Summer Training Report

By

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With warm regards,
Harleen Kaur

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LIST OF ABBREVIATIONS

CDC - Center Of Disease Control And Prevention

CFR - Case Fatality Idea

CoV - Corona viruses

COVID - Corona virus disease

DENV - Dengue Virus

DHF- Dengue hemorrhagic fever

DSS - Dengue Shock syndrome

EID - Emerging Infectious diseases

GOARN - Global Outbreak Alert and Response Network

GoI - Government of India

IDSP - Integrated Disease Surveillance Programme

JHU - John Hopkins University

MERS - Middle East Respiratory Syndrome

MoHFW - Ministry of Health and Family Welfare

NSPCD - National surveillance programme for communicable diseases

NVBDCP - National Vector Borne Disease Control Program

PICO - Participants Interventions Comparisons Outcomes

PPE - Personal Protective Equipment

SARS - Severe Acute Respiratory Syndrome

WHO - World Health Organization

Work-From Home

(Assigned by Faculty)

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TEACHINGS FROM PAST: LESSONS LEARNT FROM THE PAST PANDEMICS

A Report by

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ABSTRACT

With changes in human behavior, increase in population, increased migration along with high level of urbanization; it has become easier for infectious diseases to emerge and spread. With instances of life-threatening outbreaks such as the Spanish flu and Ebola fever in the 20th century, the 21st century also brought along with it, many pandemics that raised global concern. The world is painstakingly fighting the COVID-19 pandemic, looking for old or new prevention and control measures to end its reign. The three pandemics of 21st century that also raised international concerns and caused million of deaths around the globe; the SARS 2002-04 pandemic, the Dengue outbreak 2006, and the Swine flu(H1N1) outbreak of 2009 and 2015, are discussed here. This paper highlights the preventive and control measures implemented to curb the pandemics, and what do we learn for the future from these past outbreaks.

KEYWORDS: Pandemics, Swine flu H1N1, Dengue, SARS, COVID-19, India

INTRODUCTION

The year 2020 took a turn for the worst, with the emergence of COVID-19, the novel coronavirus. This deadly virus raised concern and unsettled the entire human civilization nationally and globally. There has been the emergence of more than 30 infectious diseases over the past three decades, due to changes in human behavior and environmental factors. Factors such as over-population, political instability, increased mobilization, urbanization and climate change encourage spread of pathogens. (Nkengasong, J., 2020).

In December 2019, symptoms similar to pneumonia were seen in people in Wuhan city, China. The virus spread took place in seafood market in Wuhan city, Hubei Province of China. On 30th January 2020, WHO declared COVID-19 as a "public health emergency of international concern". But till then, this coronavirus had spread to different parts of the world affecting about 66 countries through migration of infected passengers from China. Then, reports started coming about confirmed cases from many countries without direct relation to Wuhan. And on 11th March 2020, WHO characterized COVID-19 as a "pandemic". **(**World Health Organisation, 2020, June 29).

As of 17th March 2020, 179,112 cases and 7,426 deaths caused due to COVID-19 worldwide have been reported to WHO. (World Health Organization, 17 March 2020). And as of 1st July 2020, it has caused 10,538,577 cases and 512,689 deaths worldwide.

It is not the first outbreak that has struck us, when least prepared. There have been many outbreaks in India alone in the 21st century, raising international concerns.

Table 1:Outbreaks in 21st century in India

S.No	Pandemic	Year	Virus	REMARKS
1	Plague of Northern India	2002	*Yersinia pestis*	Case-fatality ratio- 25% 16 cases with 4 deaths
2	Dengue Epidemic	2003	DENV-3 and 2	mortality rate 3% 12,754 cases and 215 deaths.
3	SARS Epidemic	2003	SARS -CoV	3 probable and 10 suspect cases
4	Meningococcal Meningitis Epidemic	2005	Neisseria meningitides serogroup A	55 cases Mortality rate was 14.6%
5	Chikungunya Outbreak	2006	*Aedes aegypti*	3.4 million cases 2,944 deaths
6	Dengue Outbreak	2006	DHF/ DSS	10,344 cases and 162 deaths
7	Gujarat Jaundice epidemic	2009	Hepatitis B	125 cases with 49 deaths
8	H1N1 Flu Pandemic	2009	H1N1 virus	10193 deaths with 1035 deaths
9	Odisha Jaundice Epidemic	2014	Hepatitis E and A virus	About 3966 cases and 36 deaths
10	Indian Swine Flu Outbreak	2015	H1N1 virus	33761 cases with 20135 deaths
11	Nipah Outbreak	2018	Nipah virus	19 cases with 17 deaths
12	COVID-19 Outbreak	2019	SARS-CoV-2	585,493 cases with 17400 deaths

In this paper, we look at the SARS outbreak of 2002-04, that affected the whole world and is a relative of the current pandemic. Along with it we may also learn from the Dengue outbreak of 2006 and the H1N1 swine flu pandemic that emerged in 2009 and then again in 2015.

The SARS outbreak of 2002-04, the first epidemic of 21st century, was caused by *Severe Acute Respiratory Syndrome Coronavirus* (SARS-CoV or SARS-CoV-1). On 16th November 2002, in the Foshan city of Guangdong province of China, this outbreak was identified,. By March 2003, it spread to Hong Kong and Beijing, making the latter an epicenter of SARS outbreak. By the end of epidemic, SARS cases were reported by 32 countries. (Feng, D et al 2009). About 8422 cases and 916 fatalities were reported, from 1st November 2002 to 7th August 2003. India reported three “probable cases” and

10 “suspect cases”. (World Health Organization, 2003). With incubation period of upto 10 days, this virus was transmitted worldwide by air travel, mostly showing no symptoms. (Chan-Yeung, M., 2003)

The Dengue outbreak of 2006 was caused due to dengue viruses transmitted by *Aedes* mosquitoes, which can vary from infection with no symptoms or low fever to severe Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). (Gubler & D. J., 1998). Dengue is known to be prevalent in more than 100 countries, and is known to be responsible for about 50 million infections annually.*(Chakravarti A, et al 2012).* The 1st case of dengue was reported in 1945 and since then there have been many outbreaks of dengue. In Delhi many dengue cases are reported each year, the first outbreak being reported in 1967, thereafter in the years 1996, 2003, 2005 and 2006.(Siddiqui, O., et al 2016). In August 2006, dengue fever struck India again along with chikungunya fever. By end of November 2006, about 10,344 cases and 162 deaths due to dengue (DHF/ DSS) had been reported. (Singh, B. 2007). In 2015, the MoHFW reported about 21,000 new dengue infections.(Bagcchi, S. 2015).

Then came the H1N1 pandemic in 2009 caused by a new strain of Influenza-A virus that led to varying degree of respiratory infections ranging from mild flu to severe and life-threatening pneumonia, bronchitis, acute respiratory distress syndrome, and even death. (Khanna, et al 2008). H1N1 was first reported from Mexico and USA in April 2009 and soon expanded globally. (Sardar, J. C.,et al 2016). In India, the first case was identified on 16th May 2009, in Hyderabad.(Kshatriya, et al 2018). Between 2009-10, around 18,300 deaths had taken place across 74 countries worldwide. (Cheng et al, 2012). The International Health Regulations (IHR) of WHO declared Influenza-H1N1, a seasonal strain on 10th August 2010.(Al Hajjar, S., et al 2010). Last resurgence of H1N1 was observed in India between December 2014 to March 2015 that caused 30000 cases and 2000 deaths countrywide. (Mishra, B. 2015).

HISTORY AND TIMELINE

SARS

On 16th November, 2002 the SARS outbreak of 2002-04, was identified in Foshan city of Guangdong province, China. It was caused by *Severe Acute Respiratory Syndrome Coronavirus* (SARS-CoV). By March,2003, it had spread to Hong Kong and Beijing, making the latter an epicenter of SARS outbreak. By the end of epidemic, SARS cases were reported by 32 countries.(Feng, D.et al ,2009)

SARS quickly spread from mainland China to several countries accounting for numerous deaths across the globe. The most affected region after China was Hong Kong, followed by Taiwan and then Canada.

Table 2:Total cases, deaths and CFR in affected regions

Areas	Total	Number of deaths	CFR (%)
Canada	251	41	17%
China	5327	349	7%
Hong Kong	1755	300	17%
Taiwan	665	180	27%
India	3	0	0%
Viet Nam	63	5	8%

Source: World Health Organization, 2003

About 8422 cases and 916 fatalities were reported worldwide, from 1st November 2002 to 7th August 2003. India remained largely unaffected by SARS outbreak, with only three "probable cases"- from West Bengal, Karnataka and Gujarat. There were ten suspected cases- 3 from Karnataka, 2 from Maharashtra, and 1 each from Delhi, Tamil Nadu, Chhattisgarh and Rajasthan. Only 1 'probable case' had pneumonia. The other 2 'probable cases', who initially were only 'suspect cases', also tested positive PCR test and hence were considered as 'probable cases'. (Agarwal, et al 2003)

DENGUE

In spite of formation of NVBDCP in India, there have been continuous outbreaks of vector borne diseases. Since 1996 there have been continuous periodic surges in number of cases, as per MoHFW. There was a re-emergence of mosquito borne diseases in India in 2006; dengue fever struck India again along with chikungunya fever in August 2006.

Delhi is endemic for Dengue virus since long and still remains so due to the high immigration of international passengers and the increased breeding of *Aedes aegypti* .The outbreak of 2006 started in August and was at its peak in October. An estimated 10,344 cases and 162 deaths had taken place by November 2006.

