Summer Training Assignment

Under the Guidance of

Dr.SD Gupta

Chairman IIHMR University, Jaipur

RESEARCH REPORT

COVID-19 IN INDIA: AN ANALYIS

ONLINE COURSE

INTRODUCTION TO SYSTEMATIC REVIEW & META ANALYSIS

By

JOHNS HOPKINS UNIVERSITY

A REPORT

By

RISHABH SINGH

MBA Hospital and Health Management

2019-2021

ACKNOWLEDEMENT

At the outset I would like to thank the kind patronage, inspiration and guidance which I received from my mentor **Dr. S D Gupta** (Chairman, IIHMR University) without whose support, guidance, encouragement and suggestions this research and the online learning would have been impossible.

I express my deep sense of gratitude to the continuous support and love provided to me by my family and friends.

I am thankful to my friend and colleague Ms.Juhi Singh for collaborating with me in various parts of the research work which helped us accomplish the assignment in an orderly and systematic manner.

I am also thankful to the faculties of Johns Hopkins University Ms **Kay Dickersin, PhD** Professor, Epidemiology, Bloomberg School of Public Health and Ms.**Tianjing Li**, MD, MHS, PHD Assistant Professor, Epidemiology for their great lectures on Systematic Review and Meta-Analysis which helped me grasp the nuances and conceptual clarity of the course.

At last but not the least I am thankful to all my friends who directly or indirectly helped me to complete this report,

Any omission in this brief acknowledgement does not mean lack of gratitude.

Thanking You

Rishabh Singh

TABLE OF CONTENTS

REPORT 1: AN ANALYSIS OF COVID-19 IN INDIA

ABSTRACT

Since the time of the outbreak of COVID-19 the healthcare infrastructure in the various countries are experiencing enormous pressures to perform and deliver. There has been an unprecedented socio-economic cost which the epidemic has entailed on the population of most of the countries that now have COVID-19 footprints. Various debates have centred on the Lives v/s Livelihood, Cure v/s Continuity of Virus and Public v/s Private Healthcare issues. The present study deals with the assessment of the current situation of the COVID-19 in India. It also examines the trends of the outbreak across the various Indian states along with an analysis of their respective health systems in action. There is also a brief analysis of the age-sex pattern of the COVID-19 deaths and the impact of Comorbidities on the total fatality due to the virus. The report points out to the various trends, patterns and interventions done by the various public health agencies across the country to reduce the surge of the cases and increase the recovery rates of the diseased along with concerted efforts to reduce mortality.

The efficacy of the national lockdown to manage the uptick of the cases of COVID-19 and the phenomenal rise in the cases post unlock in various clusters of the country, especially those states who have been known to be economically forward states having robust health care infrastructure as compared to the other parts of the country have been discussed in detail. The brief research has tried earnestly to incorporate various social, economic, political, technological, environmental and legal implications of the outbreak on the country, its resources and its people

INTRODUCTION

In late December, the public health officials began sounding the alarm about the emergence of a novel corona virus which is now referred to as COVID-19 and in a very short time this new respiratory disease which was first detected in Wuhan, China has quickly spread to other parts of the world. The virus's spread in the countries around the world is a grave concern to its public health systems. Apart from affecting the health systems across the world stretching its resources, with cases soaring and deaths rising, while the hospitals and the health workers scampering to provide relief to millions affected by the virus. With the virus establishing its foothold in most parts of the world, there is an imminent threat to the future of the health and well-being of mankind. Apart from having a public health implication it is also having an impact on the global economy. There are perceptible disruptions to supply chains, disruptions to daily business activity, to travel and to many other aspects of an individual's life.

The number of Corona virus cases in India has now crossed the 7 lakh with a record of over 20,000 new cases reported for five days consecutively as on 8th July,2020.The death toll in India stands at over 20,000.The latest 5,000 deaths took 11 days, previous one took 9 days, hence we can see a slowing rate of death overtime in the country. Hence India's death rates per 10,000 of its population are still much lower than the global experience. It is 0.15 deaths per 10,000 of its population as compared to the US which has around 4 deaths per 10,000 people and around 6,65 in the UK according to reports of Reuters. With over 4 lakhs cases recovered and around 2.6 lakhs active cases with a recovery rate of 61%.With the 'Test, Trace, Treat' firmly in place, over one crore tests have been conducted in India for COVID-19 Over a period of time India has ramped-up its testing capacity substantially (7,500 tests per million population) but needs to be improved further. India has only tested 0.8% of its population while other high caseload nations such as Russia has tested over 16% of its population, United States has tested 11% of its population, China having equivalent population has tested over 6% of its population, while Brazil whose political leadership has dismissed any threats from Covid-19 and has not undertaken testing proactively has also tested around 1.5% of its population. India has also become self-sufficient in the production of PPE kits and Protective masks and other gears.

India is the third worst hit nation in the world in terms of the number of cases of Corona Virus behind only Brazil and the United States. Meanwhile Maharashtra, Tamil Nadu and Delhi continue to remain the worst hit regions in India. Together these three states have more than 46% of the total cases reported across India. India is also seeing the emergence of new COVID-19 hotspots where places like Bengaluru has seen sharp rise in cases in only a months' time (from 5% of the total number of cases in Karnataka it now accounts for more than 60% of the caseload of the state).Experts suggests that places that went for unlocking early is seeing an exponential rise in the total number of cases.

All in all the pandemic has seen an emergency response by a health system which was not prepared to handle the crisis. Over a period of time the authorities and the policy makers of the public health in our country have managed to strengthen many an aspect of the health care delivery mechanisms in the context of COVID-19 in the country yet much is left to be done. It is indeed a learning curve both for the health worker community and the public policy makers across the world. Being one of the most threatening virus to have overtaken humanity in a long time, the world along with India is also confident that it shall be the first virus that could be controlled through the scientific efforts and the resolve of all the people in India and the world.

Key-Terms

Novel Coronavirus, Pandemic, COVID19, Analysis, Classification, India, World, Recoveries,Death Rates, Positive Cases, Health Systems, Hospitals, Data analysis Lockdown,SocialDistancing,Measures,Spread,Containment,Assessment,Trends,National, States,PHCs,CHCsSteps,Policy,Strengtheing,Government of India, Caseloads

METHODOLOGY

The COVID-19 in India: An Analysis report is built from the publicly accessible COVID-19 datasets and it was taken from the various websites, the sources of the datasets are the Ministry of Health and Family Welfare, India.

The data contains the numbers of cumulative confirmed cases, recovered cases and death cases from January 30,2020 to July 8th,2020.

I have undertaken a general analysis of the trends of cases and fatalities with respect to various States and Union territories in India along with a focus on the age-gender and comorbidities datasets of the deaths due to Covid-19.I have utilized the various data available to me through news reports, statistical websites and other Indian database created through the various crowd sourcing channels primarily dedicated to COVID-19 outbreak

Based on the health care infrastructure, workforce, patient data available in the public domain along with the status reports of Healthcare in India regularly published by the Government of India's various agencies of Public Health ,Ministry of Health and Family Welfare and Niti Aayog and also collating the data provided by the state health agencies and ministries and the various health care consulting firms the containment policies of the Government of India and the State governments towards tackling the corona virus pandemic situation and other strategies to combat the rising cases of the disease and management of the epidemic was analysed and presented.

FINDINGS & DISCUSSIONS

The findings generated by the analysis of the various data sets are hereby presented in the following sections:

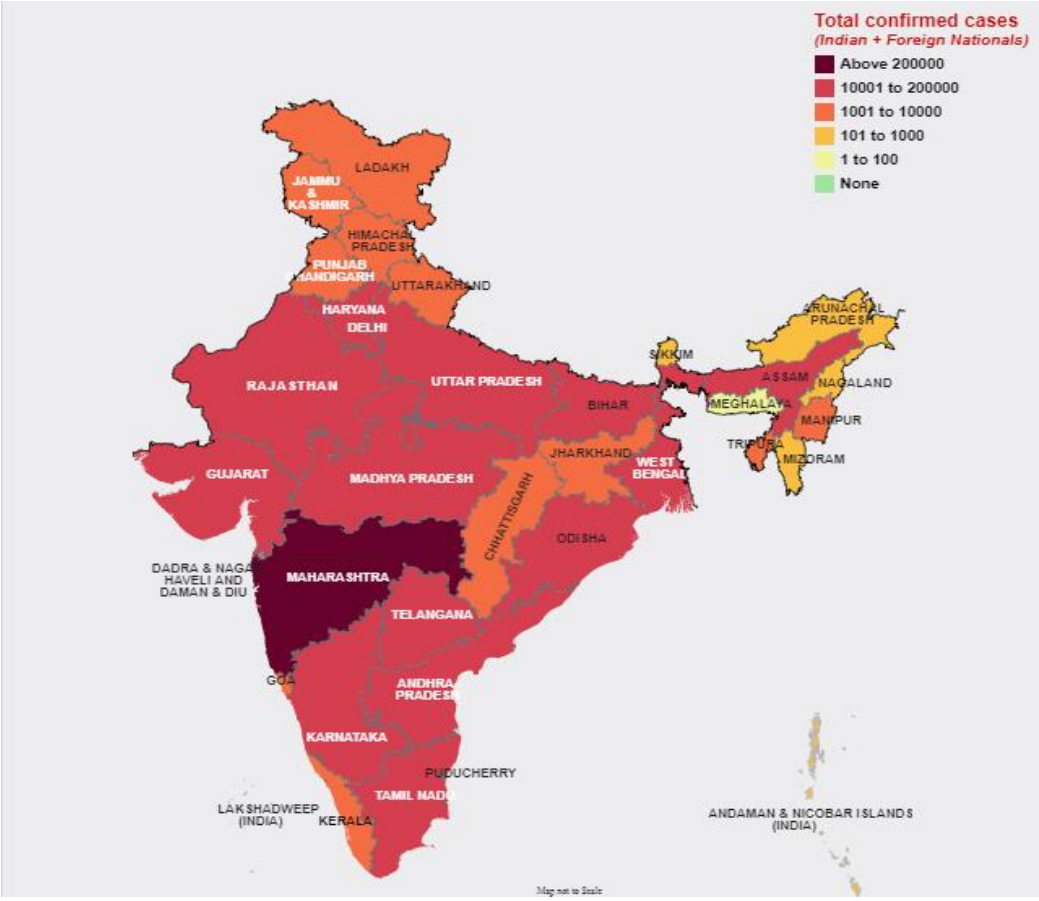
ASSESSING THE SITUATION OF COVID-19 ACROSS INDIA

The global spread of Corona Virus is impacting communities, individuals, markets and businesses in a way we have never experienced before. After the first confirmed COVID-19 case was detected in the State of Kerala, India today has more than 6 lakhs Corona Virus Cases and now the world's 3rd most affected nation. A 10-week nation wide lockdown ordered in March was supposed to give the country's public health system a chance to prepare for the pandemic while also stifling the further human-to-human transmission of the disease. But as parts of India reopened people are struggling to get the attention of the health system they need while there is a surge of cases on a daily basis with decreasing number of days as the country adds each lakh cases to its tally.

INDIA'S COVID-19 COUNT RATE OF INCREASE PER LAKH CASES*(Table 1)*

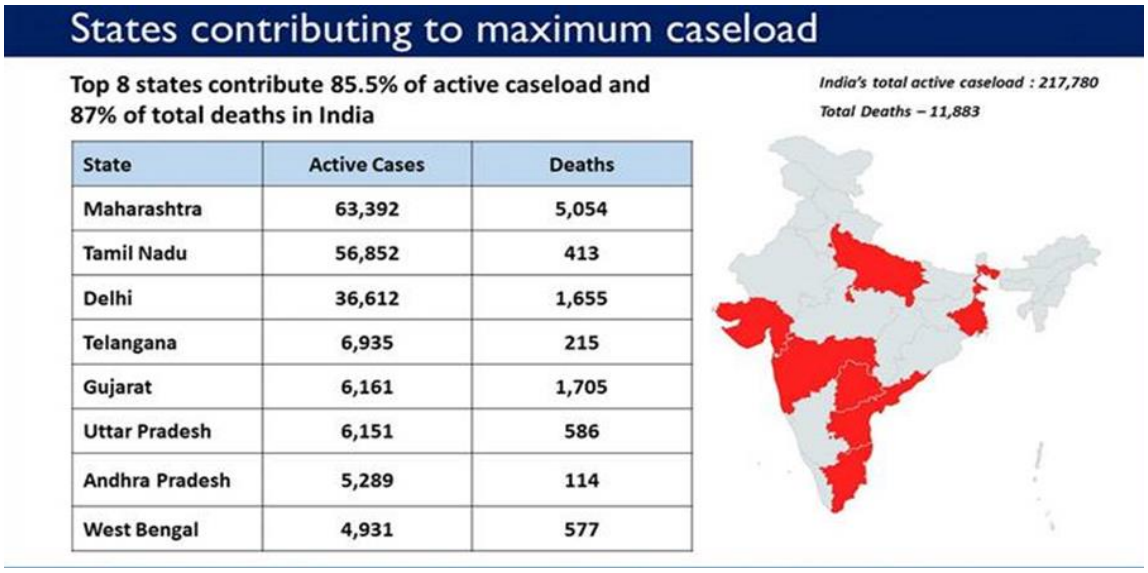
CASES	NUMBER OF DAYS
0-1 Lakh	139
1-2 Lakh	16
2-3 Lakh	11
3-4 Lakh	9
4-5 Lakh	7
5-6 Lakh	5
6-7 Lakh	4

Figure 1



It has been found out by the Union Health Ministry that 8 states which include-Maharashtra, NCT of Delhi, Tamil Nadu, Gujarat, Uttar Pradesh, West Bengal and Andhra Pradesh has contributed to more than 85% of the total active corona virus caseload and has also been responsible for more than 87% of the total number of deaths due to the virus.

