpaid volunteers to take coronavirus swabs. Jen Mill. Metronews. May 13, 2020.
45. Japanese flu drug 'clearly effective' in treating Coronavirus, says China, The Guardian March 18, 2020.
46. Roche initiates Phase III clinical trial of Actemra/RoActemra in hospitalized patients with severe COVID-19 pneumonia, Clinical Trials arena, News May 28, 2020
47. What is PPE?Health, Leah Growth, April 03, 2020
48. Rational Use of Personal Protective Equipment for Coronavirus disease (COVID -19): interim guidance.WHO, February 27,2020.
49. COVID -19 Personal Protective Equipment (PPE), Public Health England, Guidance, May 21, 2020
50. Medscape Medical News, In Memoriam: Healthcare workers who have died of COVID- 19. April 2020
51. Every UK manufacturer is helping to produce PPE and equipment for NHS workers. News. Jonny Williamson. The Manufacturer. April 16, 2020.
52. Guidance
53. COVID-19 personal protective
54. Updated May 21, Funding 2020