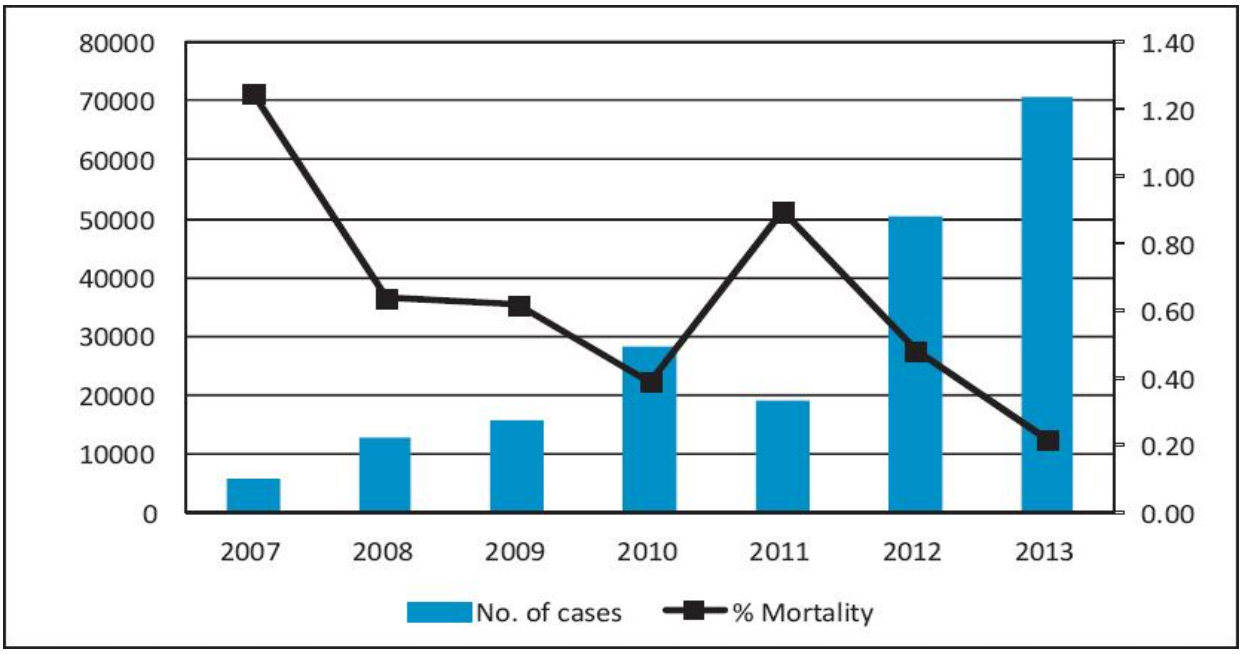
In 2010, 28,292 cases and 110 deaths have been reported. Delhi suffered with about 15000 confirmed cases and upto 60 deaths in 2015. (Cecilia, D. 2014). In 2015, most cases were reported in New Delhi followed by Punjab, Haryana, West Bengal, Gujarat, Karnataka, Maharashtra, and other states. (Mukherjee, S.,2017).

Table 3:Dengue cases and deaths in India from 2012-19

YEAR	CASES	DEATHS
2012	50,222	242
2013	75,808	193
2014	33,320	86
2015	99913	220
2016	129166	245
2017	188401	325
2018	101192	172
2019(till Nov.)	136422	132

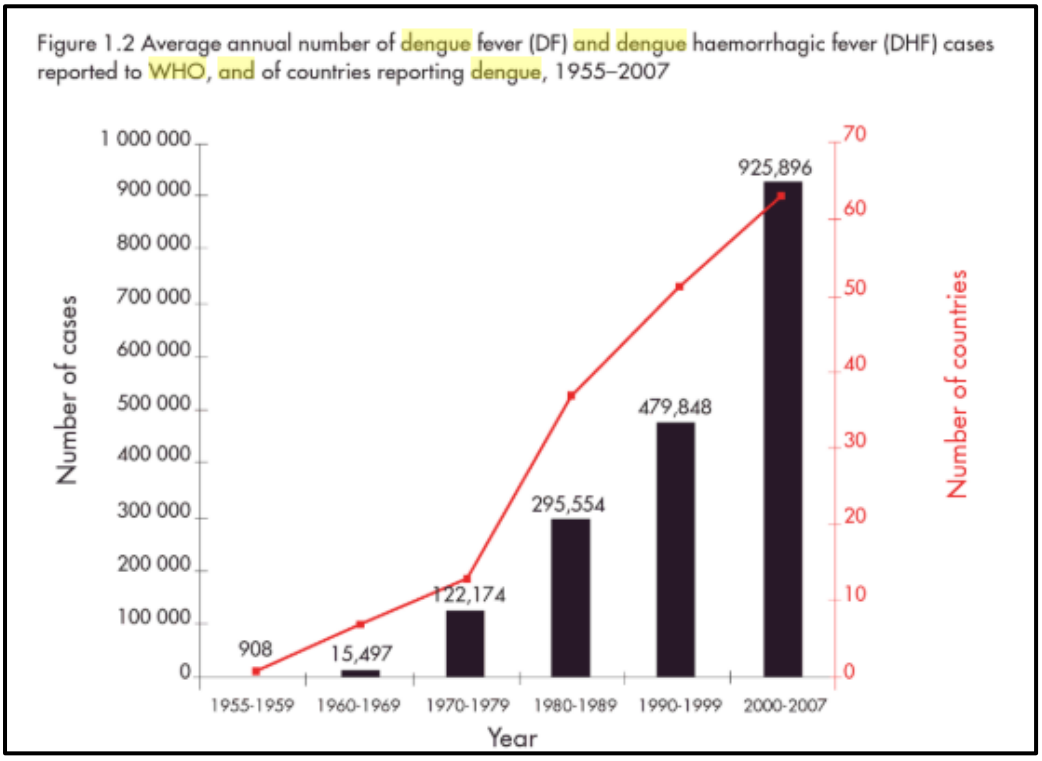
Source: Ministry of Health & Family Welfare-Government of India. (2020).

Figure 1: Total dengue cases reported to NVBDCP and mortality rate in India, 2007–2013.



Source: Cecilia, D.,2014

Figure 2: Average annual number of Dengue cases as reported to WHO, 1955-2007



Source: World Health Organization. (2019).

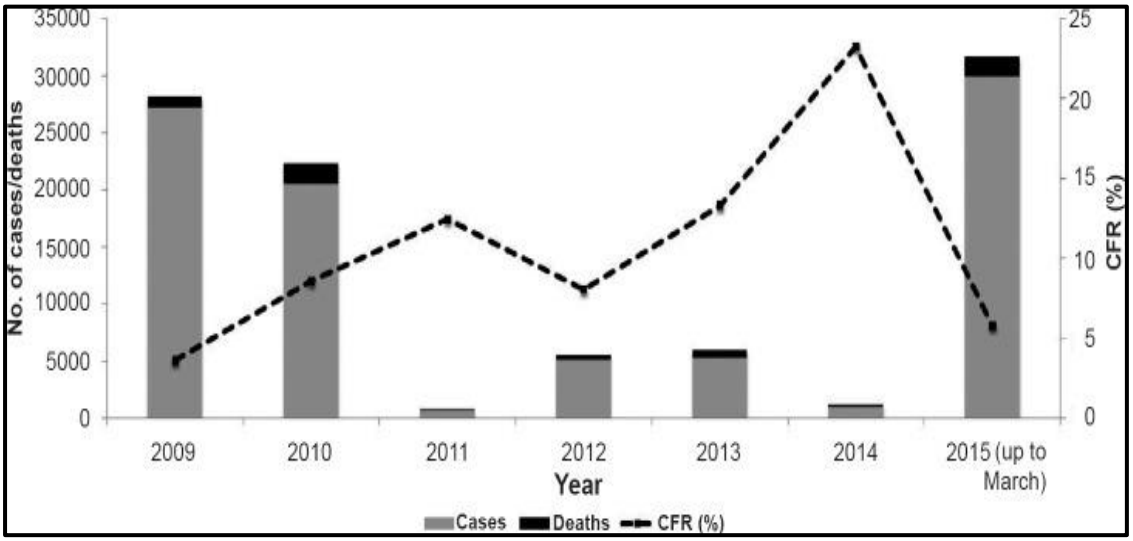
SWINE FLU

The first flu pandemic was known as "Spanish flu" and it originated in 1918 and killed approximately 50 million people globally. The second flu pandemic (Asian flu) originated in 1957 and the third flu pandemic (Hong Kong flu) in 1968, both causing about two million fatalities.(Sharma, et al 2015)

The "Swine flu" H1N1 began in May 2009 in Mexico and spread globally by 11th July, 2009. On 10th August 2010, with about 18,449 deaths by end of the August, the pandemic was declared to end. (Mishra et al 2015). During the 2009 pandemic, India reported 27,236 cases and 981 deaths. In 2010, the WHO announced that Swine flu will continue as seasonal influenza virus.(World Health Organisation, 2010)

As per the data from the MoHFW, India reported more than 62,000 laboratory confirmed cases with nearly 5000 deaths, from 2010-15. On 28th March, 2015, a total of 30,000 cases and 2000 deaths were reported countrywide. Rajasthan and Gujarat reported most number of confirmed cases of 4,549 and 3,107 and 214 and 2,017 deaths respectively.(Murhekar, et al 2016). Although the H1N1 outbreak was declared over by May 2015, India still witnesses cases on seasonal bases due to weakened healthcare system.(Upadhyay, A., 2020)

Figure 3: Reported H1N1 cases, deaths and CFR, 2009-2015



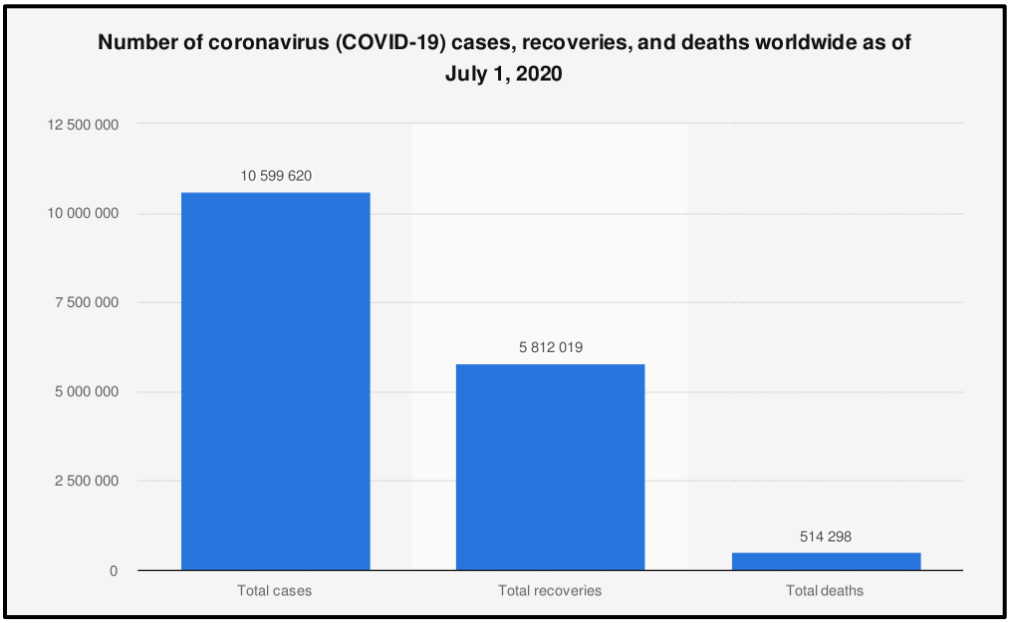
Source: (Murhekar, 2016)

COVID-19

Coronavirus Disease of 2019 was first identified in Wuhan city of Hubei province in China in December 2019. The first case turned up in Hubei on 17th November 2019. WHO declared COVID-19 to be a "public health emergency of international concern", on 30th January, 2020. And on 11th March 2020, WHO characterized COVID-19 as a "pandemic". (World Health Organisation, 2020, June 29). As of 1st July 2020, 10,538,577 cases have been reported, resulting in 512,689 deaths and 5,395,571 recoveries across 188 countries and territories. (John Hopkins University, 2020).