Table 2 ***Figure 2***



State	Active Cases	Deaths
Maharashtra	63,392	5,054
Tamil Nadu	56,852	413
Delhi	36,612	1,655
Telangana	6,935	215
Gujarat	6,161	1,705
Uttar Pradesh	6,151	586
Andhra Pradesh	5,289	114
West Bengal	4,931	577

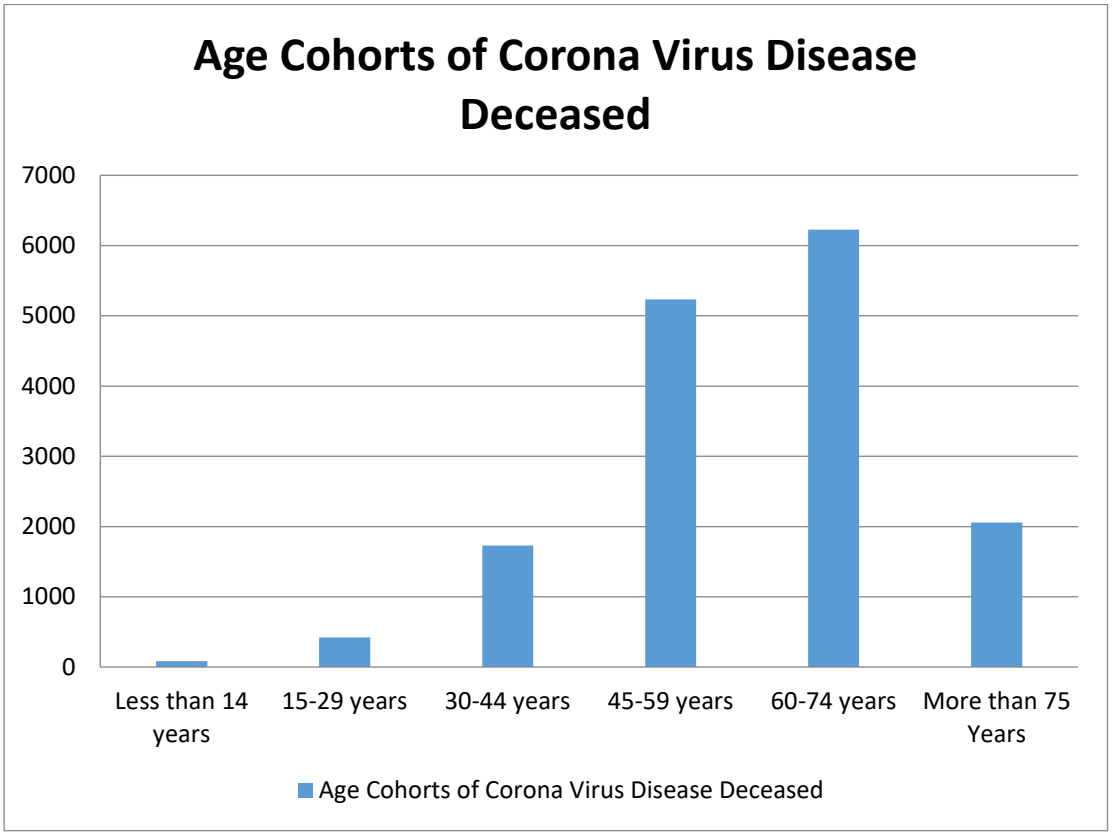
AGE SPECIFIC ANALYSIS OF FALITY DUE TO COVID-19 IN INDIA

According to a study done recently by the Integrated Disease Surveillance Programme, a body which is involved in the tracking and analysis of all infectious diseases in India and works under the overall aegis of the Ministry of Health and Family Welfare(MoHFW) has reported that 57% of the patients in our country who had succumbed to COVID-19 had pre-existing health conditions or comorbidities which accentuated their risk to the disease and led to their deaths. However, 43% of them had no pre-existing health conditions co-occurring with Corona Virus disease and yet resulted in deaths.

The study also conducted an age-wise split of deaths and revealed the following analysis:

- Around 0.5% of the total deaths were in children who were less than 14 years of age
- Around 2.6% of the total deaths were in individuals who were between the ages of 15-29
- Around 11% of the total deaths in individuals between 30-44 years of age
- Around 33% of the total deaths in individuals between 45-59 years of age
- Around 39% of the total deaths in individuals between 60-74 years of age
- Around 13% of the total deaths in individuals who were over 75 years of age

Chart 1



Source: Integrated Disease Surveillance Program Analysis

The split analysis of ages shows that while more than 50% of the total deaths are happening among the elderly persons who have been frequently urged to stay indoors in their homes even post unlocking process was initiated there is a remarkable share of deaths in the age category of 45-59 years-almost one in three Corona Virus deaths are occurring in this age bracket-which is often assumed to be the most productive years on a person's lifetime.

When the COVID-19 pandemic started unfolding across the world it was an accepted norm that the risks associated with the virus infection was directly proportional to the age of the population at risk. The new analysis has claimed that almost half of the death due to the corona virus was inflicted on individuals who were below the age of 60 years definitely casting huge doubts over the earlier claims by the governments and experts that the younger and healthier population were averse to any significant risk from the virus.

Having said that India still has one of the world's lowest case rates of COVID-19 of 505.37 per million of the population against the global average of 1,453.25.However that can also be attributed to a low testing rate. India has only tested 0.8% of its population while other high caseload nations such as Russia has tested over 16% of its population, United States has tested 11% of its population, China having equivalent population has tested over 6% of its population, while Brazil whose political leadership has dismissed any threats from Covid-19 and has not undertaken testing proactively has also tested around 1.5% of its population.

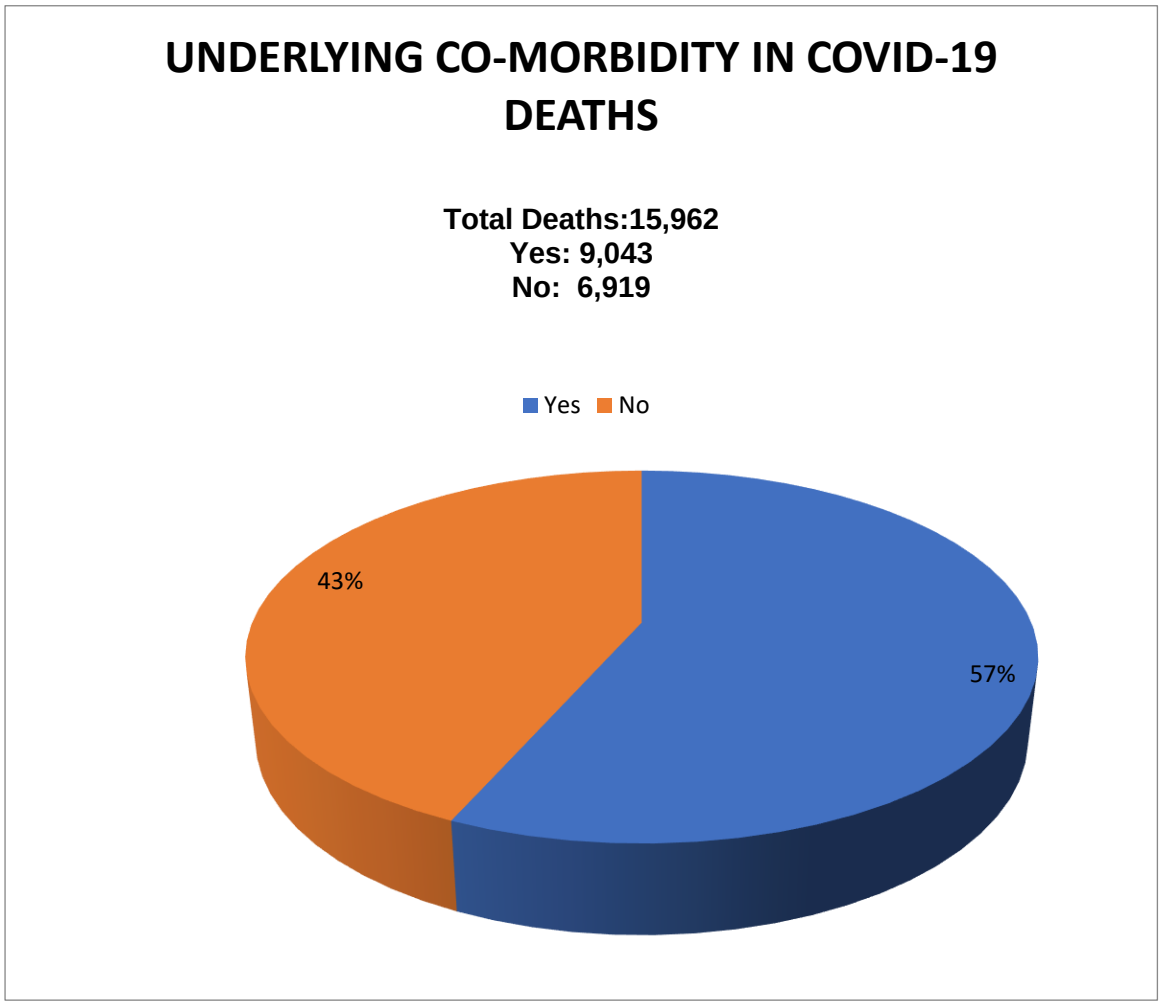
India's mortality rate due to COVID-19 is also one of the lowest in the world. The death rate due to the virus is around 14 per million populations much lower than the world average of 68 per million populations.

Comorbidities

It is a well-known fact that Corona patients with existing health complications are more endangered than others by the COVID-19 exposure. Having said that the latest analysis conducted by the IDSP indicates that 43% of the deaths resulted from the disease alone and not any prior co-morbidities.

Hypertension, Diabetes, Heart Diseases, Cancer, Respiratory Diseases, Obesity are some of the common comorbidities that make Corona Virus patients at a greater risk of fatality.

Chart 2



GENDER SEGREGATION OF THE COVID-19 DEATHS

The case fatality ratio in India on 2 July stood at 3 per cent. Case fatality ratio is the percentage of deaths from among all reported cases, as opposed to infection fatality ratio that takes into account undiagnosed cases at the population level too.

India's case fatality rate at present is around 3%.Case fertility ratio is defined as the proportion of deaths from a disease as compared to the total number of people diagnosed with the disease for a specified period of time.The Infection fatality rate is similar to CFR but it also takes into account all the undiagnosed/asymptomatic cases as well.

The IDSP analysis reveals that 68% of all deaths related to Corona in India were among Males.

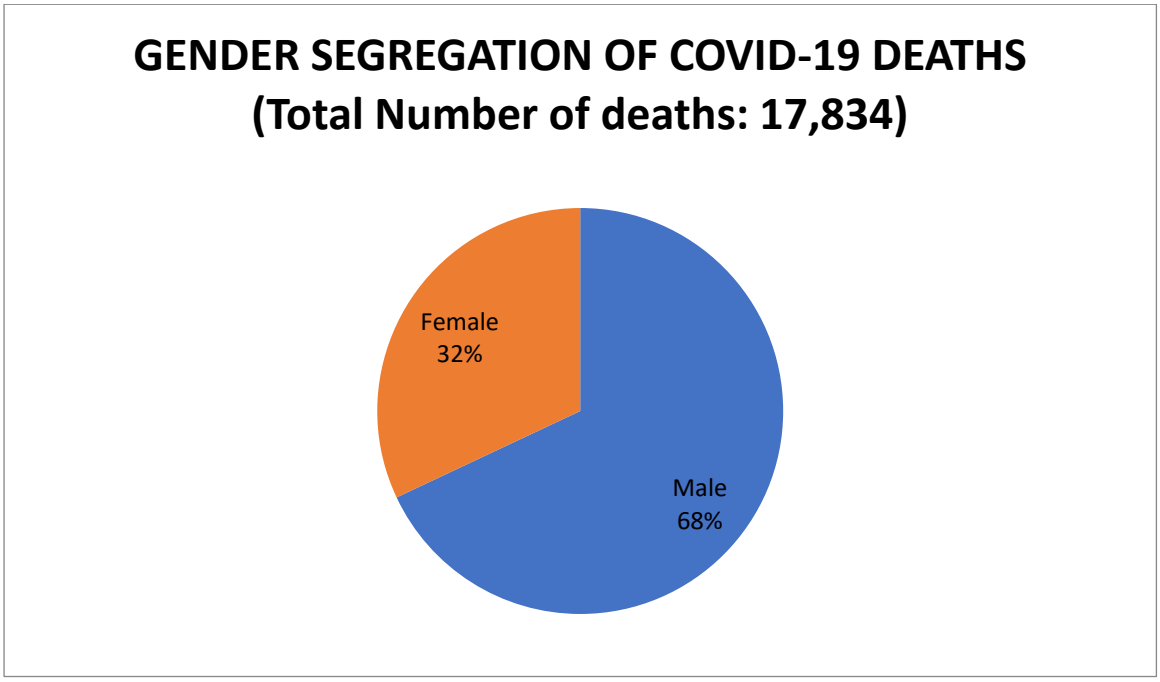


Chart 3

In most of the other countries grappling with high cases and deaths due to COVID have seen more men being infected by the disease than women and also a higher percentage of men fatalities than women in the population

The reasons for a higher caseload and subsequent fatalities in men than women are attributed to a large number of factors which is consistent with the various epidemiological and demographical theories:

1. Higher chances of comorbidities or pre-existing health conditions such as cardio-vascular diseases, hypertension, respiratory diseases etc. in men than women
2. In most populations men indulge in greater health-risk behaviour than women(eg: men smoke more than women in most countries)
3. Studies have shown that men observe lesser hygiene than women such as washing their hands less frequently than women
4. Biologically women have a more robust immune defence mechanism than men.

But a study done by a group of scientists on India's COVID patterns shows a different picture.

While it may appear that more men are succumbing to Corona Virus, these findings have pointed out that the Case Fatality of Women is higher than men which is surprisingly uncommon across the world.

In other words, this research points out that women are up against a higher chance to die from corona virus than men. It is based on the data of COVID-19 fatalities until 20th of May,2020 and estimated that around 3.3% of the total cases in the women were dying as compared to 2.9% of the cases who were men up until 20th May,2020 in India.

Particularly, it pointed out that in the age group of 40-49 years more women succumbed to COVID than men in the same age cohort.(3.2% of the overall cases in the women died as

compared to 2.1% of the overall cases in the men between the age groups of 40-49 years).It also revealed shockingly that in the age bracket of 5-19 years only females have had the fatalities due to Corona Virus..