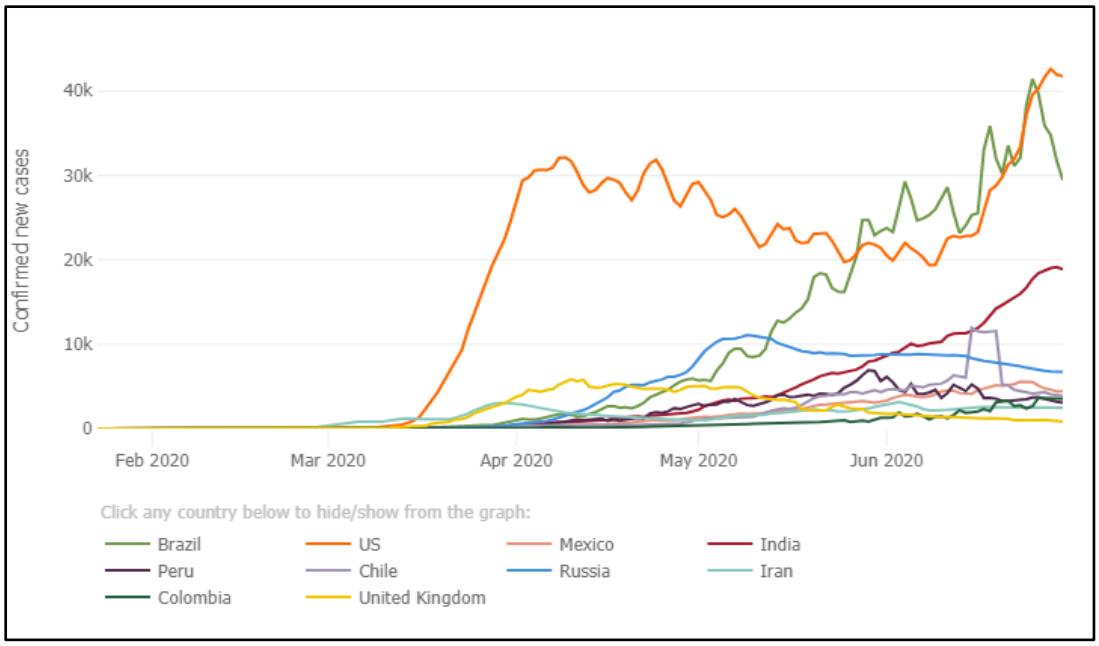
In India, the first case of COVID-19, was reported, in Thrissur, Kerala of a student who came home from Wuhan University, China on 30th January 2020. (Rawat & Mukesh, 2020).As of 1st July 2020, the MoHFW has confirmed a total of 585,493 cases, 17400 deaths and 347,979 recoveries (including 1 migration) in the country. India currently has the fourth highest confirmed cases after United States, Brazil and Russia.

Figure 4:Total COVID-19 cases, recoveries an deaths worldwide as of 1st July,2020



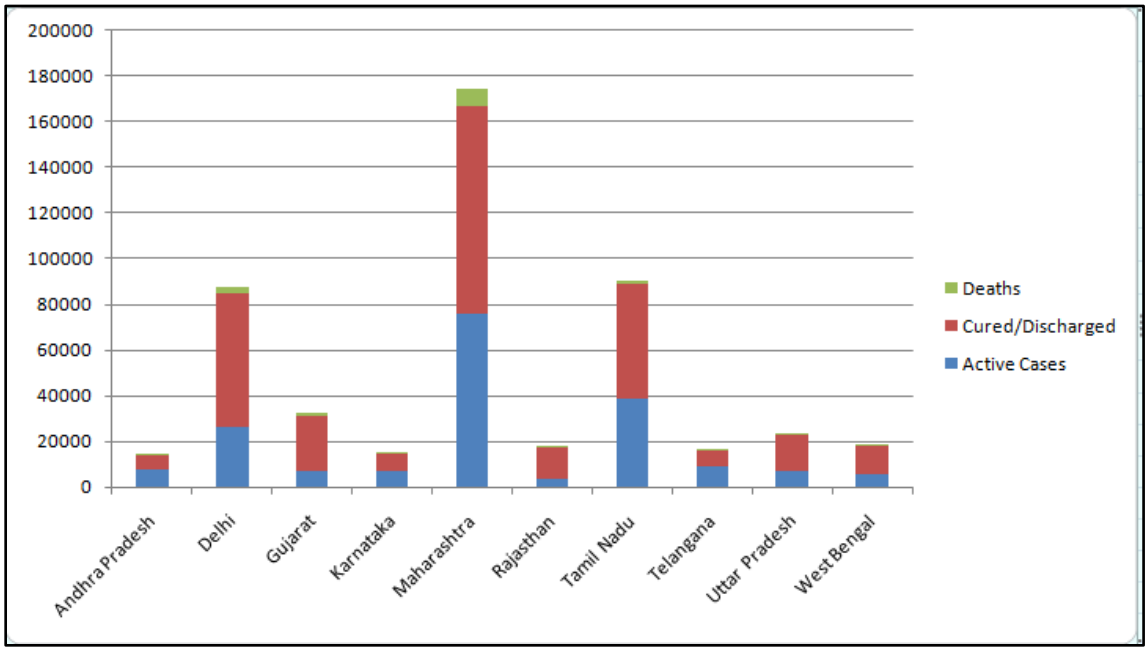
Source: (John Hopkins University, 2020)

Figure 5:Daily new confirmed cases as on 1st July,2020



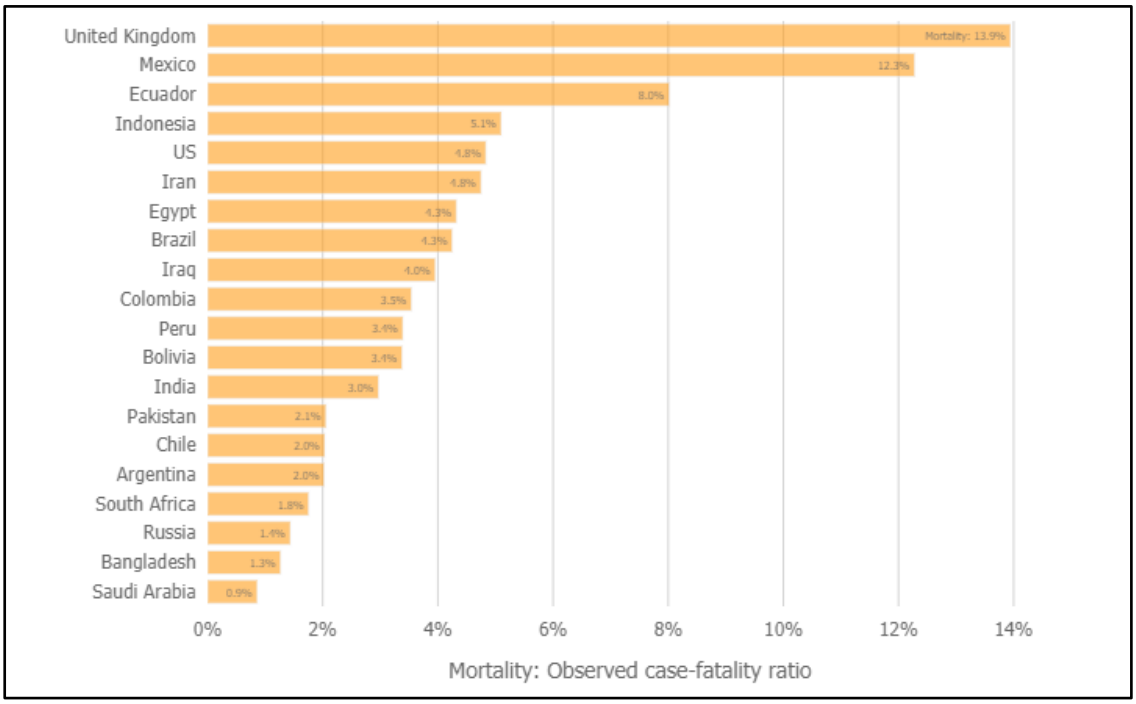
Source: (John Hopkins University, 2020)

Figure 6:Top 10 states with total cases, deaths and recoveries as of 1st July,2020



Source: Ministry of Health & Family Welfare-Government of India. (2020).

Figure 7: Observed case-fatality ratio worldwide as of 1st July,2020



Source: (John Hopkins University, 2020)

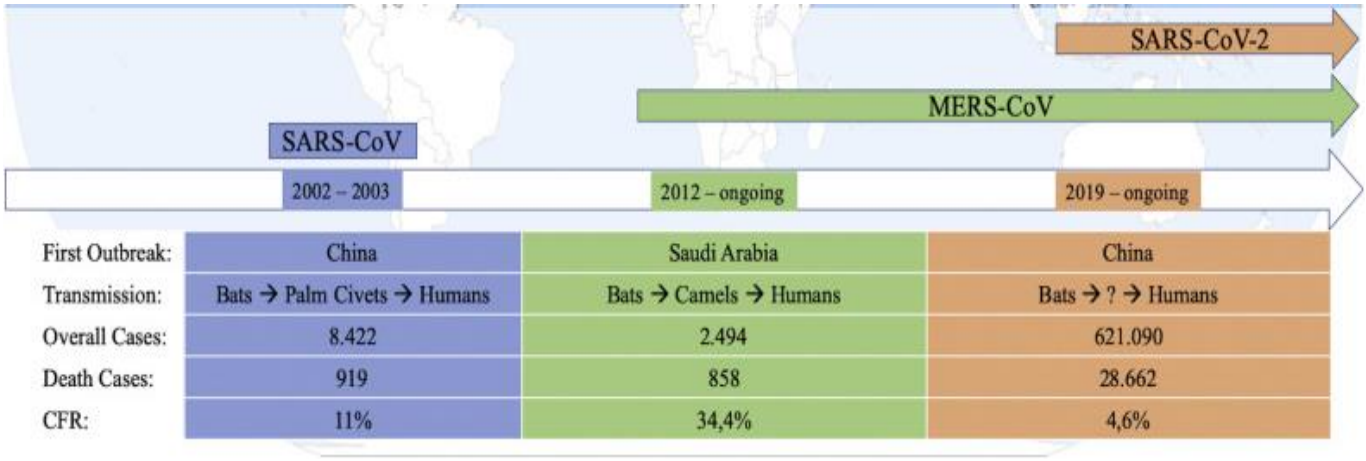
SPREAD AND TRANSMISSION

SARS

The SARS outbreak of 2002 was caused due to Coronaviruses that belong to family *Coronaviridae* and are zoonotic pathogens.(Habibzadeh, P., et al 2020). They have spiked projections on their surface that gives it a crown-like appearance hence its name. Four corona viruses, namely HKU1, NL63, 229E and OC43 are present in humans, and are known to cause mild respiratory illness. (Singhal and T., 2020). Other 3 subtypes SARS-CoV, MERS-CoV) and the novel Coronavirus caused the SARS 2002 outbreak, MERS 2012 outbreak and COVID-19 pandemic, respectively.

SARS was known to spread through droplets and close contact; also through contaminated skin, secretions and excrete of patients were also considered modes of transmission. (Brida, et al 2020).

Figure 8: Coronavirus pandemics



First Outbreak:	China	Saudi Arabia	China
Transmission:	Bats → Palm Civets → Humans	Bats → Camels → Humans	Bats → ? → Humans
Overall Cases:	8.422	2.494	621.090
Death Cases:	919	858	28.662
CFR:	11%	34,4%	4,6%

Source: (Brida, 2020)

DENGUE

Dengue viruses belong to the genus *Flavivirus* of family *Flaviviridae*. They are mosquito-borne and *Aedes aegypti*, a female day-biting domestic mosquito is the principal vector. (Bharaj, et al 2008). These mosquitoes breed from dawn to dusk, both indoors and outdoors and prosper in areas with still water which includes puddles, containers, water tanks etc.

Dengue illnesses can be due to any of the 4 related viruses; DENV-1, DENV-2, DENV-3 or DENV-4. Infection with any of these may cause Dengue fever, but sometimes may lead to severe Dengue Hemorrhagic Fever and then to Dengue Shock Syndrome. (Bharaj, et al 2008).

Factors like uncontrolled population expansion and urbanization, increased air travel, lack of effective health intervention and deteriorated heath infrastructure are responsible for resurgence of dengue fever. (Chaturvedi, et al 2008).

SWINE FLU

Human influenza viruses belong to 3 types, A,B and C. Influenza A that of the *Orthomyxoviridae* family is a single stranded, negative sense RNA genome that causes acute respiratory illness in humans. (Sharma, et al 2015).

The Asian flu of 1957 (H2N2) outbreak transpired through gene-reassortment of human H1N1 and avian H2N2 virus. Likewise, the Hong Kong (H3N2) outbreak was due to human-adapted H2N2 virus. The 2009 H1N1 outbreak also emerged due to gene-reassortment between the avian, human, and swine influenza viruses. (Tharakaraman, et al 2015)

India is the 7th largest country in the world and any contagious disease may spread very quickly due to increased migration between cities every day. (Tosh, et al 2010) The Swine flu is passed from person-to-person, by inhalation of the virus or by coming in contact with contaminated surfaces followed by touching the mouth or nose. Nasopharyngeal droplets shed by infected people are suspended into air during coughing, sneezing or talking. (Tosh, et al 2010). Transmission can also occur through exposure to fomites that may be infected with respiratory or gastrointestinal matter. (Mukherjee, et al 2015). People working in close proximity to poultry and swine are at increased risk of zoonotic infection. (Gray, et al 2009)

COVID-19

Coronaviruses (CoVs) of family *Coronaviridae* , produce diseases that range from common cold to fatal illness. (Dhama, et al 2020). The virus causing COVID-19 is of the same family as SARS-CoV, and is named SARS-CoV-2 and is inferred through genomic analysis that the latter is phylogenetically related to the former.

SARS-CoV-2 virus is infectious and can be spread by close contact with an infected person through coughing, sneezing or respiratory droplets (Chakraborty, et al 2020).Transmission can occur from infected mothers to the newborns or even through the conjunctiva.(Lu, et al 2020)

CLINICAL FEATURES AND EPIDEMIOLOGY

SARS

The typical incubation period of SARS lasts from 2-10 days but may last as long as 16 days.(Lowand D.E. 2004).This asymptomatic period is generally followed by ILI (Influenza-like-illness) that lasts around 3-7 days. The symptoms include fever, headache, malaise, chills, anorexia and fatigue, with rarely occurring diarrhea. (Mehta, et al 2007).

This is followed by the lower respiratory phase which is characterized by complaints of dry cough . Usually in second week of illness, this may progress to breathlessness and may lead to hypoxemia. In about 10-20% of cases, mechanical ventilation and tracheal intubation is required. (Sampathkumar, et al 2003). The recovery phase starts about 14-18 days from the onset of symptoms.

As of 7th August 2003, 8422 cases and 916 deaths were reported to the WHO, The overall mortality rate was 11%.(Agarwal, et al 2003). The mortality rate may be as high as 45% in patients aged > 60 years, especially people with preexisting co-morbidities. (Peiris, et al 2003).

Table 4:Clinical features of SARS

Symptom	% Occurrence
Persistent fever >38°C	99–100
Non-productive cough	57–75
Myalgia	45–61
Chills/rigor	15–73
Headache	20–56
Dyspnoea	40–42
Malaise	31–45
Nausea and vomiting	20–35
Diarrhoea	20–25

Source: (Hui, et al 2004).

DENGUE

Dengue infection though mostly symptomatic, can be asymptomatic in some cases. The person develops illness, 4-7 days after the bite. The patients develop high fever (39-40°C) with headache, nausea, vomiting, myalgia and retro-oribital pain.(Chaturvedi, et al 2008).

The illness can develop to DHF , characterized by severe abdominal pain, diarrhea, convulsions, and uncontrolled bleeding. The situation may progress to Dengue Shock Syndrome causing heart failure and shock, and also death. (IAMAT, 2020). Thrombocytopoenia and rising haematocrit due to plasma leakage can be detected before the onset of DSS along with abnormal temperature variations and circulatory disturbances lasting for 1-2 days.(Chaturvedi, et al 2008)

The extrinsic incubation period of Dengue virus is about 8–12 days indicating that, the transmission cycle can be blocked, if mosquito control is done before this period.(Barde, et al 2018)

SWINE FLU

Like other flu symptom, swine flu is also characterized by fever, chills, headache, arthralgia, fatigue, vomiting, myalgia, abdominal pain and diarrhea. The respiratory tract symptoms include cough, sore throat, irritated watering and reddened eyes and shortness of breath.

The incubation period in humans ranges from 1 to 7 days; more likely 1-4 days. The infectious period may last from a day before the onset of symptoms till 5-7 days after the onset of symptoms or until symptoms resolve. (Mukherjee, et al 2015).

Children <5 years old, people of age 65 years or above, children and adolescents receiving long-term aspirin therapy, pregnant women, adults and children with chronic disorders all are at high risk of infection.(Centers for Disease Control and Prevention,2019)

The Health Ministry conducted age and sex-wise analysis of H1N1 deaths. The analysis shows 17% deaths are in ages 18-30 while 12% deaths in 60+ age category. The analysis further stated that among the total deaths, 50.35% of them were females while 49.65% males. **(**PTI, 2015)

COVID 19

According to data obtained worldwide SARS-CoV-2 was found to be similar to SARS-CoV infection. According to Guan et al, the median age of the infected patients in their study was 47 years and about 58.2% of them were males.(Guan, et al 2020).

The most common clinical symptoms are: fever, cough, shortness of breath, which can progress to severe pneumonia with respiratory failure and septic shock.(Backer, et al 2020). Some patients also showed rhinorrhoea, pharyngalgia, and diarrhea. In about a week, dyspnea and hypoxemia, could advance to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes (MODS). Although all age groups are equally vulnerable to the viral infection, the older populations with co-morbidities are at higher risk.

The SARS-CoV-2 is a highly infectious virus. The incubation period is about 4-8 days post-infection. (Rabaan, et al 2020).The incubation period for COVID-19 remains comparable to SARS (2-7 days) , but it is longer than swine flu (1-4 days). (Chatterjee, et al 2020).

The overall case-fatality rate (CFR) was higher amongst patients with cardiovascular disease, chronic respiratory disease, diabetes, hypertension, and cancer. (Wu, Z., et al 2020). The R_0 for SARS-CoV-2 was reported to be 2.68 which is closely similar to the reports by the WHO and the Chinese Center for Disease Control (Rabaan, et al 2020).

PREVENTION AND CONTROL STRATEGIES

Over the last 3 decades, several outbreaks, such as the SARS outbreak of 2002, the H1N1 outbreak of 2009, and the Zika virus outbreak of 2015, caused great concern. These events showed the consequences of delayed response to outbreaks; illness and mortality of national populations including health workers, potential spread to other countries, and significant disruptions of travel and trade. They also highlighted the importance of surveillance and adequate response plan. (Heymann,2004).

SARS

Global Response

At a global level, front-line heath care workers were infected the most. It was realized that personal protective equipment (PPE) can prevent infection from SARS. This method is being used now also, for protection against Covid-19.(Dutta K Prabhash, 2020)

Concerned of the spread of SARS-CoV, WHO formed a SARS working group that comprised of eleven research laboratories worldwide for identification of the causative agent and development of diagnostic tests. The CDC also issued guidelines that were periodically updated.

SARS outbreak was the first time when the GOARN (Global Outbreak Alert and Response Network) set in 1997 by WHO, identified and responded to an outbreak. The WHO Global Influenza Surveillance Network was alerted, when the Canadian Global Public Health Intelligence Network (GPHIN) got reports of an outbreak in China, both the former and the latter being partners in GOARN. Another partner, the U.S. Global Emerging Infections Surveillance and Response System (GEIS), simultaneously, suspected Influenza B for the outbreak.

GOARN collected reports and details of cases from Chinese authorities and analysed them and connected the best in the field of science and healthcare electronically, to collect information about the cause of the outbreak.

This real time surveillance helped WHO from guidelines and recommend measures to health workers on management and protective measures to prevent further spread, and on 5th July, 2003, the SARS outbreak came to an end. (Stöhr, K. 2003)

Indian response

With the alarming speed SARS spread in some countries and with no vaccine in hand, India was concerned about community spread of the virus. India was able to contain the virus, by surveillance of international passengers migrating to India. In early 2003, about 1.20 lakh per week international passengers migrated to India as compared to about 6 lakh per week in January- March 2020, that helped contained and monitor the virus, as compared to COVID -19. (Dutta K Prabhash, 2020).The passengers were screened for SARS and those with illness were hospitalized and healthy passengers were

recommended to self-quarantine for 10 days and report, if symptoms appear. This approach is very similar to the one used now, for screening of Covid-19.