Researchers have attributed such distortions in the fatality rates between men and women defying the global COVID experience in India to the fact that women when infected with do not have a distinct advantage of survival as compared to men. The reasons are:

1. **The differential opportunities to get tested by men and women in India. Women generally have limited access to healthcare and diagnostic facilities especially in the lower/lower middle class strata of the society in India due to their social settings.**
2. **There are more aged women in than men in India as they live longer than their male counterpart.**
3. **Women in India also generally do not go in for an immediate consultation with the doctors on the appearance of the symptoms and are more likely to opt for self-medication. Hence it may be a possible cause of their higher fatality that they turn in late for testing and treatment for the disease.**
4. **More women in India's lowest socio-economic strata live in unhygienic, ill-ventilated and clogged households having a higher chances of contracting the disease than men who invariably stay outside their homes for the greater part of the day.**

However inadequate sharing of the age-specific data of COVID-19 cases and fatalities by the various state governments have hindered a complete analysis for the development of a holistic estimates of Covid-19 deaths and hence have not led to any concrete results to support policy initiatives.

HEALTH SYSTEM & COVID-19

Healthcare systems around the world are under stress as more and more patients are seeking care and treatment pushing public and private health institutions around the world to the brink of collapse. In India in particular the healthcare is largely privatized where around 72% of people in rural areas and 79% of the people in the urban areas utilize private healthcare services. In efforts to cut costs many private hospitals and clinics in India have reduced staffs and stretched resources that are now urgently needed overwhelming their capacities to deal with the Pandemic. Exponential rise in the costs of healthcare has further exacerbated health inequity and has pushed thousands of households in the brink of poverty and destitution.

The Public health system in India on the other hand is handling most of the cases related to COVID 19 especially in the states where there is a near absence or inadequacy of private healthcare facilities. A combination of the lack of investment in the public health infrastructure which has denigrated India to have one of the least beds available per capita amongst all of the developing countries in the Public hospitals/Govt.Medical Colleges, inadequate capacity development of Primary Health Care Services(all public health activities such as prevention, detection and testing are directly undertaken by PHC staffs in COVID-19 in many states),understaffing in public health institutions, lack of basic protective gears for frontline health staffs during this epidemic and lack of development of comprehensive public health services even in the glittering metropolitan cities have all lead to a major crisis of our public health system in managing COVID-19

India had enforced prompt surveillance from January 17, 2020 much before the 1st case of COVID-19 was detected. There were travel advisories and qualified restrictions and brisk efforts to bring back and quarantine all the Indian nationals from abroad. However India's has one of the lowest testing rates in the world which is a big hurdle in timely treatment and prognosis of the disease. As per the International database FIND which tracks testing per million of the population, India does around 4000 tests per million of the population while the global average is over 30,000 tests per million population. However the daily testing capacity has certainly increased and is increasing in India in recent days with over 3 Lakh tests per day now..

Post a day of "Janta Curfew" trial, India decided to go in for a full lockdown from 24th March,2020.The total positive corona virus cases and fatalities at that point in time was less than 500 and 10 respectively. The lockdown had serious consequences for millions of daily-wagers and other low income workers and their families who faced economic hardships and food shortages and had to walk lock, stock and barrel to their native places, many dying en-route due to hunger, dehydration and train accidents. There were also many who flee the overcrowded and ill-equipped quarantine centres set up by the Government. However the Government did swung into action later and made provisions of rations for the migrant labourers, but it happened more than 40 days after the lockdown was set into place.

The movement of lakhs of migrants (estimated between 2-10 million impacted by corona virus and the subsequent economic turmoil that they were embroiled into)for days on end had serious ramifications for other health programs too. An analysis done by NHM on the inpatient and outpatient data reveals that between 100,000-200,000 children missed their routine vaccination during the period of Februar-March, 2020.Treatment of other diseases such as TB also showed a drastic fall.

An analysis of the PM Jan Arogya Yojana claims data which is an insurance scheme for the economically weaker section households revealed that during the entire phase of the lockdown the claims for various interventions like the cataract eye operation, cardiac surgeries, joint replacement surgeries, oncology and even child delivery services saw massive declines. These findings rings an alarm bell of the possible revival and renewal of preventable/infectious/chronic diseases in India

DIFFERENTIAL IMPACT OF COVID-19 ACROSS STATES

As in the case with other countries, the distribution of Covid-19 cases in India has not been uniform. The data of state-wise distribution of cases shows that three states- Gujarat, Maharashtra and Tamil Nadu, along with the NCT of Delhi have been the most severely affected consistently. This, however, is not arbitrary. The high concentration of cases in these states, and also within few cities/districts within these states must be viewed in the light of the two most important aspects: these states are among the most industrialised states which house a significant portion of urban population, and consequently have high population densities.

Source: 2011 Census data*(Table 3)*

State / UT	Total population	Rural population	Urban Population	Percentage of urban population	Area	Population density
Maharashtra	112374333	61556074	50818259	45.2223009	307,713 km2	365/km2
Tamil Nadu	72147030	37229590	34917440	48.39761249	130,058 km2	555/km2
Gujarat	60439692	34694609	25745083	42.59631733	196,024 km2	308/km2
Delhi	16787941	419042	16368899	97.50391069	1,484 km2	11,297/km2

The current pandemic situation has highlighted the poor state of urban health in India, particularly in the above states. With close to half of these states' population living in urban areas, it has led to the over-burdening of the public health infrastructure. This situation has only been aggravated due to the high burden of covid-19 cases in these states. It would not come as a surprise that there are projections that these states will fall short of the critical care infrastructure including ICU beds and ventilators, not to mention the trained workforce required to tackle the pandemic. The public hospitals are struggling to keep up their inventory, which is also being challenged by the increase in the confirmation rate. Delhi is suspected to run out of the supplies like isolation beds before June ends. The projections for Maharashtra and Tamil Nadu are no less scary. Maharashtra may run out of ventilators by July end itself, followed by shortage of ICU beds by August first week. Given the current trends, other states like Karnataka, Haryana, West Bengal, Madhya Pradesh and Jammu and Kashmir will also face challenging times ahead in the near future to ensure lack of shortage of critical care. Another important aspect here is that of the confirmation rate. The states of Maharashtra, Delhi and Telangana have confirmation rate of more than 10%. This is also an indicator of more testing.

The data of distribution of cases within the different wards of Mumbai conforms to the trend of higher number of cases in areas of greater population density, as follows: **(*Table 4)***

Population density (persons per sq. km)	%age of Covid-19 cases
< 15,000	5.65%
15,000 to 25,000	13.72%
25,000 to 35,000	26.52%
> 35,000	54.11%

The general contention is that urbanisation is synonymous with economic prosperity. This, however might to a part of the truth if viewed purely from the perspective of income. However, such approach often masks the issues peculiar to the urban settings, particularly where the urbanisation has largely been unplanned. This unplanned approach manifests in the form of environmental degradation and most evidently in the form of poor urban health, arising due to the socio-economic reasons. The poor urban health stems from the overburdening of the public health facilities, since private care, even though present in abundance is largely out of reach in terms of accessibility and affordability. Certain diseases were thought to affect not the entire urban population but certain sections of it. For example, urban slums were most susceptible to water borne and other seasonal communicable

diseases while the sedentary population was more affected by the non-communicable or 'lifestyle' diseases. However, these demarcations are getting blurred, more so in the times of the ongoing Covid-19 pandemic.

Traditionally, less attention has been paid to urban health in terms of an encompassing comprehensive approach. The efforts, before the onset of the NUHM (National Urban Health Mission) were largely fragmented and did not lead to a substantial impact. The current situation of the Covid-19 pandemic has brought these issues to the surface and presented a case for strengthening the health systems at the urban level.

Since Gujarat, Maharashtra and Tamil Nadu, along with the NCT of Delhi account for more than 70% of the total burden, it is time to reflect upon the health infrastructure at the state level. Gujarat has 50% shortfall of PHCs, while it is 54% for Maharashtra and 41% for Tamil Nadu. As per the statistics, only Delhi can boast of the absence of shortfall in the number of PHCs. This shortfall is not limited to the number of PHCs, but extends to the manpower also. It takes the form of vacant positions for Female health workers / ANM across states.

It must be mentioned here that the first Indian state where the first confirmed case of Covid-19 was detected- Kerala, and which showed an upward trend initially was quite successful in the containment of the pandemic. Of course, it cannot be ignored that Kerala ranks consistently in the forefront in the comparison of health indicators across states. The source of these achievements is the robust public health infrastructure which has been the result of healthcare getting its due in the State budgets. This is coupled with the decentralised approach adopted by Kerala as early as 1996, when People's Campaign for Decentralised Planning movement was launched. As a result, the local governments received as high as 40% of the state budget which gave the local bodies their much needed financial independence. This also lead to the grassroots level strengthening of the public infrastructure thereby reducing the burden at the secondary and tertiary levels. It must be mentioned here that since Health is a state subject, the necessary impetus for decentralised approach and community involvement was given by the 74th Amendment which led to the creation of the Nagarpalikas or the ULBs (urban local bodies). They however, are heavily dependent on their respective state governments for their funding as their revenue generating capacity is limited.

Table 5

NUMBER OF SUB-CENTRES, PHCs, CHCs & HWC FUNCTIONING IN RURAL & URBAN AREAS

S. No.	State/UT	(As on 31st March 2019)									
		Sub centre		PHCs		HWC-SC		HWC-PHC		CHCs	
		Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban
1	Andhra Pradesh	6825	21	0	121	612	0	1145	243	140	55
2	Arunachal Pradesh	307	0	101	4	78	0	42	0	63	0
3	Assam	4015	19	698	6	628	0	248	49	177	2
4	Bihar	9865	0	1480	0	84	0	419	95	150	0
5	Chhattisgarh	4555	364	657	30	650	0	135	15	170	4
6	Goa	219	0	0	0	0	0	24	0	5	0
7	Gujarat	8353	0	704	247	813	0	772	71	362	14
8	Haryana	2440	32	193	25	164	0	186	72	115	13
9	Himachal Pradesh	2089	8	566	20	0	0	20	0	87	7
10	Jammu & Kashmir	2900	0	526	34	125	0	96	15	84	0

11	Jharkhand	3644	0	203	7	204	0	95	50	171	6
12	Karnataka	9187	251	1995	364	571	0	132	71	198	9
13	Kerala	5380	0	678	83	0	0	170	0	227	2
14	Madhya Pradesh	10226	0	1039	107	0	0	160	29	309	21
15	Maharashtra	9729	0	1349	538	939	0	479	0	364	37
16	Manipur	429	0	85	9	61	0	5	0	23	0
17	Meghalaya	445	0	110	0	32	0	8	0	28	0
18	Mizoram	370	0	57	8	0	0	2	2	9	0
19	Nagaland	377	20	124	2	56	0	2	3	21	0
20	Odisha	6595	0	461	5	93	0	827	82	377	7
21	Punjab	2511	0	79	16	439	0	337	0	89	63
22	Rajasthan	13382	47	1777	320	130	0	305	57	571	24
23	Sikkim	148	0	24	1	28	0	5	0	2	0
24	Tamil Nadu	7728	2183	706	249	985	0	716	214	385	15
25	Telangana	4658	0	0	0	86	97	636	249	85	10
26	Tripura	932	34	82	0	40	0	26	5	18	4
27	Uttarakhand	1804	0	243	0	43	0	14	0	67	0
28	Uttar Pradesh	20056	0	1990	237	726	0	946	387	679	12
29	West Bengal	10195	0	640	448	162	0	268	0	348	39
30	Andaman & Nicobar Islands	96	0	22	0	28	0	0	2	4	0
31	Chandigarh	0	4	0	36	0	0	0	10	0	2
32	Dadra & Nagar Haveli	47	0	6	2	24	0	3	0	2	0
33	Daman & Diu	4	2	0	0	19	1	4	0	0	2
34	Delhi	12	192	5	535	0	0	0	0	0	0
35	Lakshadweep	14	0	4	0	0	0	0	0	3	0
36	Puducherry	53	27	9	2	1	0	15	13	2	2
	All India	**149590**	**3204**	**16613**	**3456**	**7821**	**98**	**8242**	**1734**	**5335**	**350**

Table 6

SHORTFALL IN PRIMARY HEALTH CENTRES AS PER MID YEAR POPULATION (as on 1st July 2019) IN INDIA in URBAN AREAS						
S.No.	**State/ UT**	**Estimated mid-year population for Urban areas (as on 1st July 2019)**	**PHCs and HWC-PHCs**			
			Required	**In Position**	**Shortfall**	**% Shorfall**
			R	**P**	**S**	

1	Andhra Pradesh	17935000	359	364	*	*
2	Arunachal Pradesh	374000	7	4	3	47
3	Assam	5202000	104	55	49	47
4	Bihar	14397000	288	95	193	67
5	Chhattisgarh	7486000	150	45	105	70
6	Goa	1108000	22	0	22	100
7	Gujarat	32010000	640	318	322	50
8	Haryana	11503000	230	97	133	58
9	Himachal Pradesh	748000	15	20	*	*
10	Jammu & Kashmir	4001000	80	49	31	39
11	Jharkhand	9599000	192	57	135	70
12	Karnataka	28140000	563	435	128	23
13	Kerala	23675000	474	83	391	82
14	Madhya Pradesh	23618000	472	136	336	71
15	Maharashtra	58240000	1165	538	627	54
16	Manipur	979000	20	9	11	54
17	Meghalaya	663000	13	0	13	100
18	Mizoram	648000	13	10	3	23
19	Nagaland	874000	17	5	12	71
20	Odisha	7956000	159	87	72	45
21	Punjab	12125000	243	16	227	93
22	Rajasthan	20248000	405	377	*	*
23	Sikkim	276000	6	1	5	82
24	Tamil Nadu	39465000	789	463	326	41
25	Telangana	16748000	335	249	86	26
26	Tripura	1407000	28	5	23	82
27	Uttarakhand	382200	76	0	76	100

		0				
28	Uttar Pradesh	53100000	1062	624	438	41
29	West Bengal	34247000	685	448	237	35
30	A & N Islands	168000	3	2	1	40
31	Chandigarh	1178000	24	46	*	*
32	D & N Haveli	359000	7	2	5	72
33	Daman & Diu	389000	8	0	8	100
34	Delhi	19768000	395	535	*	*
35	Lakshadweep	64000	1	0	1	100
36	Puducherry	1056000	21	15	6	29
	All India/ Total	**45357600 0**	**9072**	**5190**	**4026**	**44.4**

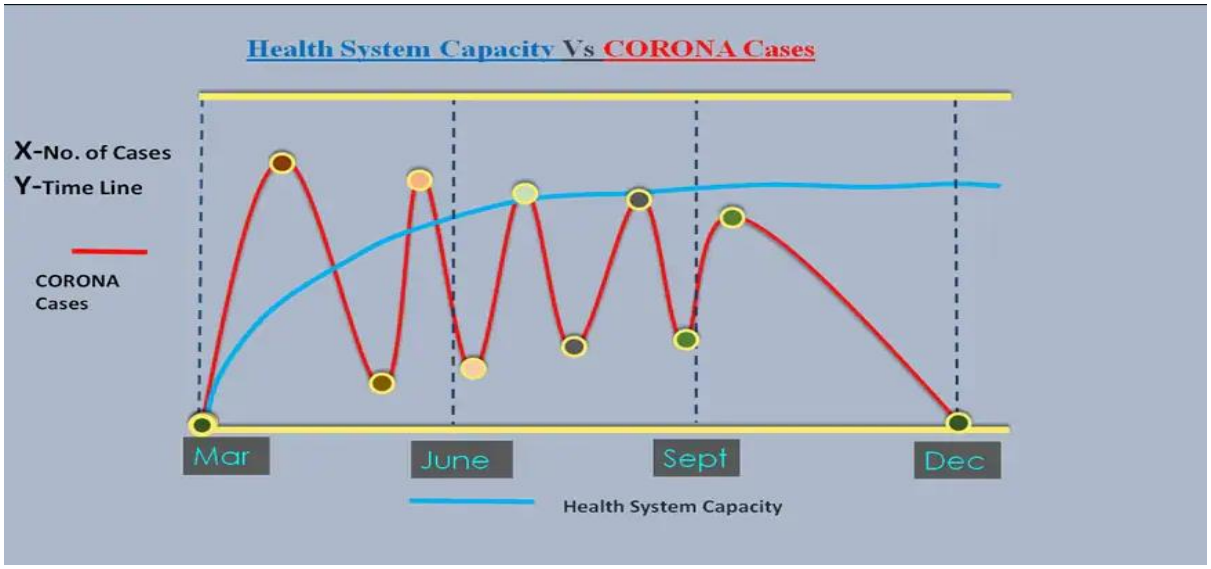
Table 7

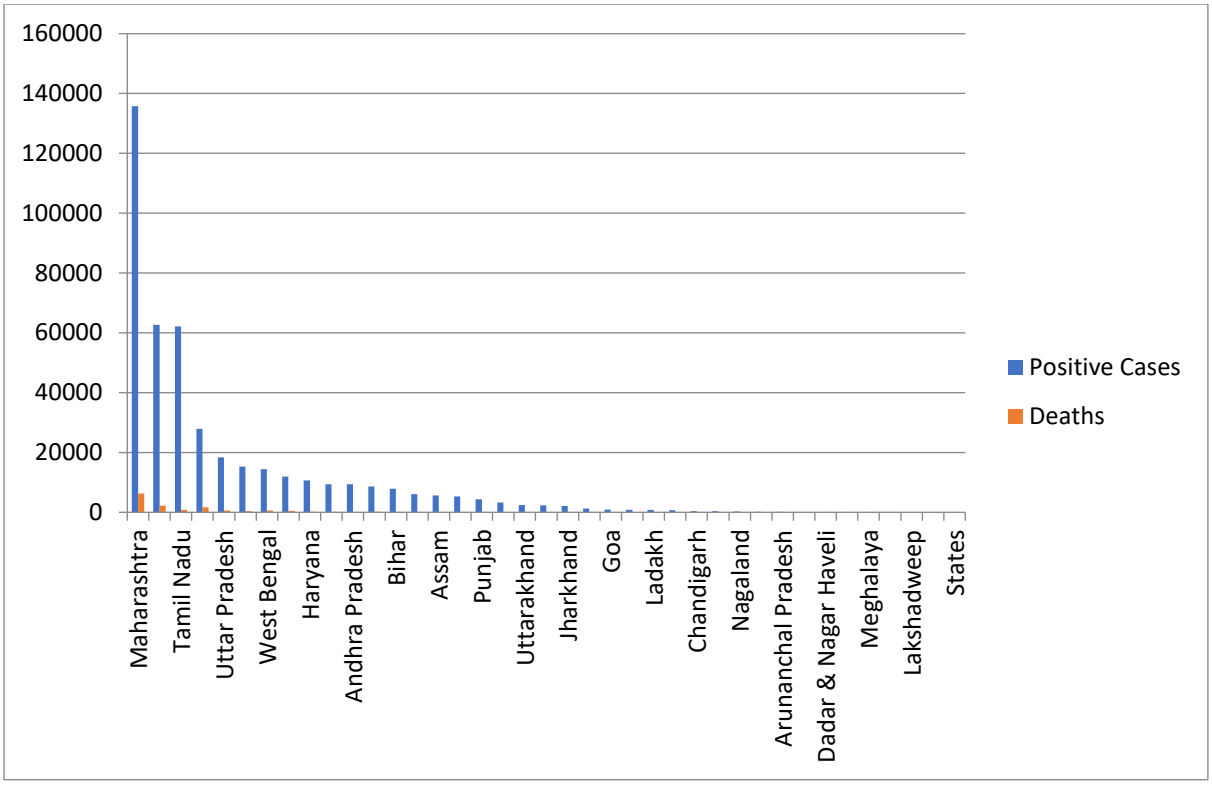
HEALTH WORKER [FEMALE] / ANM AT PHCs in Urban Areas						
S. No.	**State/UT**	**(As on 31st March, 2019)**				
		Required[1]	**Sanctioned**	**In Position**	**Vacant**	**Shortfall**
		[R1]	**[S]**	**[P]**	**[S-P]**	**[R1-P]**
1	Andhra Pradesh	1820	784	751	33	1069
2	Arunachal Pradesh	20	0	9	*	11
3	Assam	275	NA	211	NA	64
4	Bihar	475	NA	95	NA	380
5	Chhattisgarh	225	664	376	288	*
6	Goa	0	0	0	0	0
7	Gujarat	1590	3064	1947	1117	*
8	Haryana	485	831	808	23	*
9	Himachal Pradesh	100	10	10	0	90
10	Jammu & Kashmir	245	256	143	113	102
11	Jharkhand	285	311	202	109	83
12	Karnataka	2175	2247	2177	70	*
13	Kerala	415	1686	1749	*	*
14	Madhya Pradesh	680	67	321	*	359
15	Maharashtra	2690	1361	1092	269	1598

16	Manipur	45	NA	13	NA	32
17	Meghalaya	0	0	0	0	0
18	Mizoram	50	NA	16	NA	34
19	Nagaland	25	NA	15	NA	10
20	Odisha	435	122	200	*	235
21	Punjab	80	44	80	*	0
22	Rajasthan	1885	1122	756	366	1129
23	Sikkim	5	NA	1	NA	4
24	Tamil Nadu	2315	2248	2087	161	228
25	Telangana	1245	1065	747	318	498
26	Tripura	25	NA	68	NA	*
27	Uttarakhand	0	0	0	0	0
28	Uttar Pradesh	3120	NA	857	NA	2263
29	West Bengal	2240	110	86	24	2154
30	A& N Islands	10	0	0	0	10
31	Chandigarh	230	NA	115	NA	115
32	D & N Haveli	10	16	16	0	*
33	Daman & Diu	0	0	0	0	0
34	Delhi	2675	1081	1645	*	1030
35	Lakshadweep	0	0	0	0	0
36	Puducherry	75	4	227	*	*
	All India/[2] Total	**25950**	**17093**	**16820**	**2891**	**11498**

The 10 most affected states are Gujarat, Haryana, Karnataka, Madhya Pradesh, Maharashtra, NCT of Delhi, Rajasthan, Tamil Nadu, Uttar Pradesh and West Bengal. Of these, Maharashtra, NCT of Delhi, Tamil Nadu, Gujarat, Uttar Pradesh, Rajasthan West Bengal and Madhya Pradesh have cases which are more than the national average.

Figure 3





(Chart 4)

The least affected areas are the North eastern states (except Assam, Tripura and Manipur) and the Union territories like Puducherry, Dadra and Nagar Haveli. The initial cases in Tripura were reported from a BSF camp in district Dhalai, where around 150 personnel tested positive. These states also showed a surge by the end of May, resulting from the return of migrant workers from different parts of the country. There is also huge disparity in the number of deaths and recovery rates across states in the North-East. As of now, Assam has quite an impressive recovery rate of 68.63%, while Arunachal Pradesh is struggling with below 33%.

Uttar Pradesh saw its first positive case on March 4th, in Ghaziabad district. It has close to 20,000 cases by June end with 600 deaths. Around the end of June, there was a surge in the recovery rate of the state, reaching close to 70%, as the discharge protocol was relaxed. Earlier, that is before 21st june, an asymptomatic patient was discharged only after the second test after the 12th day of the first result was found to be negative. With the revised norms, asymptomatic patients are discharged after a period of ten days in the hospital, followed by home isolation for a week. Similar numbers for number of cases and deaths are observed for West Bengal, where the first case was confirmed on March 17th. After that, the infection has been rising rapidly with the return of migrant workers. Both states have mortality rate below 5%, with that of Uttar Pradesh slightly more than West Bengal.

Haryana witnessed a worrisome doubling time of eight days till mid-June and recovery rate was as low as 37%. The situation in the districts of Faridabad and Gurugram were particularly bad because of the proximity to the NCT of Delhi. However, by the end of June, Haryana was able to improve the doubling time and the recovery rate, while mortality rate reached around 1.57%. Another point of concern is tnat the majority of the patients belong to

the age group of 24-34, while majority of deaths occurred in 65+ age group. Out of the 255 deaths so far, at least 100 patients did not have any co-morbidities.

While the fear of 'second wave' or 'migrant wave' loomed large, a surprising observation has been made in the case of Bihar. It does not feature in the ten most affected states, while simultaneously demonstrating an impressive recovery rate and has been successful in keeping the mortality rate below 1%.

Below is a snapshot of the recoveries, as of 02nd July: ***(Table 8)***

CHANDIGARH	82.3%
MEGHALAYA	80.8%
RAJASTHAN	79.6%
UTTARAKHAND	78.6%
CHHATTISGARH	78.3%
TRIPURA	78.3%
BIHAR	77.5%
MIZORAM	76.9%
MADHYA PRADESH	76.9%
JHARKHAND	76.6%
ODISHA	73.2%
GUJARAT	72.3%
HARYANA	70.3%
LADAKH	70.1%
UTTAR PRADESH	69.1%

A special mention would be that of the state of Rajasthan. It has consistently fared well in its management of the infection and has been a pioneer in keeping the doubling rate above the national average and the death rate below the national average. It also topped the virus management index, which was released by the central government based on parameters like active cases, recovery and mortality rates.

Based on the current status of COVID-19 and the lessons from its early response, India ought to be prioritizing five measures:

1. **Expand Testing Capacity:** India has massively ramped-up its testing abilities from 1.5 Lakh tests per day to more than 3 Lakh tests per day now. It should further remove any bottlenecks in the seamless testing of COVID-19 by augmenting the number and the capacity if test laboratories. India has become self-sufficient in the

production of PPE kits and has unleashed major reforms in developing and scaling up diagnostics capacity and should continue to do so in the future.

2. **Welfare of the Economically Weaker Section:** Proactive steps should be taken to bring the lives and livelihood of the poor back on track through the introduction/strengthening of poverty alleviation programs such as guaranteed employment in the various developmental activities of the Government, provision of essential supplies such as food, medicines and other basic needs of the poor.

3. **Importance of Essential Heath Care Services:** It must be realised by the Health Leadership of our country that an effective presence of all critical health services and programs is of ultimate importance in any health system. Despite our dedicated focus on the fight against COVID-19 we cannot afford the resurgence of vaccine preventable, infectious or chronic diseases by neglecting their potential spread.

4. **Enforce Mitigation/Prevention Measures Strictly:** It is very important to not lose sight of the precautionary measures to be adopted to curtail the spread of Novel Corona Virus. Preventive norms of social distancing, compulsory mask-wearing in public, maintaining proper health-hygiene routine, credible quarantine procedures along with enhanced detection, isolation and mitigation measures are the norms that must be followed for some times to come.

5. **Ensure effective data management**: At present there is no uniformity in the data disseminated by the various state governments particularly in relation to the age-gender data of cases/fatalities, supporting infrastructure such as the number of PPE kits available or the data on the number of patients availing Oxygen/Ventilator support. There should be fixed national parameters on which the state governments must compulsorily provide data for informed evidence based policy decision-making and generate reasonable inferences for research activities.

COVID-19 RESPONSE BY THE GOVERNMENT

The inherent challenge in formulating an effective strategy to combat the spread of Covid-19 is its virtually complete dependence on individual human beings to observe and uphold the norms of hygienic health practices, human-to-human distancing, mask-wearing habit in public. In the wake of the spread of the COVID-19 following measures were taking by the Government to prevent the spread of the Virus in the country:

1. The first measures to tackle COVID 19 were initiated in January whereby the Government started compulsory thermal screening of all passengers who were in-bound from China at all major airports of the country. Later it was extended to most of the other South-East Asian countries such as Thailand, Singapore, Japan, South Korea, Vietnam, Indonesia, Malaysia, Hong Kong and even Nepal. However by then mere Thermal Screening was not found adequate to deal with COVID-19 and the Government was working on other plan of action to deal with the disease.

2. Various containment plans were being drawn by the Government to set up additional quarantine and treatment facilities in the country. For the first time “Social Distancing” advisory was given to the people of India to prevent the spread of the virus.