Standard precautions such as hand washing and minimal contact were made necessary. For all healthcare workers, use of gloves, gowns and masks were also recommended.(Mehta, et al 2007).

IDSP (Integrated Disease Surveillance Programme) was established in India in November, 2004 with the assistance of World Bank for the detection and surveillance of diseases quickly. Information technology network was launched with the assistance of National Informatics Centre and Indian Space Research Organization (ISRO) for tasks of data entry, video conferencing, and outbreak discussions. District laboratories were also strengthened for surveillance of infectious diseases. (Mukherjee, S. 2017). Also, The National surveillance programme for communicable diseases (NSPCD) was expanded from 5 to 100 districts

DENGUE

Global Response

In the case of dengue outbreak in 2006, WHO deployed a team from its headquarters in February-March 2006 to the South-West Indian ocean, to analyze the control measures used and form a plan for surveillance and control of the virus along with national authorities. (WHO. 2015). In October 2006, Dengue Scientific Working Group was formed that consisted of 60 experts from 20 countries, to review existing knowledge and establish strategy for future research for the aim of improvement of dengue treatment, prevention and control. (Farrar, J et al 2007)

Indian Response

India deployed a multidisciplinary team from 13th to 17th February to help local healthcare authorities, in strengthening of virus surveillance, control of vector, clinical management of cases and social mobilization. No travel bans were implemented or trade restricted, however individuals were recommended to protect themselves by using insect repellents and wearing clothes that minimize skin exposure. (WHO, 2015).

There was a significant need in improvement of health infrastructure in slums, which may help in prevention of vector breeding. Despite of various awareness campaigns, a targeted approach was required for mosquito net promotion and increasing utilization of public health services.(Podder, 2019).

SWINE FLU

Global Response

Public health emergency was declared by 25th April, 2009 and accordingly the nations took preventive actions against the virus. (Sharma, et al 2015).WHO recommended periodic monitoring and surveillance of swine flu cases to prevent another outbreak.

Acknowledging the importance of Herd immunity plays, many countries adopted the strategy of mass vaccination for Swine flu pandemic which resulted in high seropositivity and in turn lowered the rate of infection during the next wave. CDC had also released a "Flu vaccination pledge for 2014-2015". On 26th February 2015, Advisory Committee on Immunization Practices (ACIP) recommended an annual influenza vaccination, which could have restricted the severity of resurgent wave of H1N1.(Mishra, B. 2015).

WHO recommended vaccination for high-risk groups, and also for healthcare personnel operating in close contact to influenza patients. (Mukherjee, et al 2015).

India's response

The measures developed by the GoI aimed at preventing the entry of virus, to curb its spread in urban areas and to reduce mortality. GOI issued guidelines suggesting social distancing, due to limited treatment options. From midst of April, all international passengers were screened at 18 international airports and people with ILI were sent for testing.(Sharma, et al 2015).

Ministry of Heath launched various public awareness campaigns through visual and print media. It also supplied required drugs to affected areas. Diagnostic kits of H1N1 were ordered and so were additional stocks of oseltamivir and N95 masks. Due to increased no. of cases, there was a shortage in medicine for swine flu, Oseltamivir and there were limited pharmacies licensed to sell the drugs.(Upadhyay, A. 2020). CDSCO (Central Drug Standard Control Organization) stepped in and monitored various centers in the nation for the availability of diagnostic kits, drugs and vaccines. Drug controllers of the states were also recommended to provide help wherever required. (Sharma, et al 2015).

Vaccination was recommended for health-care personnel and staff who came in contact with influenza patients, laboratory personnel and people of "Rapid response team" who were involved in investigating the outbreak.(Mishra, B. 2015). MoHFW set some guidelines for categorization of the symptomatic patients as follows:

Table 5: Categorization of symptomatic patients

Category-A.	mild symptoms such as cough, fever and sore throat
Category-B.	symptoms of category-A + severe sore throat and high fever + high risk group with symptoms of category-A They are recommended for Tamiflu.
Category-C	symptoms of category-A and B + severe health complications. Recommended for immediate hospitalization and treatment.

(Khan, 2015)

People who believed to have been infected were being told to quarantine themselves, maintain proper hygiene, cover their mouth when sneezing or coughing, avoiding crowds or endangering members of family. (Upadhyay, A. 2020)

COVID

Global response

Quarantining along with measures to maintain personal hygiene, ban on mass gatherings and events, closure of school and workplace, and travel restrictions were earliest measures taken during the COVID-19 outbreak to help curb the spread. (Stein, R. A. 2020).

Based on previous knowledge, the WHO recommended precautionary actions such as avoiding close contact with patients, regular hand washing, maintaining cough etiquette, and avoiding unprotected contact with farm or wild animals etc.

Anti-viral drugs such as Chloroquine and hydroxychloroquine are being used for mass sanitization as they have been found to be effective against COVID-19. China has temporarily banned wildlife trade of animals as 60% of emerging transmissible infections start from animals, and 70% of such from wild animals. (Chakraborty et al 2020).

Another intervention that was implemented was thermal screening at some airports, which would be globally most impactful if exit screening was also carried out.

Real-time statistics about the pandemic are available online by a virus tracker developed by researchers at Johns Hopkins University, based on information collected from the WHO, CDC, the European CDC, China CDC (CCDC), China's National Health Commission (NHC), and DXY. (Stein, R. A. 2020).

China enforced "round the clock closed management" system, alert, France announced "nationwide ban on gatherings," Italy declared the "red zone" and USA implemented "containment areas" are just some examples of how countries are tackling COVID-19.(Gudi, et al 2020).

Indian response

MoHFW initially advised to refrain travelling to China and quarantine of people coming from there. Those who returned from Wuhan, China, after 15th January, 2020 were to be tested. Thermal entry screening was established at 21 airports across India. (Mandal, et al 2020).

On 24th March, PM Modi ordered complete lockdown for 21 days. By 6th April, doubling rate of COVID-19 cases slowed from 3 days to 6 days. This lockdown was extended till 3rd May, on 14th April. Following this were two-week extensions from 3rd and 17th May with gradual relaxations. On 17th May, the lockdown was extended till 31st May all over India. (Banerjea, A, 2020). Starting from 1st June, GoI started "*unlocking*" the nation in three phases, and divided the country into 3 zones.

Table 6: Division of zones

Red zone (Hotspots)	high doubling rate + high number of active cases
Orange zone (Non-hotspots)	fewer cases
Green zone	without confirmed cases / without new cases in last 21 days

PTI. (2020)

The Ministry of Electronics and Information Technology also launched **Aarogya Setu** which is a smart-phone application to curb the spread of COVID-19 pandemic.

LESSONS LEARNT

1. **Surveillance and reporting:** Regulation of infectious diseases is dependent on a credible response framework which in turn depends on reliable surveillance system. Surveillance is very essential as it provides timely information on new cases, the source, and the contacts. (Parashar, et al 2004). An effective nationwide data reporting system is an essential need for a public health system. (Feng, D, et al 2009). It is very essential to enhance surveillance globally, more so in the developing regions of the world. Unique patient identifiers can be used to record case information along with web-based systems, in which the information is fed regularly on one centralized database. (Anderson, et al 2004).

2. **Adequate monitoring system:** A worldwide monitoring system with wide-spread network is very crucial for early alerts during the time of an outbreak. Lack of an efficient monitoring set-up was one of the reasons of failure to control the SARS outbreak.(Zhong, N. S., et al 2003). Contact tracing and monitoring travel at entry and exit ports is very crucial as they provide an opportunity to isolate or quarantine contacts and also gives information to estimate distributions patterns, and modes of transmission.(Anderson, et al 2004)

3. **Strengthening Of Public Health Systems:** The strengthening of health systems should be the utmost priority as a weakened healthcare system can aid the amplification and spread of infections. The surge in number of SARS patients exposed the weakened healthcare system of China with pressure on health services, requirement of facilities for isolation, and the use of mass screening, contact tracing, active surveillance of contacts and enforced quarantine. (Heymann, et al 2004). Realizing the importance of herd immunity in containing the subsequent waves of pandemic. Many countries adopted mass vaccination strategies for H1N1 2009 resulting in high seropositivity and lowered rate of infection during the next pandemic wave.(Mishra, B. 2015)

For COVID-19, the hospitals in USA implemented disaster-readiness plans; they stocked up equipment and PPE kits. China also built 2 hospitals with around 30 ICUs and numerous beds in just a few days to fight the rapid-spread of virus. (Gudi, et al 2020)

4. **Co-ordination among systems:** Co-ordination and collaboration are very crucial in control of infectious diseases. China proven to control infectious diseases in past, failed to control the SARS outbreak because of absence of internal collaboration. Co-ordination and collaboration at every level is very essential for the containment of any disease. (Feng, D., et al 2009).
   At the time of SARS, scientists together reported the identity of SARS virus and then complete sequence of its RNA. This a great example of International collaboration Through this collaboration, scientists all around the world were able to discuss which treatments and strategies were effective, the modes of transmission of SARS and understand the clinical spectrum of disease. (Heymann, 2004). The communication of an outbreak is very crucial for its containment. Strong communication between health authorities of neighboring regions is required in such times to alert health personnel of a potential issue. (Chan-Yeung, et al 2003)

5. **Non-pharmaceutical interventions:** In the absence of vaccines, non-pharmaceutical interventions play a huge part in elimination the spread of infection and containing the outbreak. The SARS outbreak was mostly contained because of the relative inefficient SARS-CoV transmission which was possible due to quarantining.(Rabaan, et al 2020).
   The scare of coronavirus in people has significantly led them towards maintaining personal hygiene, which could help decrease the spread. Precautions like maintaining hygiene, maintaining cough etiquette, use of sanitizers and face masks, avoiding touching mouth, nose and eyes, and social-distancing techniques are being promoted and followed to a remarkable extent.
   Social distancing is a crucial practice during outbreaks to prevent the spread of infection. Alas, social distancing was not practiced in China until too late resulting in rapid transmission. The implementation of non-pharmaceutical interventions such as social-distancing helped flatten the curve. Similarly, South Korea by adopting measures like social distancing, is now significantly flattening its curve.(Gudi, et al 2020)

6. **Vaccine development and research:** It is comforting to say that science has reached a point where pathogen can be quickly identified and its biology made known, and global health protected, in times of an outbreak. As in the case of COVID-19, modern science can identified and sequenced the new virus within days. (Stein, et al 2020).
   Synthetic approaches or alternative vaccine formats, can be used to lessen the time taken from the advent of a new strain to the production of its vaccine. The use of antibody to treat influenza has known to be successful in absence of a vaccination strategy.
   Timely access to both antivirals and vaccines is crucial for halting an epidemic outbreak. It should be a priority to develop infrastructure for production, storage and distribution of appropriate countermeasures at the time of need. Also, development of a universal vaccine can be very helpful in mitigating the risk

of high mortality.(Tharakaraman, et al 2015). In the 2009 H1N1 pandemic, the vaccine manufacturers and public health authorities worked relentlessly for the previous decade to produce large quantities of vaccines safely when and as the need the arose. This record level of preparedness allowed for safely combating the H1N1 pandemic, with the vaccine approved after just 3 months into the pandemic. (Abelin, A., et al 2011).