3. A COVID-19 Economic Task Force was instituted which led to measures to ensure food security, allocation of surplus funds to healthcare, allocation of funds to states, sector specific economic stimulus, extension of the deadline to file tax returns. Other

liquidity injection measures in the economy included slashing of the interest rates by the Reserve Bank of India to ease credits for the public at large and also providing special finance to SIDBI,NABARD and NHB to accelerate economic activities in industrial, agricultural and infrastructure sectors of the economy.

4. Launch of the economic self-reliance scheme or the Atma Nirbhar Bharat Abhiyan to the tune of Rs.20 Lakh Crore consisting of measures to boost infrastructure, provide relief to businesses in distress, and other economic and financial reforms to attract investment in the various sectors of the economy.
5. Almost all the Indian states made wearing of a face mask to prevent the spread of the contagion compulsory and various guidelines were issued by the Government to facilitate movement of stranded Indians in the country and abroad to their homes.
6. Issue of new Visas were prohibited by the Government and all outstanding visas issued were also suspended in the wake of the rising cases of COVID-19
7. All returning Indians and Foreign Nationals coming from Covid affected countries were made to self-quarantine for 14 days in India
8. Government launched Covid-19 tracking application Aarogya Setu which shares the user data with the government in case anyone has been in contact with a COVID-19 positive person.
9. Without adequate testing capacity to test most of its 1.3 billion strong population initially, India relied on the power of the masses to stay at home for 21 days initially (starting from 25th March,2020) and then extended it to 68 days (approximately 10 weeks till 31st May,2020) which not only helped to retard the growth rate of the pandemic but also gave the public health system time to brace for impact of a future rise in the cases once unlocking of the nation takes place.
10. The various districts of the country were divided into 3 zones based on their current spread of the virus-Red, Orange and Green and strategies of containment of virus and relaxations on movement of people and goods initiated according to it.
11. From complete lockdown, stay at home guidelines and closure of all economic and social activities, the nation moved to the initiation of unlocking. The Public health system was also comparatively better equipped to deal with the crisis at hand as the cases continued to rise unabated. India today is self-sufficient in the production of PPE kits and N95 Masks which it had faced massive shortages initially.
12. India has also moved to strengthened its testing capabilities significantly in the last couple of months, from being able to test 1.5 lakh samples per day to more than 3 lakh sample as on 3rd July,2020 with the total Corona tests crossing a Crore mark at present. Due to India's "Test,Trace,Treat" strategy
13. Launching of the Ministry of Health and Family Welfare Toll-Free number for prompt guidance to any individual experiencing symptoms of the Virus.
14. From having limited number of Ventilators in states of the country, the Union Government have dispatched more than 11,300 'Make in India' Ventilators to various states.
15. Pradhan Mantri Garib Kalyan Anna Yojana was launched and all the families) all the beneficiaries under TPDS will be given 5 kilograms of free rice/wheat along with 1 kilogram of Gram(Chana) till the end of November,2020.A total of 80 crore people shall be benefitting from the scheme
16. 'Prime Minister's Citizen Assistance and Relief in Emergency Situations Fund (PM CARES Fund) has been launched by the government to collect funds to tackle COVID-19 challenges.
17. All the sanitation workers, nurses, ward boys, paramedics, technicians, ASHAs and other health workers along with doctors and specialists have been provided an insurance cover of Rs.50 Lakhs each

18. World's largest Covid Care Centre and Hospital has been set up in the national capital with a capacity of 10,000 beds under one roof.
19. Continuous training and capacity development of the frontline health workers at the Primary Level have ensured that lakhs of ASHAs workers have conducted vulnerability mapping surveys of Crores of households across the states. They are also screening inter-state passengers, migrant workers, and others for Covid-19 symptoms.
20. Private practitioners can now prescribe Covid-19 tests in addition to Government affiliated doctors.
21. Private Laboratories are free to test any individual as per the ICMR guidelines.
22. India's Bharat Biotech is in the process of developing its first indigenous corona virus vaccine COVAXIN and will soon undergo human trials. The vaccine is being developed in collaboration with the Indian Council of Medical Research (ICMR).Another indigenous vaccine has got the permission to conduct human trials by the Drugs Controller General of India(DCGI).It is being developed by Gujarat based Zydus Cadila Healthcare Company.

These measures and more have ensured that the recovery rates of Covid-19 in India has crossed 60% and aiding to contain the spread of COVID-19 and providing relief to the general population.

CONCLUSION

It's been more than 100 days since India went for a nationwide lockdown to combat the Corona virus pandemic. Since then restrictions on the movement of people, goods and services have been gradually eased but a return to normalcy seems still distant. With four consecutive days of record highs of new cases, India with around 7 Lakh cases as on the 6th July, 2020 has overtaken Russia and is now at the 3rd worst hit country across the world just after the United States and Brazil. The Case fatality rate of 2.8% is however the silver lining where we are much lower than the global rate of 4.7%.Also on the bright side our recovery rate is much better than the global rate. We are at 60% whereas the global recovery rate is around 56.6%.But the overall figures of the positive cases and the volume of new cases being added each day are consistently a cause of concern for us.

On the other side, India has progressed rapidly in its testing capacities compared to where we were a couple of months ago. India has crossed the threshold of 10 million samples tested and our average daily testing is around 200,000 samples and are looking to increase this to around 350,000 samples testing daily on an average basis which is our optimum capacity at present. This is a huge improvement on how things were in February,2020 where we could only achieve around 10,000 sample testing daily across the country from only 13 labs which were able to test for COVID-19.Now we have more than 1,100 Labs countrywide which are able to test for the Corona Virus.

India has also recently opened the World's largest Covid Care Centre and Hospital in New Delhi which is managed by the ITBP forces and has the capacity of more than 10,000 beds under one roof and size which equals to a cumulative 15 Football fields divided into two wings. This would give an shot in the arm for the treatment and critical care infrastructure for Covid-19 in India.

India also may be looking to change its HCQ or Hydroxychroloquine anti-malaria drug protocol after WHO has halted its trials and have asserted that it does not reduce mortality. Virus. India is relooking at its use of HCQ in this light. India uses HCQ not just to for

treatment for COVID-19 but is also being to frontline health workers to reduce their chances of contracting Corona virus.

Economically a survey by FICCI has revealed that only 17% of the companies in India are currently working at a capacity of more than 80%.With the exports diminishing, investment and capital formation rate plummeting and increase in the unemployment rates has added to the general gloom in the overall economic sentiments of the country. However the economy has started showing signs of sharp revival from previous months and there an uptick in demands of goods and services, exports, investment and other productive capacities of the economy while the supply side bottlenecks are slowly easing out to give way to a full run of the economy. Therefore there are multiple greenshoots in the economy now and a sustained effort by both the policy makers and the economic agents will surely bottom-out the slowdown currently experienced by the economy.

Finally we may conclude that the lockdown has been able to keep the Covid-19 reasonably well located in number of specific places namely Maharashtra, Gujarat, Delhi, Tamil Nadu and Rajasthan with its core concentration in the economically developed urban centres. It is very challenging to control the disease in very densely populated urban cities. The dedication and the tenacity with which the frontline health workers and the other health workers are working to effectively implement the government's Testing,Tracing,Treatment,Tracking and Teamwork strategy. While the number of cases may be high considering the absolute number but compared to the population of the country is not a very large number. Also the percentage of the positives on the testing has consistently been around 3-4%.With the unlocking of the country now underway and its commensurate movement of the people there is naturally going to be an uptick in the cases but it should be looked at a way that finally the infection has to go into the community to cause a build-up of a herd immunity and that is a long-term mechanism through which this COVID-19 infection can be reduced. We must realise that it can never be stopped all together but its severity and the number of people it infects can only be reduced. Historical experiences of many viruses and bacteria in the past has shown that it actually become less virulent over a period of time and so it spreads more without actually causing a severe disease or fatality.

The Government today has developed a capacity over a period of time to supress outbreaks of a major proportion in future because it has the various constituents of the health system in position and better prepared by experience than the initial outbreak of Covid-19. Hopefully with the right planning and execution in the future we may see stabilization in the number of cases and a further improvement in the rates of recovery and a far less fatalities than we are experiencing in the present scenario.

REPORT 2

Summer Training Assignment

Under the Guidance of

Dr.SD Gupta

Chairman IIHMR University, Jaipur

ONLINE COURSE

INTRODUCTION TO SYSTEMATIC REVIEW & META ANALYSIS

By

JOHNS HOPKINS UNIVERSITY

A REPORT BY

Rishabh Singh

MBA Hospital and Health Management

2019-2021

TABLE OF CONTENTS

REPORT 2: SYSTEMATIC REVIEW & META-ANALYSIS

ONLINE COURSE

ON

THE INTRODUCTION TO SYSTEMATIC REVIEW

AND

META-ANALYSIS

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

Course description:

A review article/paper is one that summarises the current understanding of a topic. It attempts to consolidate all the known information about a particular topic from previously published papers and present in a very comprehensive manner. It may also narrate the recent advancements and help to identify areas where gaps exist. However, it was felt that they have certain shortcomings, for example, the search strategy is not very replicable and often important individual studies are left out of the purview of the review. Hence, the idea of systematic reviews was conceptualised wherein it was held that the methods to collect the relevant data should be much more objective and should follow a scientific method. In addition, they should not only summarise the relevant studies but also critically evaluate them. So, in contrast to the review papers which seek to summarise all the current information, systematic reviews instead focus on answering a research question. The search strategy followed in systematic reviews is much more objective and scientific, and consequently more replicable. The main purpose of doing a systematic review is that no study relevant to the topic should be left out, which in turn would mean that redundant studies will be carried out.

Systematic reviews often, though not always, include what is called a 'meta-analysis', which refers to the statistical analysis of the quantitative data pooled from all the individual research papers. Since often there are multiple research studies done to answer the same question, it is a good idea to aggregate all the information and make a more robust estimate regarding the same. Appropriate statistical tools are employed depending upon the scope and rationale behind the meta-analysis.

Systematic reviews and meta-analysis are now being used widely in various fields, most prominently in public health and public policy. They are an important pillar of evidence based decision making. They are done by independent researchers as well as organisation such as Cochrane (a British international charitable organisation), the AHRQ (Agency for Healthcare Research and Quality and the NICE (National Institute for Health and Care Excellence).

Course objectives:

1. **To learn the steps of doing a systematic reviews and meta-analysis.**
2. **To read the relevant literature critically**
3. **To be able to integrate the results of the systematic review into the current work.**

Learning methodology for the entire course is a combination of video lectures, quizzes and readings

1. INTRODUCTION TO SYSTEMATIC REVIEW

- The course instructors introduce themselves and outline the major objectives of the course. They also brief about the flow of lectures during the course.
- All the necessary information regarding the course is mentioned in the brief reading. It covers the learning objectives, grading policy and other detailed aspects of the course. Next, a short survey aims to gauge the student in terms of his familiarity with reviews, systematic reviews and meta-analysis. It also tries to understand the purpose of the student for taking up the course, whether out of personal interest or to fulfil any academic purpose.
- Systematic reviews use explicit methods to identify, select, appraise and synthesise results from similar but separate studies. They may or may not include a meta-analysis. Meta-analysis is the statistical method of analysing a large collection of results from individual studies. Before proceeding ahead in order to understand the steps involved in doing a systematic review, it is essential to understand why we need them. The need for doing a systematic review arises because of the growing importance of evidence based decision making. Also, for any research/clinical question, there is a plethora of information in various forms- newspaper reports, case studies, research papers etc. But often the entire information is pretty much scattered and it is highly possible that in an attempt to gather all the information, some of it might be missed out. This might, in turn, effect the decision taken on the basis of the incomplete evidence. Hence we rely on systematic reviews. It is essential to understand here that systematic reviews differ from traditional narrative reviews in four aspects- identification of all the relevant evidence,

selection of most appropriate evidence, appraisal of the quality of the evidence and ultimately its summarisation. The distinguishing feature of systematic reviews is their scientific approach towards each step. Also, they are focused towards answering a specific question.

Thus the following steps are involved in a systematic review:

- ***Step1: Gather your Team***
- ***Step 2: Develop your Protocol***
- ***Step 3: Data collection- Locate, Screen and Collect Studies***
- ***Step 4: Abstract Data and Appraise Risk of Bias in Individual Studies***
- ***Step 5:Synthesise Findings, Interpret and Assess Overall Body of Evidence***
- ***Step 6: Write a Report***
- ***Step 7: Update***

They find application in various fields like evidence based healthcare, medicine, public health, policy making etc.

Evidence based decision making can thus help in the most efficient use of available resources as supported by newer concepts like CER (Comparative Effectiveness Research)

- After defining the meta-analysis as previously stated, an example of a 'forest plot' is given which is among the most frequently adopted tools for it. A forest plot combines visual representation of the 95% confidence intervals of all the short-listed studies for the meta-analysis. It then answers questions like: what is the direction of effect/association? What is the size of the effect? Is the effect consistent across studies? What is the strength of the effect for the association? Hence an effective meta-analysis helps to assess strength of evidence, combine results quantitatively (as they combine into a single summary result) and investigate heterogeneity across studies (i.e. to investigate the reason behind the differences in the studies). An important pre-requisite before combing the results of all the individual studies is to ensure that they specifically address the issue at hand. This is where the role of the researcher becomes paramount. He should look into the studies and filter out any such study which is not relevant to the analysis because of differences in the study population, methodology or any other details etc. it should be noted here that one should refrain from doing a meta-analysis if the

individual studies are not of much significance, or their credibility or authenticity is questionable.

- Majority of the systematic reviews are done by independent authors, independent researchers, clinicians who are interested in a particular topic. The most prominent organisations involved with systematic reviews, either for their own interest or doing contractually for the government- include:
    - **The Cochrane Collaboration (The Largest International Organisation alone producing around 40% of all Systematic Reviews)**
    - **The AHRQ (Agency for Healthcare Research and Quality)**
    - **The NICE (National Institute for Health and Care Excellence).**
    - **Hayes**
    - **ECRI (Economic Cycle Research Institute)**
- The Cochrane collaboration has published a handbook which often serves as a guide for people involved in doing systematic reviews.
- In the last few years, systematic reviews are being increasingly employed by policy makers, healthcare purchasers, and other regulatory authorities because they minimise bias (systematic errors) and reduce the probability of coming to chance conclusions, provide more precise estimates and allow decision making to be structured on the holistic evidence.

Key learnings:

- **We started by understanding the concepts of systematic reviews and meta-analysis, and why they are required in the first place. As much as it is important to do clinical research, it is equally important that all the developments at a certain point of time are summarised and presented in a review. However, systematic reviews have a certain edge over traditional narrative reviews owing to their scientific and more objective methodology. In systematic reviews, the search strategy employed is more scientific and structured, and hence more replicable. It leaves little room for any relevant study to be left out. At the same time, inclusion and exclusion criteria are well defined and researchers incorporate a study only after ensuring its credibility and relevance.**
    - We then learned the steps involved in doing a systematic review.
    - An excellent example of why systematic reviews and meta-analysis are required is thrombolytic therapy in preventing death in people who already had a heart attack. Though the first study was published in the 1960s, conclusive evidence

came late and multiple randomised controlled trials kept on happening till 1990s. Thus, a lot of lives could have been saved if we had been keeping track of the current evidence.

2. FRAMING THE QUESTION

1. **Resources for How to Frame Your Question**: The first and foremost step is to frame the research question. There are a few suggested frameworks which prove useful. One example is PICO (Problem/People, Intervention, and Comparison). A useful guide is the book “Finding what works in Healthcare: standards for systematic reviews” published by the institute of Medicine. It contains the standards which need to be followed while doing and writing the systematic review. For example, an important consideration is how to manage bias and conflict of interest among the members. Such issues need to be addressed before the actual review starts. This is followed by discussion among the group members to assert the need for a fresh review on the topic. After this, the process of formulating the research question starts. After coming up with a rough idea of what the research question should be, the group meets frequently till the research question is refined. Another much useful resource is the Cochrane Handbook for systematic reviews of interventions. It gives detailed explanations about the framing of the research question and is freely available on the internet. It can thus be referred as and when required.

2. **Deciding the Type and Scope of Your Question**: An important aspect of framing the research question is deciding the type of the question. Since we are dealing with decision making related to healthcare, our focus may be on any particular aspect of the entire spectrum of the epidemiology of the disease. Hence it should be first identified whether the focus is on incidence, prevalence, intervention or any other aspect of the disease. It is important to correctly identify the type of question because it will ultimately decide the further course of action for the systematic review, as different study designs will be involved. Others include therapy, screening, diagnostic accuracy, prognosis, harm and etiology type of questions. Consequently, an appropriate study design among surveys, cohort studies, clinical trials, cross sectional and case control studies is chosen. It is because of these reasons that systematic reviews are considered the most refined form of evidence.

The importance of framing the ‘right’ research question cannot be stressed enough. An important feature of a good research question is that it is neither too broad nor too

narrow. Problems arise in both cases. If the question is too broad, it often becomes vague and one might end up comparing apples and oranges. The search on multiple databases thus yields too many results and summarising them becomes daunting. On the other hand, if the question is too narrow, finding sufficient amount of evidence becomes difficult. They may also give spurious or biased findings which will defeat the purpose of doing the systematic review.

3. **Elements of the Question**: The framing of the research question usually starts with the framing of a preliminary one. Then all the related aspects are looked upon, for example the symptoms of the disease, the suspected risk factors, any particular preventive or treatment therapy or the side effects of a treatment. After carefully analysing these different aspects the researchers must agree to narrow down to a particular aspect only, since the approach to address different questions will require different study designs. This is known as refining the question. It is a very crucial step as it will guide the further steps- like defining the inclusion and exclusion criteria, and also help in developing the search strategy.

   Next, the elements of a research question are detailed. As previously mentioned, one of the most frequently used framework for designing the research question is the PICO framework. P stands for people, population or patients. As for any step, defining everything explicitly always helps. Hence, the disease condition should be defined clearly, either in line with that of the included studies or stated otherwise. Other details of the population- community or hospital based etc. should be mentioned clearly. Exposure or Intervention should clearly state details like the duration, mode, dosage, route of administration etc. Choosing an appropriate comparison group while taking into consideration all the ethical issues is also important. The comparison group should also meet the required criteria. Defining outcomes is quite challenging and should be finalised after consider the viewpoints of all the stakeholders. Thus, a well-defined research question should have all these components.

4. **Refining the Question**: Refining of the question often involves mentioning the specific metrics of each element of the research question. For example, for people we may want to specify what age group we are considering, exact definition of the disease, the demographic factors, other relevant characteristics etc. For interventions, details like dosage, mode of delivery and duration; and answering questions like whether variations should be included, whether interventions involving some other additional intervention should be included. For outcomes, it should be mentioned as to which domain, for

example anxiety is of interest. How exactly will that be measured for example Hamilton Anxiety Rating Scale. What method of aggregation would be used? Will it be mean, median or some other measure?

Another way of refining the research question is adding elements like time (PICOT) wherein details like duration of minimum follow up is mentioned. Setting of the systematic review (PICOTS) may also be included like primary care, speciality, or inpatients, to enhance the applicability of the findings of the study. Lastly, it is good to have an open mind while framing and refining the question. It means that it is good to have a fair idea about the topic before proceeding, and improvise the question gradually. One must also take care to not be swayed by the data gathered from the search databases.

5. **Some Examples**: The basic idea is to include all the components of the PICO (or PICOT/PICOTS) framework, though not necessarily in that order. It means that the outcome, let's say, may precede the intervention in the research question. Also, sometimes it is not feasible to include all the components in the research question. In that case, those elements should be then clearly included in the abstract and at relevant places in the main text. A good research question, therefore, not only includes all the components but also defines them very clearly so as to remove any scope for ambiguity. Examples mentioned in the video are: "Does moderate to heavy alcohol consumption reduce the risk of stroke?" Here the P represents adults with previous stroke episode. The exposure was alcohol consumption which had quite a broader definition, as it didn't mention explicitly whether it was to be measured in terms of daily or monthly consumption, in terms of volume etc. the comparison group was non-drinkers, and the outcome was ischemic or haemorrhagic stroke or both.

6. **Analytic Frameworks**: Also known as conceptual frameworks, logic models, influence diagrams, theoretical frameworks etc. They are particularly useful when multiple questions are addressed in a single review. They are more concerned about the 'bigger picture' and how everything is connected rather than the details. They often use graphic depictions symbols. Having the component of analytical framework helps to decide if the collected data is sufficient or not.

Key learnings:

- **A few brainstorming sessions are required for the team to come up with a preliminary question. The two most useful resources for this step are "Finding**

what works in Healthcare: standards for systematic reviews" and the Cochrane Handbook for systematic reviews of interventions.

- **The type of question to be addressed should be decided early in the process as it will determine the course of subsequent steps. Since different question types require different study designs, it is essential to correctly identify it. Also, the question should not be too broad or narrow, as both have their own demerits.**
- **The PICO framework is the most commonly used one for guiding the structure of the research question. P stands for people, population or patients, E for Exposure or Intervention, C for comparison group and O for outcomes. Additional elements like time and setting may be added if deemed necessary.**
- **All definitions should be explicitly mentioned, as they may otherwise become ambiguous later on. Details like specific metrics should be clearly stated and additional elements if time and setting may be added for further refining of the research question.**
- **An additional component of the systematic review is an analytical framework. They enhance the objectivity of the entire process and help to incorporate data in a more systematic manner.**

3. FINDING THE EVIDENCE- SEARCHING PRINCIPLES

1. **Finding the Evidence: Searching Principles**: Once the research question has been framed and refined, the next step is to find the relevant evidence. For this, few things should be kept in mind. The researchers should be thorough with the inclusion and exclusion criteria and it is a good idea to review them before starting the search. For highly sophisticated systematic reviews, one might want to include an information specialist so that no precious information is left out. At the same time, it must be noted that searching a single database is not enough. After developing the complete search protocol, hand searching may also prove to be useful and must not be skipped. Documentation of the entire process is very essential and will be needed if step needs to be revisited. It will also ensure that any source of bias will be removed.

2. **Identifying Key Sources and Techniques for Searching**: One of the most helpful search strategies is the use of 'controlled vocabulary'. It refers to the standardised arrangements used to describe a text which facilitates retrieval. One should always search multiple databases and not restrict to one or two, as each database is likely to yield unique search results.

The major bibliographic databases are listed below:

- Medline/Pubmed (https://pubmed.ncbi.nlm.nih.gov/
- EMBASE (www.embase.com)
- Cochrane central register of controlled trials-CENTRAL (www.thecochranelibrary.com)
- LILACS (www.lilacs.bvsalud.org)
- CINAHL (www.ebscohost.com/academic/cinahl-plus-with-full-text)
- PsychINFO (https://www.apa.org/pubs/databases/psycinfo/)
- OTSeeker (www.otseeker.com)
- Web of Science (www.thomsonreuters.com)
- Scopus (www.scopus.com)

The presence of features like subheadings and descriptors in PubMED are quite useful. One can also try using broader and narrower terms and play around other features of PubMED and other bibliographic databases to get search results. One should try to use all possible synonyms of the keywords to generate all the relevant research articles. Searching the relevant material for observational studies can be challenging as they require more diverse and broader terms. Web of science is much broader in terms of the disciplines it covers.

Another useful approach is something called as ‘snowballing’. One should go through the list of references of each article or the ones which cited those articles. This method also yields relevant articles. However, in many databases, one can find such articles under the heading ‘similar’ or ‘related’.

One must also consider the ‘grey literature’, which is the unpublished literature or those articles/white papers/working papers of organisations other than the academic ones. For this www.scrius.com might prove useful as it is tailored to fing high quality literature and various sources from the open web. Similarly, if the systematic review is concerned with clinical trials, one must visit the FDA website to get the latest updates. Lastly, the opinion of industry experts or other people working on that topic might give additional insights as well.

3. **Building a High-Quality Search Strategy**: The basic principle behind building any high quality search strategy is that it should be replicable. Also, each and every step should be well documented. One should start with a relatively simple search, and retrieve the initial results. Then the keywords in each article/review should be carefully analysed and all such keywords can then be summarised in a tabular form. It should then assessed as to which keywords would add value to the search strategy, and the search should be

repeated after that. It is equally important to document all those terms which did not yield valuable results to avoid redundant work later.

The research question should be broken down into smaller concepts using the PICO framework. Then, controlled vocabulary, including truncation, and Boolean logic words like 'AND', 'OR', 'Not' should be used to get manageable set of results. It is a good idea to review the search details that are displayed to avoid any unwanted results. As in the case with PubMED, for example, filtering of the search results according to the publication type, changing the display settings (to view the abstract only/citations/references etc.) should be done. Field codes identify the specific fields where that particular piece of information has been put. Other filters like study design, type of the article, year of publication, original language etc. can be used. This entire process is iterative and needs to be repeated until the optimal search strategy has been framed.

4. **Documenting Your Search and Conclusions**: For documentation of the entire process, bibliographic management softwares can be used. A few of them are EndNote, RefWorks, Reference Manager and QUOSA. One should record when the search was performed, i.e. the date and time, along with details like the sources, the databases and the exact strategy used. The number of results thus generated should also be noted.

   A standard for reporting systematic reviews is PRISMA. It contains certain checklists and serve as a guide to check if the systematic reviews meets their criteria for publishing. According to it, one must also mention the number of duplicate articles found, if any, and the final number of studies included in the synthesis after screening.

   Documentation of the entire process would also help to clear any ambiguity, if it arises at a later point of time. It will also be useful if any step needs to be revisited.

Key learnings:

- **Before starting the actual process of finding the relevant literature, inclusion and exclusion criteria must be specified in a very clear manner. If needed, an information specialist may also be included in the team.**
- **Searching a single database would not do justice to the systematic review. One must search multiple databases and even manual searching must be used. All the features of a particular database must be explored sincerely in order so that none of the relevant articles is left out.**
- **The relevant literature should be searched strategically using techniques like controlled vocabulary, Boolean logic words, synonyms, truncation and snowballing.**

- **The search strategy should not be limited to the conventional databases and the 'grey literature' should also be searched.**
- **The key idea is to break the research question into smaller concepts using the PICO framework. The preliminary search strategy should be simple and revised time and again until it yields manageable search results.**
- **Lastly, each and every step should be documented so that any ambiguity, if it arises later, can be resolved and the search strategy revised accordingly. For this purpose, one might use any bibliographic management softwares like EndNote, RefWorks, Reference Manager and QUOSA.**

4. ASSESSING THE RISK OF BIAS IN CLINICAL TRIALS

1. **Why Bias in the Individual Study is Important to a Systematic Review and Meta-Analysis?** : The aim is to have low risk of bias, both in the individual studies as well as the systematic review. In order to do that, we need to understand its importance and the potential sources of bias included in the systematic review. First of all, one should realise that including studies with risk of bias, or 'low quality studies' might render the entire exercise useless. In other words, the entire systematic review will become biased. By reading a study, one can assess its internal and external validity to a limited extent only. There will still be many things which will be difficult to ascertain about the study like the authenticity of the data, adherence to the respective guidelines etc. This leaves room for bias and hence should be taken care of, because the resultant quality of the systematic review and meta-analysis depends on that of the individual studies. Three types of bias may occur – selection bias, information bias and bias in the analysis.

2. **Selection Bias**: Selection bias occurs when there is a failure to achieve true randomisation. Subjects are randomly assigned to any of the treatment groups to account for the known and unknown confounding factors. Nowadays, sophisticated computer programs are available which can do that. If not randomised, the results are biased and hence lead to incorrect conclusions.

   Allocation concealment happens at the very outset of the clinical trial and brings an additional way of ensuring that no one knows to what treatment group a subject will be assigned. There is evidence that allocation concealment prevents skewing of results and hence having it in place is beneficial. However, it should be executed properly otherwise

it might result in distorted results. In case any of the staff is involved in allocating the group, safeguards must be ensured to prevent any leak of information.