7. **Research and Development:** The most important and initial task to curb a pandemic is to find its roots, the agent that led to such mortality and morbidity and to establish its novelty. Information on novelty can be easily gathered for known pathogens from the sequence data in the public databases. The SARS pandemic is an example of effective international collaboration that resulted in the complete genome sequence of the virus being available so early in the pandemic, which played a huge role in its containment. (Anderson, et al 2004).

   Studies on viruses enable the researchers to not only track their evolution but also predict future potential outbreaks. These studies can then be used to prevent further spread during an outbreak. Open-access databases such as "National Center for Biotechnology Information (NCBI) Influenza Virus Resource", Influenza Research Database, and EpiFlu facilitate the sharing of viral genome sequences and encourage collaborative research world over. The United States (38.4%), China (7.2%), United Kingdom (6.5%), and Singapore (6%) contribute to the majority of the deposited influenza sequences in the databases, whereas India lies on the 14th rank with less than 1.5% contribution. Further, only two sequences were deposited in 2014–2015 from India that shed light on poor surveillance. (Tharakaraman, et al 2015)

8. **Training Of Health Personnel:** Training and education of health personnel should be strengthened locally as inadequate training can result in absence of vital skills necessary for collection of data and its analysis. The plight of USA in the time SARS showed that the training of health personnel should be regular and timely.(Feng, D., 2009)

9. **Emerging and Re-Emerging Diseases**: in the past few decades, the emergence and resurgence of many infectious diseases, have threatened the health of the population. The contributory factors responsible for emergence and re-emergence are given below.

Figure 9: Factors responsible for emergence and re-emergence

The microbial agent	The human host	The human environment
Genetic adaptation and change	Human susceptibility to infection	Climate and weather
Poly-microbial diseases	Human demographics and behavior	Changing ecosystem
	International trade and travel	Economic development and land use
	Intent to harm (bioterrorism)	Technology and industry
	Occupational exposure	Lack of public health services
	Inappropriate use of antibiotics	Animal populations
		War and famine
		Lack of political will

Source: (Mukherjee, S. 2017)

EIDs have proved to be a global threat but some places are known as hotspots for EIDs such as countries related to the Indo-Gangetic Plain and the Mekong River Basin. Literature reveals that around 75% of the EIDs that have affected humankind over the past three decades were zoonotic in nature. (World Health Organization. 2011). Nipah virus (NiV), Crimean-Congo hemorrhagic fever (CCHF), and AI A (H5N1) are examples of diseases that have recently emerged.

In 2009, the India Global Disease Detection (GDD) Regional Center was established at India's NCDC, for the purpose of establishing the India Epidemic Intelligence Service and to work with local, regional, and global public health entities to better detect, identify, and contain EID threats.(Mukherjee et al 2017)

10. **Wildlife Trade:** The seafood market of Wuhan, China, was where it all began. China has temporarily banned wildlife markets where animals such as civet, bat, pangolin etc. are sold alive. 60% of transmissible emerging diseases originate from animals, out of which 70% in wild animals. (Chakraborty, et al 2020). This unrestricted wildlife trade increases the risks of new emerging viruses.
    putting a stop to the widespread use of exotic animals as food or traditional medicine and the practice of central slaughtering of livestock can decrease the transmission of viruses. (Chan-Yeung, et al 2003)

11. **Communication with the masses:** The promotion of public health measures to be undertaken, in the time of need is as crucial as their reinstatement. Timely information need to be provided to the masses to ensure cooperation. Various creative measures have been undertaken by the countries, to spread awareness about the pandemics, and the measures that need to be kept in mind. At the time of SARS outbreak, the South Korean government started the practice of alerts flashing on smart phone screens that updated the public on new infections in their area. Health authorities in Hong Kong also regularly update a map showing which buildings Covid-19 patients live in or last stayed at.

12. **Air travel:** The infectious diseases have a similarity of rapid global spread through air travel. The ease to reach any continent within a short time puts us at a disadvantage at times of such outbreaks as now. In 2013, the annual number of passengers exceeded 3 billion, and has been increasing since then.(Stein et al 2020). In January- March 2020, the number of international passengers was about 6 lakh per week that led to the rapid spread of COVID-19. For a significant impact on delaying the spread of virus, it is important to screen every passenger, also the asymptomatic ones. Entry screening or travel restrictions have proved to be beneficial in reducing the risk of outbreak in countries which have relatively low connectivity to China. (Mandal, et al 2020).

13. **Digital Technology And Health:** With the technological advancements on the rise, this year of 2020 has pushed the acceleration on digitalisation, speeding up the development and maturation of several digital technologies that can be applied to tackle major clinical problems and diseases. The IoT gave opportunities access data for monitoring of the COVID-19 pandemic to public-health agencies. Johns Hopkins University's Center for Systems Science and Engineering also developed real-time tracking map for COVID-19 cases worldwide. The big data also provided opportunities not only for analyzing viral activity through modeling studies but also provide assistance to healthcare policymakers to strengthen preparation for the pandemic. Many social-media platforms are being used to provide 'real-time' updates by healthcare agencies. (PR Newswire, 2020).

    AI and deep learning can be used to enhance the detection and diagnosis of COVID-19. An online medical 'chat-bot' that records patient's data can prevent unnecessary hospital consultations. Digital technology can act as a pioneer in the advancement of Healthcare systems. The concept of 'virtual clinics' set up with the help of tele-medicine consultations is on the rise. This would not just ensure standard clinical care to all patients but also reduce physical crowding into hospital premises.(Ting, 2020).

CONCLUSION

This year has been a struggle for the entire world with its fight with pandemic like COVID-19, which came unannounced. With weaken communication and collaboration between countries and increased migration patterns over the years, this virus spread rapidly to all parts of the world, affecting the millions of lives. Pandemics are inevitable as infectious diseases are bound to emerge or resurge every 20-40 years.

The world has braved many pandemics over the past centuries and will continue to do so with the help of certain precautionary and control measures. There is a lot that can be learnt from these past pandemics, about how nations were able to contain them and save lives. This knowledge is of utmost importance and can act as basics for the future. Effective surveillance and monitoring measures are the utmost priority in containment of infectious diseases. It is very crucial to maintain a collaborative approach towards such infectious diseases. COVID-19 has been a burden on already weakened health-care systems that need to strengthen for next outbreak. It has become really important to train healthcare professionals and to provide information to the masses. Steps such as proper hygiene, maintaining

healthy lifestyle, good food habits and ban on wildlife trade can go a long way. Also, this era of advent of digitalization can open new doors for the healthcare sector.

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Online Course by

John Hopkins University at Coursera

April 1, 2020- June 30,2020

INTRODUCTION TO SYSTEMATIC REVIEW AND META-ANALYSIS

A Report by

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Under the Guidance of

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MBA- Hospital and Health Management

2019-2021

COURSE DESCRIPTION

The course on "Introduction to Systematic Review and Meta-analysis" requires is a 6 week detailed course provided by the John Hopkins University. It introduces the basics of systematic reviews and meta-analysis of randomized clinical trials. This course also helps in the formulation of a credible research question, description of exclusion and inclusion criteria's, the collection and examination of the evidence, evaluation of bias and completion of meta-analysis. Students are able to take this course on their own pace, with flexible hours of study. The course was further divided in a span of 6 weeks.

- Week 1: Overview of basics and use of systematic review and meta-analysis.
- Week 2: Elements required for framing, refining, and scope of the research question.
- Week 3: About the pursuit of evidence, search strategy and assessment of the bias.
- Week 4: Minimizing different types of biases, transparent reporting, and interpretation of results.
- Week 5: Meta-analysis and the statistical approaches for meta-analysis.
- Week 6: Summarizes the key concepts with the submission to Peer Review Assignments

COURSE CONTENTS

This Course is provides complete knowledge of the basics of Systematic review and Meta-analysis which is imparted using various learning methodologies. These include:

1. VIDEO LECTURES: The video lectures were taken by the speaker directly addressing the participants or PowerPoint presentations to improve the understanding of the topic. All the videos need to be watched entirely to complete the course.
2. READINGS: Readings given in the modules helped in understanding the way of how a systematic review should be written. All the readings were to be marked to complete the course as well.
3. QUIZZES: Graded quizzes are an integral part of the course that helps in easy evaluation of understanding of the topics. The course included seven quizzes with a minimum passing percentage of 70%.
4. PEER REVIEW ASSIGNMENTS: Peer Reviews offers the answers of the participants to be reviewed by other participants taking the same course simultaneously. With two peer-review assignments, the minimum score of 70% is needed to pass both the assignments.
5. FIELD VIDEOS: Short videos were present throughout the course that had field interviews of experts sharing their experience about the application of systematic review.
6. GRADING POLICY: The final grade is calculated as follows
    i. Each quiz = 9% of the total grade. (9*7=63%)
    ii. Peer Review 1 = 15% of the total grade.
    iii. Peer Review 2 = 22% of the total grade.
7. COURSE CERTIFICATES: A completion certificate is offered after some monetary assistance and completion of all the assignments.

COURSE OBJECTIVES

The objectives of the course are as follows:

1. Describe the steps in conducting a systematic review
2. Develop an answerable question using the "Participants Interventions Comparisons Outcomes" (PICO) framework
3. Describe the process used to collect and extract data from reports of clinical trials
4. Describe methods to critically assess the risk of bias of clinical trials
5. Describe and interpret the results of meta-analyses

KEY LEARNINGS

WEEK 1

MODULE 1

I. Lecture 1A: Introduction to Systematic Reviews

A systematic review focuses on specific questions and uses explicit, pre-planned scientific methods to identify, select, appraise, and summarize similar but separate studies.