3. **Information Bias**: This refers to getting the correct information from the doctor, patients and recording it correctly. A commonly employed technique to minimise this type of bias is called masking or blinding. It simply refers to withholding information from a certain group, and accordingly, can be done at three levels- the patient, the physician and the person recording and processing the information. One should look into the individual studies to find which types of masking were used. It also must be checked whether there could have been any possible way of negating that masking (for example, surgery v/s no surgery). Those studies which offer low risk of bias, i.e. which include masking would be preferred. Conversely, those studies which do not employ masking or where they can easily be broken are at high risk of bias. Evidence shows that studies which do not employ at least double masking tend to show a more favourable result in terms of the treatment used. This effect is more pronounced when the outcome is subjective. Hence, this is one area which needs adequate attention.

4. **Bias in the analysis**: It must be noted that this is called bias in the analysis, and not analysis bias. This ultimately arises because of missing data for reasons like losses to follow up, non-compliance and withdrawals. How the team of researchers will address these issues needs to be decided before the start of the study. It will be also unsafe to say that if equal amount of data is missing from the treatment and control group it will simply negate the effect of each other. It is upon the judgement of the team to decide how much missing data will be considered as compromised.

   This type of bias can be minimised using any of the two methods- the intention to treat analysis and sticking to pre-decided outcomes instead of switching them at the end. Switching outcomes can take any form- either changing the very definition of the outcome or any detail of it; or by simply changing the time period at which it will be measured. Hence the ‘primary outcome’, ‘secondary outcome’ and so on is pre decided before the start of the study. Doing otherwise makes the study prone to ‘type I’ error wherein there is an incorrect conclusion that there is a difference between the two intervention groups, while in reality there is none. The ‘ideal’ number of outcomes is still being debated though. Another point of consideration while combining the results is to look at the level to which the outcome has been detailed. Combining results from studies which have different levels of details for the outcomes will result in a distorted conclusion. Hence to maintain uniformity, clinicaltrials.gov and other authorities suggest

five levels of outcomes. The first is domain, like pain, visual acuity, anxiety etc. Next is the specific measurement used – for example the Hamilton Anxiety Rating Scale. The third level is the specific metric used or how the change was measured- it could be change from baseline, end value or the time to event. Fourth level is the method of aggregation used- continuous (mean/median) or categorical (proportion of participants with 50% or more decrease). Final level is the timepoint, for example one year, one month etc. This is indeed an area of concern and people are trying to address it. One way is to have open access to the clinical trials data.

5. **Displaying Study "Quality" in Your Systematic Review**: Although quite subjective, study quality basically refers to minimum amount of bias. An out-dated method of doing so, however, is assigning something called as quality scores to a study. They might be generic in nature, i.e. common to all fields of study or may be field-specific. However such scores are not reliable and often have their own limitations. A few other ways to address quality are:
    a. Exclusion of all such studies from the meta-analysis which do not have randomisation; exclusion of conference proceedings
    b. Making a risk of bias table: specifically addressing the risk of bias in all the individual studies in a tabular format
    c. Setting a ‘quality threshold’ in terms of the minimum sample size or number of events
    d. Making the studies for different settings, for example, segregated in the forest plot
    e. Assign a weight to the risk of bias in a regression equation
    f. Perform sensitivity analysis, by repeating the analysis after excluding studies which have high risk of bias

The sensitivity analysis can be done along the following lines: method of randomisation, allocation concealment, masking, intention to treat analysis and completeness of follow-up. Other approaches like changing the inclusion criteria and including unpublished results can also be used. If the same conclusions can be drawn, however, it indicates that the conclusions are robust. Following certain recommendations like those of the CONSORT (Consolidated standards of reporting trails) statement, which is an evidence based set of recommendation for the reporting of clinical trials is also a good idea. Similarly, the STOBE statement (strengthening of reporting of observational studies in epidemiology) can serve as a useful guide for doing systematic reviews of observational studies.

Key learnings:

- **Since the quality of the systematic review depends to a large extent on the quality of the individual studies, it is essential to ensure that the studies being included have low risk of bias. If left unaddressed, this might cast a doubt on the credibility of the systematic review.**
- **Three types of bias may occur- selection bias, information bias and bias in the analysis.**
- **Selection bias occurs when there is a failure to achieve true randomisation. Subjects are randomly assigned to any of the treatment groups to account for the known and unknown confounding factors. Nowadays, sophisticated computer programs are available which can do that. If not randomised, the results are biased and hence lead to incorrect conclusions. This can also be addressed using allocation concealement.**
- **To minimise information bias, the most commonly employed technique is called masking or blinding. It simply refers to withholding information from a certain group, and accordingly, can be done at three levels- the patient, the physician and the person recording and processing the information. Evidence shows that studies which do not employ at least double masking tend to show a more favourable result in terms of the treatment used. This effect is more pronounced when the outcome is subjective.**
- **Bias in the analysis arises because of missing data for reasons like losses to follow up, non-compliance and withdrawals. How the team of researchers will address these issues needs to be decided before the start of the study. This type of bias can be minimised using any of the two methods- the intention to treat analysis and sticking to pre-decided outcomes instead of switching them at the end. To maintain uniformity, clinicaltrials.gov and other authorities suggest five levels of outcomes- domain, specific measurement, specific metric used, method of aggregation and time point.**
- **The way to ensure quality in the systematic review is by addressing quality in each individual study. Ways to ensure quality are excluding all those studies which have high risk of bias, summarising bias in the individual studies in a tabular format and performing sensitivity analysis.**

5. MINIMISING META-BIAS

1. **Standards for Systematic Reviews**: Having a standardised approach is important not just for searching the relevant literature but also for doing the actual review part. Till the 1990s, there was not much uniformity in how the reviews were carried out. Gradually, it was felt that there should be standardised methods for the further steps as well. Also, addressing bias in the individual studies is not sufficient. The scope of bias in the systematic review must be addressed as well. All of this must be done in accordance to some prescribed guidelines, like the ones given in The Institute of Medicine's handbook: 'Finding what works in healthcare: Standards for systematic reviews'.

2. **Selection Bias**: Meta-bias refers to the resultant bias in the systematic review. The most important selection bias is called reporting bias, which refers to the influence of the direction of the results on the nature of reporting. It may be in the form of publication bias- wherein unpublished studies tend to possess different results. It may be in the form of selective outcome reporting, wherein less severe side effects of a drug, for example, might be selectively reported. Or it may be ascertainment bias- whether the 'easy to find' studies show the same results as those which cannot be found so easily, for example those published in some regional journals. The other prominent type of selection bias is the inclusion bias, when the authors knowingly shape the inclusion and exclusion criteria because they are well aware about the topic of the systematic review. Evidence shows that publication favours positive results, and this is to be kept in mind while doing the systematic review. A study published by Su Jen Song categorises the different types of studies as inception cohorts- studies that came through some particular ethics committee and regulatory cohorts- studies that came through FDA or some other regulatory authority. The results show that there is a tendency for studies with positive results to be published more likely than those with negative results. Hence, one of the standards of the IoM says that unpublished data should also be actively looked for, as its inclusion is likely to affect the result of the meta-analysis.

   As part of the mandatory reporting of the results for every activity, the results are also published on clinicaltrials.gov in a much more comprehensive manner that in the academic journals. Hence, clinicaltrials.gov should also be consulted.

The first major report of selective outcome reporting came in JAMA in 2004. Nearly two thirds of the studies examined showed change in the primary outcome. Because of these reasons, it becomes even more important to look into the 'grey literature' rather than solely relying on published data. At times, the researchers doing the systematic review also get in touch with the authors of the unpublished data to understand it from their perspective.

3. **Information Bias**: The main concerns here are accuracy of quality assessment, accuracy of data abstraction and completeness of data abstraction. Inclusion bias in this context refers to the influence of the knowledge of investigators on any of these parameters. Studies have also addressed the effect of masking reviewers to the authors, journals, institution and study results; and it was found that there is no significant difference in the cases where masking was done and not. This was done through the method of differential photocopying to assess the potential bias to see if the reviewers were more likely to include citations from higher quality journals or from researchers whose work they were familiar with.

   Other areas of concern are when the data is deduced from a graph or short report- it may sometimes not give the complete picture about the study. Next, the impact of abstractor experience may also influence the aggregate data gathered at the end of the process. Lastly, published data cannot be relied upon blindly and care must be taken to verify it, if possible, through other sources.

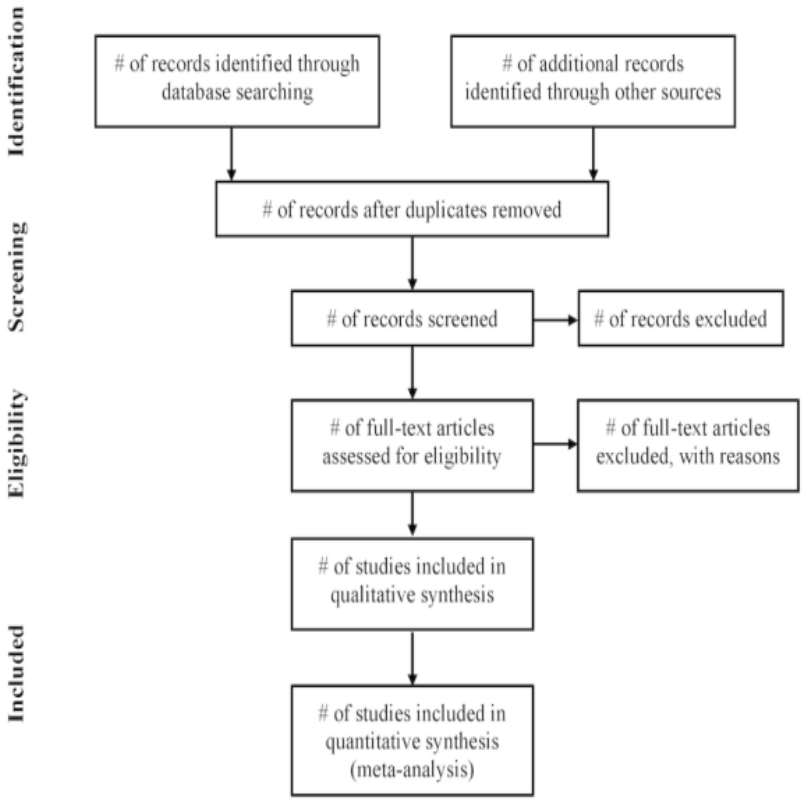
   When comparison of the error rates between novice and experienced researchers was done, it was found that the error rates were similar. The only difference, however, was that the novice researchers took more time for the process. One final way of minimising the information bias is by doing double data extraction- either by verification of the search results of one researcher by the other or by comparing the search results from two independent researchers. However, this is expensive and more time consuming, and may not work very well in resource limited settings.

4. **Bias in the Analysis**: The statistical method employed might also influence the analysis. For example, the results of the meta-analysis would differ depending upon which of the two methods were used- fixed effects or random effects model. Usually, when there is statistical heterogeneity, the random effects model is used. However, with little or no statistical heterogeneity, it does not matter much as to which model is used.

   Another intriguing thing is that systematic reviews on the same topic often have different answers. Thus, there seems to be a dichotomy in here. However, upon

closer examination, it can be understood that this steams from difference in the scientific methods used- like questions asked in the systematic reviews were quite different from each other. So, these reviews also differ in terms of the search strategy used, their inclusion and exclusion criteria and the endpoints used. This has been illustrated with the help of an example, through the comparison between a Cochrane systematic review and one published in Annals of internal medicine. Both reviews addressed the same topic – the use of *H. pylori* for non-ulcer dyspepsia. Because the Cochrane review was done some time later than the other study, it was able to include three more studies and the chance to clarify a certain endpoint with the author of one study. This resulted in the Cochrane review favouring the intervention, whereas the Annals of internal medicine study was more or less neutral. Differences in systematic reviews can also be understood in terms of transparent reporting.

5. **<u>Reporting Transparently</u>**: This basically refers to adhering to the prescribed standards or guidelines, notably the PRISMA guidelines for systematic review. They also contain certain checklists as shown below:



Another set of standards for meta-analysis is the MOOSE (Meta-analysis of observational studies in epidemiology). The most important one is the GRADE approach to summarise the body of evidence.

Study Design	Confidence in estimates	Lower if	Higher if
Randomised trial →	High	Risk of bias - 1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study →	Low		
	Very low		

Key learnings:

- **Since there was not much uniformity in the methods adopted by different investigators for doing systematic reviews, the need was felt to standardise the whole process. Apart from a standardised approach for the search strategy, all of the subsequent steps must be done in accordance to some prescribed guidelines, like the ones given in The Institute of Medicine's handbook: 'Finding what works in healthcare: Standards for systematic reviews'.**
- **Meta-bias refers to the resultant bias in the systematic review. The most important selection bias is called reporting bias, which refers to the influence of the direction of the results on the nature of reporting. Other forms are publication bias- wherein unpublished studies tend to possess different results or selective outcome reporting, wherein less severe side effects of a drug, for example, might be selectively reported. Or it may be ascertainment bias- whether the 'easy to find' studies show the same results as those which cannot be found so easily, for example those published in some regional journals. The other prominent type of selection bias is the inclusion bias, when the authors knowingly shape the inclusion and exclusion criteria because they are well aware about the topic of the systematic review. The investigators must be aware of such types of bias.**
- **Information Bias may occur with respect to accuracy of quality assessment, accuracy of data abstraction and completeness of data abstraction. It refers to the influence of the knowledge of investigators on any of these parameters.**
- **Other areas of concern are when the data is deduced from a graph or short report, the impact of abstractor experience and the need to critique published data.**
- **The statistical method employed might also influence the analysis. For example, the results of the meta-analysis would differ depending upon which of the two**

methods were used- fixed effects or random effects model. Usually, when there is statistical heterogeneity, the random effects model is used. However, with little or no statistical heterogeneity, it does not matter much as to which model is used.

- **Often, it is observed that systematic reviews on the same topic have different answers. It needs to be understood here that they might have tried to answer different questions, and employed different strategies at each step of the entire process.**
- **Of late, increasing stress has been laid upon transparent reporting. This simply means to adhere to the prescribed guidelines like PRISMA, which helps to address any ambiguity**.