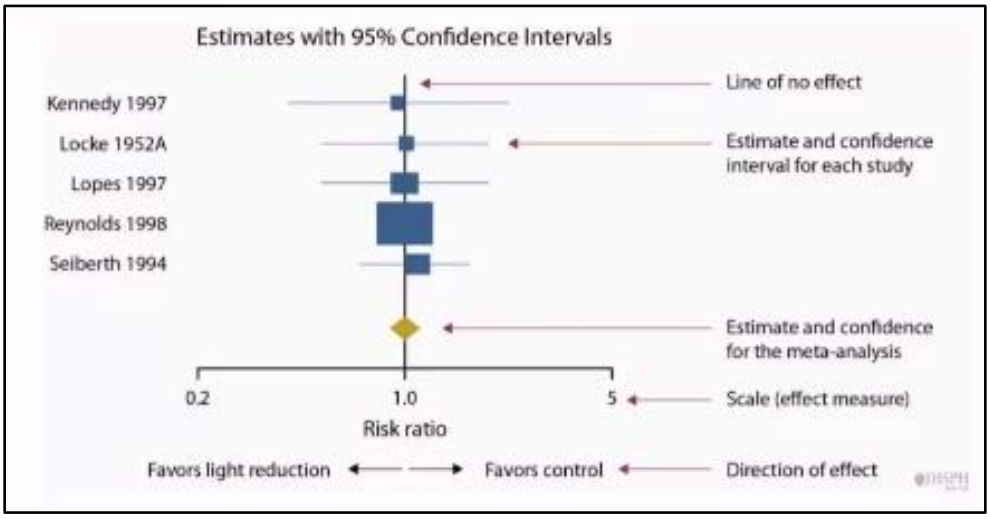
Steps of a systematic review:

1. Frame research question (PICO/PECO)
2. Develop search strategy
3. Develop protocol
4. Run search strategy in at least two decades
5. Retrieve and de-duplicate citations
6. Develop system for screening titles/abstracts and full textx
7. Screen titles/abstracts
8. Retrieve and screen full-texts
9. Develop forms for assessing 'risk of bias' and extracting data
10. Assess 'risk of bias' and extract data
11. Clean and manage data
12. Conduct qualitative synthesis
13. Conduct meta-analysis(if appropriate)
14. Write report of systematic review
15. Update systematic review.

II. Lecture 1B: Introduction to Meta-Analysis

Most meta-analysis are presented through a forest plot. Not all systematic reviews would have a meta-analysis.

Figure 10: Forest plot



Meta-Analysis can be useful in accessing **strength of evidence**. It helps to **combine the results quantitatively** and obtain a single summary result also to **investigate heterogeneity**, to examine reasons for different results among studies

III. Lecture 1C: "Producers and Users of Systematic Reviews"

Table 7:Producers and Users of Systematic Reviews

DONE BY	USED BY
Independent authors, investigators, researches, clinicians.	Individual doctors and the researchers,
Cochrane Collaboration	Patients and consumers,
Groups interested in policy, such as the professional societies, governments payers.	Guidelines producers.
Businesses like, Hayes and ECRI	Policy makers like purchasers, payers, and regulatory authorities.

Features of a systematic review: A systematic review facilitates efficient integration of information for rational decision making. It provides a clear and transparent process, and helps to demonstrate where effects of healthcare remain consistent, and where they vary. It also helps minimize bias and systematic errors in summarizing evidence. Meta-analysis can provide more precise estimates than

individual studies. And systematic reviews can be readily updated as needed with new information and new evidence. And they allow decisions based on the complete evidence.

WEEK 2

MODULE 2

IV. Lecture 2A: "Resources for How to Frame Your Question"

Formulating the topic requires:

- Confirming the need of a review.
- Development of an analytic framework
- Use of PICO format to articulate question.
- Stating rationale for each question, and
- Refining it

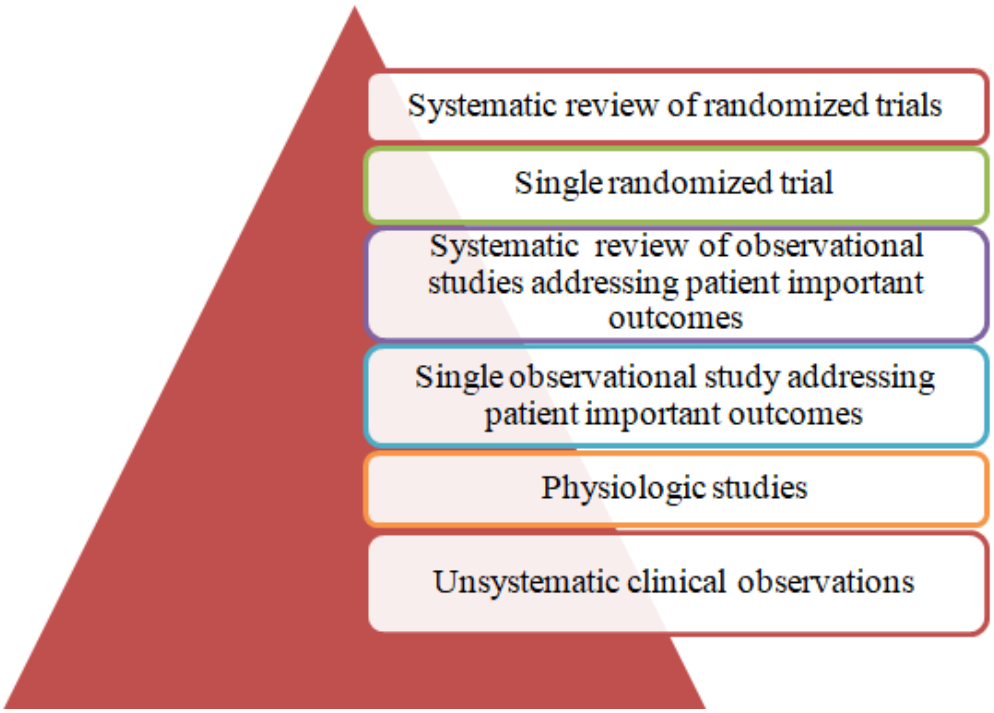
An important resource for refining or framing the question is the Cochrane handbook For Systematic Reviews of Interventions.

V. Lecture 2B: "Deciding the Type and Scope of Your Question"

Table 8:Types of Question

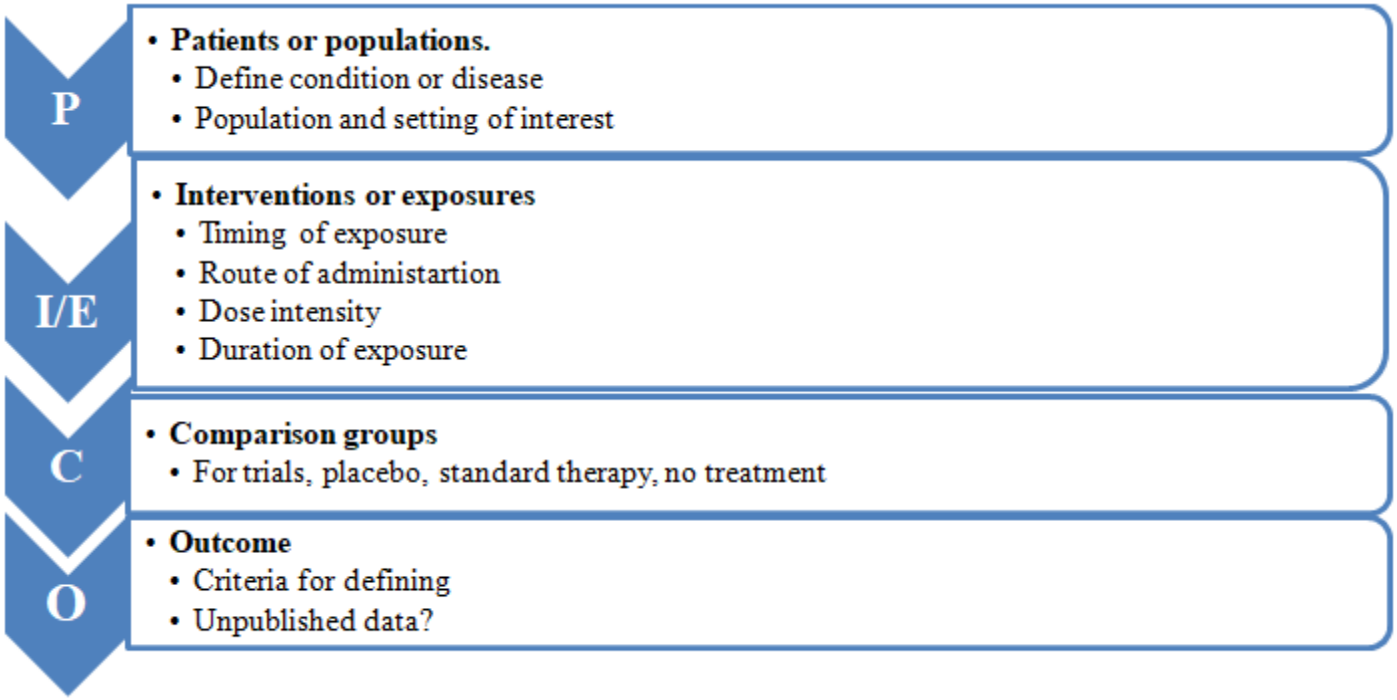
TYPE OF QUESTION	QUESTION	EVIDENCE
Incidence	What proportion of the population is newly diagnosed with this problem each year?	Surveys or cohort studies.
Prevalence	What proportion of the population is currently living with this problem?	Surveys or cohort studies.
Therapy	What should be done to treat this problem?	Clinical trials
Screening	Will detecting this problem early before I get symptoms make a difference in my health?	Clinical trial
Diagnostic Accuracy	How good is this test at detecting this problem?	Clinical trial, cross-sectional studies
Prognosis	What is the likely outcome of this problem?	Clinical trial, cohort studies
Harm	Will there be any negative effects of this intervention?	Clinical trial, cohort studies, case-control studies
Etiology	What causes this problem?	Cohort studies, case-control

Figure 11:Hierarchy of Evidence for intervention studies



VI. Lecture 2C: Elements of the Question

Figure 12: PICO Framework



VII. Lecture 2D: Refining the Question

Elements of outcomes

1. Domain.(anxiety, Heart attack, Visual acuity)
2. Measurements (Hamilton Anxiety Rating Scale, Snellen Visual Acuity)
3. Specific metrics
4. Method of aggregation
5. Time point

VIII. Lecture 2F: Analytic Frameworks

An analytic framework is also called a logic model that links the evidence and how it all fits together in the populations as it relates to outcomes. Components of an analytic framework include:

1. Specifies the population, the interventions or exposures to outcomes, and timing, settings and comparators.
2. Identifies potential modifiers and mediators of effectiveness.
3. Clarifies links between the intermediate outcomes and the health outcomes.

WEEK 3

MODULE 3

IX. Lecture 3A: Finding the Evidence: Searching Principles

After formulating an answerable research question, the next step is to **develop the protocol.** It is also important to **document what you do at every stage.**

How do you do the search?

1. Identify and document the sources to use.
2. Document the details of searches, the dates and the exact strategies.
3. Determine how you make decisions, the inclusion and exclusion criteria. Duplicate screening can be used.

X. Lecture 3B: Identifying Key Sources and Techniques for Searching

1. Major referential electronic databases- “PubMed, MEDLINE, EMBASE, ISI web of science Cochrane library, national and regional databases, object-specific databases and citation databases.”
2. For searches use of “controlled vocabulary, Medical Subject Headings(MeSH), publication type, and keywords.

3. Other sources like “Trial registers, Gray literature searching, personal contacts.” o
4. Techniques like hand-searching and “snowballing.”

XI. Lecture 3C: Building a High-Quality Search Strategy

To develop a search strategy:

1. Formulate a research question and break in into concepts using PICO format .
2. Identify synonyms and controlled vocabulary
3. Use Boolean characters like “AND”, “OR” , “NOT”
4. Revise the search strategy until optimal.
5. Use tested study design filters.

XII. Lecture 3D: Documenting Your Search and Conclusions

- Use Endnote, or RefWorks,
- QUOSA can also be used as it allows automatic, full text retrieval for some of the citations.
- Document the search. Record **when** we did the search, **which** sources were used, the **exact strategy** used and **what** were the findings..
- PRISMA, standard for transparent reporting of systematic reviews and meta-analysis.

MODULE 4

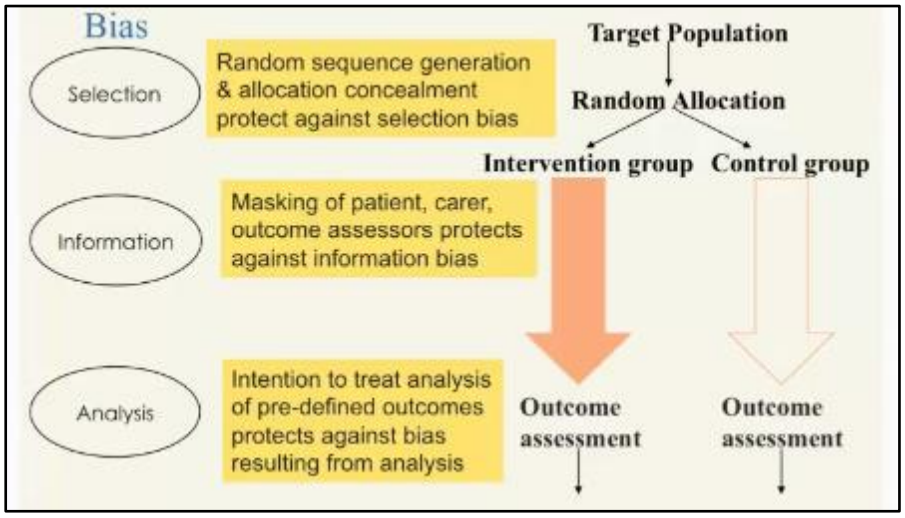
XIII. Lecture 4A: “Why Bias in the Individual Study is Important to a Systematic Review and Meta-Analysis”

Table 9: Elements of study quality that can and cannot be assessed

Elements of study quality that can be assessed	Elements of study quality that cannot be assessed
The internal validity of the study (minimization of bias).	Protocol violations
External validity is how well your study relates to the outside world.	Quality of record keeping and study procedures
Relevance, originality	Degree to which the report reflects actual study
Ethics	Falsification and fabrication

- There are mainly **3 types of bias**:
    1. Selection bias,
    2. Information bias, and
    3. Bias in the analysis.

Figure 13: Bias in studies



XIV. Lecture 4B: Selection Bias

- Selection bias: Usually refers to a bias in how the treatment was assigned.
- Allocation concealment happens at the start of a trial as the patients are being allocated to their treatment to prevent selection bias

XV. Lecture 4C: Information Bias

Masking of participants and personnel: In a randomized trial, we mask or blind the participants in the study, the doctors or other healthcare providers, and the people who are assessing the outcome in the study, to prevent information bias.

Table 10:Level of risk of information bias

Low risk of bias	High risk of bias
Masking to be used and specify who was masked.	Studies that are not masked or not blinded
Incomplete masking but the outcome is unlikely to be influenced.	Studies where the outcome is likely to be influenced.

XVI. Lecture 4D: “Bias in the Analysis”

- **Losses to follow-up**, **noncompliance**, **withdrawals** and **changes in the outcome measure** can increase bias.
- **Missing data** can also pose problems.
- **Post hoc definition of outcomes** is very important.

XVII. Lecture 4E: “Displaying Study "Quality" in Your Systematic Review”

- CONSORT statement, is for randomized trial.
- The STROBE statement is for observational studies.

WEEK 4

MODULE 5

XVIII. Lecture 5A: “Standards for Systematic Reviews”

- The crucial step in a systematic review for minimizing bias is to find and assess the individual studies.
- Bias in conducting a systematic review is called **metabias**.
- There are 3 forms of metabias:
  1. Selection biases,
  2. Information bias
  3. Bias in the analysis

XIX. Lecture 5B: Selection Bias

Types of reporting Bias:

1. Publication bias
2. Selective outcome reporting,
3. Ascertainment bias
4. Selection bias.

XX. Lecture 5C: Information Bias

1. Accuracy of our quality assessment
2. The accuracy of the data abstraction
3. Completeness of data abstraction.

Issues related to information bias

- Data from graph may not be accurately abstracted.
- Experience of your abstractor is a factor or not
- Necessity of Duplicate abstraction
- Data in publications is reliable or not

XXI. Lecture 5D: Bias in the Analysis

- There are two types of statistical models used for the meta analysis called **random effects and fix effects models**.
- The random effects model is used when statistical heterogeneity is present. When statistical heterogeneity is absent in meta-analysis, then the choice of model is not an issue.

XXII. Lecture 5E: Reporting Transparently

- Reporting guidelines for systematic review and meta-analysis:
  1. PRISMA, for systematic reviews of clinical trials, and
  2. MOOSE, for observational studies.
- GRADE, is used to summarize the body of evidence. It's a grading of the body of evidence and it's not the same as the systematic review or meta-analysis.

MODULE 6

XXIII. Lecture 6A: "Qualitative Synthesis and Interpreting Results"

- The systematic review is divided into 2 parts. The idea of doing the review systematically and then the quantitative synthesis part, called meta-analysis.
- A meta-analysis always requires a systematic review but not vice versa. That is, a systematic review does not have to have a meta-analysis.

XXIV. Lecture 6B: What is Qualitative Synthesis

Qualitative synthesis is an assessment of the body of evidence that goes beyond factual descriptions or tables. The purpose of a qualitative synthesis is to attempt to impart understanding of the data and interpret results. Qualitative synthesis helps in **describing the nature of the evidence**, **interpreting it, evaluating strengths and weaknesses of the review** and **concluding**.

WEEK 5

MODULE 7

XXV. Lecture 7A: "Planning Your Meta-Analysis Section A"

- Systematic reviews contain analysis of the primary study. There are two components of any analysis.
- The first one is qualitative analysis, or **qualitative synthesis**. And the second part is the **quantitative synthesis.**
- Qualitative synthesis refers to a structured summary, description, and discussion of characteristics of the studies that may affect the cumulative evidence.

XXVI. Lecture 7B: "Introduction to Meta-Analysis"

- Meta-analysis is statistical analysis of a large collection of analysis resulting from individual studies with the aim to integrate the findings.
- Conventional meta-analysis focus on pair-wise comparisons of inventions or exposure in outcome relationships.
- Justification for combining results are, while studies are estimating in whole or in part, a common effect and studies addressing the same fundamental, biological, clinical or a mechanistic question.

XXVII. Lecture 7C: "Why Do a Meta-Analysis?"

- Meta-analysis can help you to increase the power and precision
- We can quantify the effect size as well as their uncertainty.
- We can assess the homogeneity or heterogeneity of the results.
- Meta-analysis can also help in answering questions not raised by individual studies.
- It can also help in settling controversies that may arisie from conflicting studies.

What does a meta-analysis involve?

1. Comparisons to be formed.
2. Use of study results in each comparison.
3. Best summary of effect for each comparison.
4. Similarity of results of studies
5. Reliability of those summaries.

XXVIII. Lecture 7D: “Types of Data and Effect Measures”

Effect is often called effect measures for randomized control trials, or measures of association for observational studies. It is a way to describe the outcomes of participants treated with different interventions or exposed to different levels of risk factors.

1. Dichotomous data
2. Continuous data
3. Ordinal data
4. Counts for the infrequent event.
5. Time-to-event data.

- Effect measures for dichotomous data: Risk ratio, odds ratio, risk difference, and number needed treat.
- Effect measures for continuous data: Mean difference and standardized mean difference.

The measure to be used should convey necessary clinical meaningful information. And the choice of the summary measure should be suitable to the study design and statistically appropriate and convenient to work with.

MODULE 8

XXIX. Lecture 8A: Fixed Effect Model

Fixed model effect assumes that all studies, have common (true) effect size. It means that, if not for random or sampling error, all results in those individual studies would be identical. And under this model, we assume that there's only one source of variation which is the random errors inherent in each study. Each normal curve on the figure reflects the amount of variance in that study.

XXX. Lecture 8B: “Random Effects Model”

Under the random effects model, we assume that there is a distribution of true effects. There are two sources of variance; **within study** variance, and **between-study** variance.

Table 11:Fixed effect and Random effects model

Fixed Effect Model	Random Effects Model
We assume all studies share a common true effect size	We assume there's a distribution of true effects.
There's only one identical common effect size	Distribution of effect size
One source of variance	Two sources of variance. The within study variance, as well as the between-study variance.
$Y_i = \theta + \varepsilon_i$	$Y_i = \mu + \zeta_i + \varepsilon_i$

XXXI. Lecture 8C: "Random Effects Model"

Under the random effects model, we assume there is distribution of true effects. And that the summary effect is the estimate of the mean of all relevant true effects, and we can test a null hypothesis where the mean of effects is 0, for a difference or whether that's 1 for ratio.