6. QUALITATIVE SYNTHESIS AND INTERPRETING RESULTS

1. **Qualitative Synthesis and Interpreting Results**: The whole idea of doing a systematic review is to have the most updated information about the topic of interest, and also to transmit that knowledge to the audience. It must be noted here that meta-analysis and systematic review do not mean the same thing. A systematic review may or may not have the component of a meta-analysis which basically means to 'make sense' of the aggregate information gathered at the end of a systematic review. This should typically be included in the 'results' section of the systematic review as a separate entity. This is also one area whose differential handling gives rise to the 'differences' in the different systematic review. It is because the interpretation of the aggregate literature is quite subjective.

2. **What is Qualitative Synthesis?**: Qualitative synthesis refers to 'an assessment of the body of evidence that goes beyond factual descriptions or tables that, for example, simply detail how many studies were assessed, the reasons for excluding studies. The range of study sizes and treatments compared, or the quality of each study as measured by a risk of bias tool'. It is more about conveying the understanding of the researchers and what their judgement has to say about the evidence. How relevant they think is the evidence, what potential impact could the missing data have, and addressing similar questions. The aim of the qualitative synthesis is therefore to identify patterns in the evidence and help the readers to gain a deeper understanding of it. It also aims to introduce the reader to the clinical background of the research problem, critically analyse the evidence, and identify similarities and differences in the individual studies and therefore the difference in the results.

Hence, the following items are described in the qualitative synthesis:

- **Technical details of the individual studies like their sample size, methodology etc.**
- **Strengths and limitations of the included studies**
- **Potential sources of bias in the interpretation of the included studies**
- **How study characteristics might be related to the results/findings**
- **Significance of included studies in terms of relevance at the level of community, population, setting etc.**

In summary, **the qualitative synthesis seeks to describe the nature of evidence in the literature, interpret the possible effect of the differences among the individual studies, and evaluate the strengths and weaknesses of the evidence base**.

3. **Some Examples**: This section mentions examples of systematic reviews wherein qualitative synthesis was performed. There is no 'right' or 'wrong' way of doing it but if done properly, it adds quality to the systematic review.

Key learnings:

- **What distinguishes a systematic review is that it goes one step ahead of stating just the factual information. It makes sense of the gathered literature and helps the reader to interpret them. Thus, the purpose of a systematic review to disseminate the knowledge ascertained by the investigators to the readers.**
- **Qualitative synthesis refers to 'an assessment of the body of evidence that goes beyond factual descriptions or tables that, for example, simply detail how many studies were assessed, the reasons for excluding studies. The range of study sizes and treatments compared, or the quality of each study as measured by a risk of bias tool'.**
- **The aim of the qualitative synthesis is therefore to identify patterns in the evidence and help the readers to gain a deeper understanding of it. It seeks to describe the nature of evidence in the literature, interpret the possible effect of the differences among the individual studies, and evaluate the strengths and weaknesses of the evidence base.**

7. PLANNING THE META-ANALYSIS

1. **Planning Your Meta-Analysis**: This is an optional component of the entire systematic review. A pre-requisite to a successful meta-analysis is to pay adequate attention to all the preceding steps, right from formulating the research question to the qualitative synthesis. While qualitative analysis refers to the structured description and discussion of the included studies, a quantitative analysis involves statistical analysis and is called the meta-analysis.

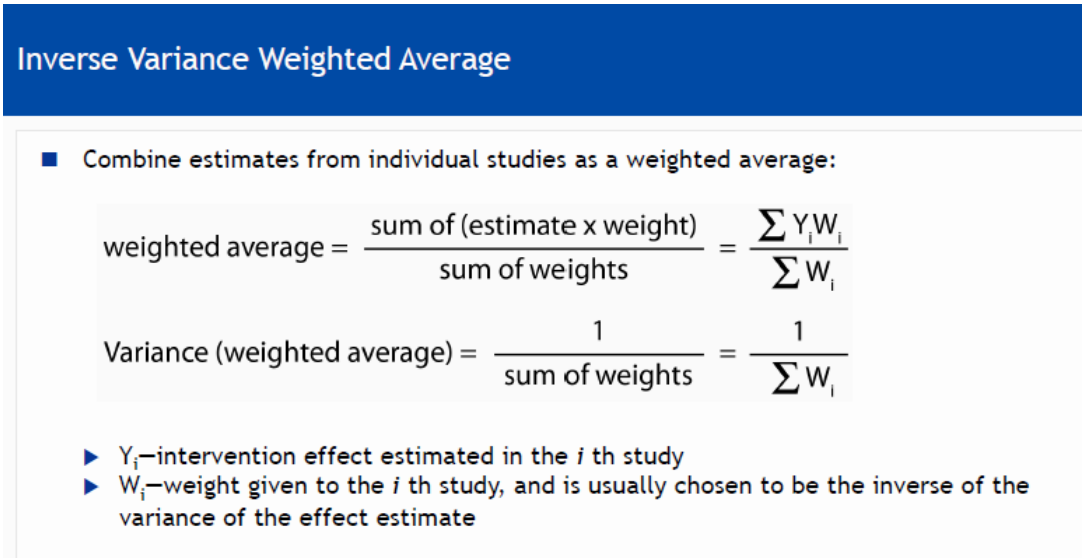
   A general framework for doing the meta-analysis involves answering the following questions: what is the direction of the effect/association? What is the size of the effect? Is the effect consistent across studies? What is the strength for the evidence?

   The method followed for the meta-analysis would depend on the aim of the review. If the aim is to obtain the size of the effect and say, two interventions are being compared, then standard pair-wise meta-analysis would be used. In case when multiple interventions for the same condition are to be compared, for example assessing multiple interventions for primary glaucoma- network meta-analysis would be used. Similarly, to investigate the relationship between the size of an effect and a certain characteristic of the study, meta-regression would be used.

2. **Introduction to Meta-Analysis**: According to Glass (1976), meta-analysis is “the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings”. Which studies should be included, though, is upon the discretion and judgement of the analysts.

   The rationale for combining results is that the individual studies are trying to address the same question and estimating a common effect. Forest plot is most commonly used for meta-analysis, which each dot (or the chosen symbol) representing the point estimate, and the line showing the 95% confidence interval. The overall measure of effect is a weighted average of the results of the individual studies.

   One can also use the inverse variance weighted average as shown below:



The process of assigning weight to a particular study starts with finding the odds ratio after making the 2X2 table. Next, Yi is calculated as the log of the odds ratio, and Wi as the inverse of the variance. All these parameters are then calculated for all the individual studies, and then tabulated. Since variance is an indicator of the precision of the study, logically a study with less variance should be allotted more weight. Hence, weight is the inverse of the variance of that particular study. The product of variance and weight is then divided by the sum of the weights to get the weighted average.

To get the pooled OR, back calculation is done to get the value from the weighted average. Once the OR is obtained, it is easy to get the 95% confidence interval using the standard approach. Any of the available softwares can be used for the meta-analysis, like MetaStat, MetaWin, RevMan etc.

Utmost care must be taken for the interpretation of the results of the meta-analysis. If the results are statistically significant, it does not necessarily mean their clinical significance also. Also, if the results are not statistically significant, they might still hold some clinical significance.

3. **Why Do a Meta-Analysis?:** The reasons for doing meta-analysis include:
    - To increase the power and precision: as it helps to improve precision by giving narrower confidence intervals
    - To quantify effect sizes and uncertainty: since there is sampling variation, it leads to uncertainty in individual studies which can be addressed in the meta-analysis
    - To assess homogeneity/heterogeneity of results: meta-analysis helps in quantifying the variation across studies

- To answer those questions which could not be answered by the individual studies, for example, comparative effectiveness of multiple interventions
- To settle any conflict between studies

Doing a meta-analysis is often the first step towards generating a new hypothesis, as one can clearly see the deficiencies in the existing literature. Another important matter of concern is when not to do a meta-analysis. The first principle here is that of 'garbage in – garbage out'. It simply means that if the related literature is of questionable quality, i.e. there is a concern regarding any bias in the individual studies, then it is advisable not to proceed for meta-analysis. In such a case the resultant meta-analysis will not add any value to the existing literature. Also, the studies should be comparable enough. If that is not the case, one will end up in comparing apples with oranges.

4. **Types of Data and Effect Measures**: In systematic reviews, the 'effect' may refer to the effect of healthcare interventions, or the measurement of incidence or prevalence, or the association between an exposure and an outcome. They are called effect measures or measures of association. The appropriate measures are used like odds ratio, relative risk, or any other measure which is considered suitable for the context and type of data. To recap, types of data and appropriate measures of association may be:
    - Dichotomous (dead/alive) – RR (risk ratio), OR (odds ratio), risk difference, NNT (number needed to treat)
    - Continuous data like blood pressure – mean difference or standardised mean difference
    - Ordinal data (none/mild/severe)
    - Counts of infrequent events like number of strokes
    - Time-to-event like survival times – hazard ratios

Risk ratio is easy to interpret but can only be used if there is a comparison group and in case of multivariate analyses. On the other hand, odds ratio can be calculated in certain cases like case-control study where absolute risk cannot be determined. However, their interpretation can be challenging, especially when the baseline rate is more than 20%. One must be cautious to not confuse OR and RR. If OR is misinterpreted as RR, it tends to overestimate the intervention effect. Sometimes studies dealing with rare diseases show zero values for observations. In that case, the software used for analysis takes care of it, usually by assigning a fixed value of 0.5 to all the zero-cells. If, however, there are no events in both scenarios of intervention and no intervention, it is advisable to exclude such studies from the meta-analysis. Alternatively, risk difference can also be used as it gives a direct

estimate of the number and hence easy to interpret. Another advantage of risk difference is that it can be calculated for any study design.

Mean difference is simply the difference between the means, whereas the standardised mean difference is the number of standard deviations difference between groups. It can be found by dividing the difference in mean outcome between groups by the standard deviation of outcome in the participants. Standardised mean difference is used when the units or scales of the means differ.

Key learnings:

- **A pre-requisite to a successful meta-analysis is to pay adequate attention to all the preceding steps, right from formulating the research question to the qualitative synthesis.**
- **The method followed for the meta-analysis would depend on the aim of the review: the different methods being pair-wise meta-analysis, network meta-analysis and meta-regression.**
- **The rationale for combining results is that the individual studies are trying to address the same question and estimating a common effect. Forest plot is most commonly used for meta-analysis, which each dot (or the chosen symbol) representing the point estimate, and the line showing the 95% confidence interval. The overall measure of effect is a weighted average of the results of the individual studies.**
- **Utmost care must be taken for the interpretation of the results of the meta-analysis. If the results are statistically significant, it does not necessarily mean their clinical significance also. Also, if the results are not statistically significant, they might still hold some clinical significance.**
- **A meta-analysis should not be done if the related literature is of questionable quality, i.e. there is a concern regarding any bias in the individual studies, or if the studies are not comparable enough.**
- **After careful identification of the data, appropriate measures of association should be used.**

8. STATISTICAL METHODS FOR META-ANALYSIS:

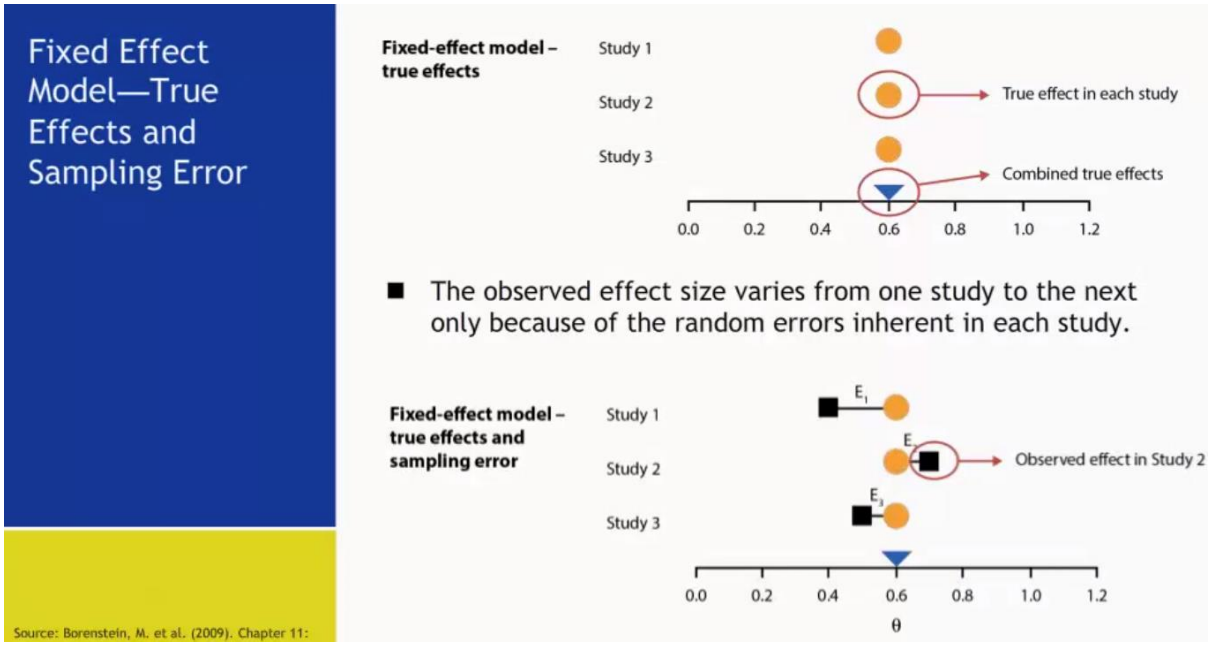
A Meta-analysis is an optional component of a systematic review. Which means not every single systematic review would have a meta-analysis, although every single systematic review would have the qualitative synthesis.

Meta-analysis is the statistical analysis which combines the results of several independent studies considered by the analyst to be combinable hence a systematic reviewer has to make the decision whether the studies are similar enough to be put together in a meta-analysis. So for meta-analysis, we including a set of individual independent studies taking weighted average of each study. So the weight reflects the varying importance of each study in one's meta-analysis. We assign more weight if there's more information in that particular study. And the more information is primarily affected by the sample size, as well as the number of events that occurred in that study. So more information will lead to increased precision in the individual study, and more precision overall will lead to increased precision in one's meta-analysis results.

There are two types of models for meta-analysis:

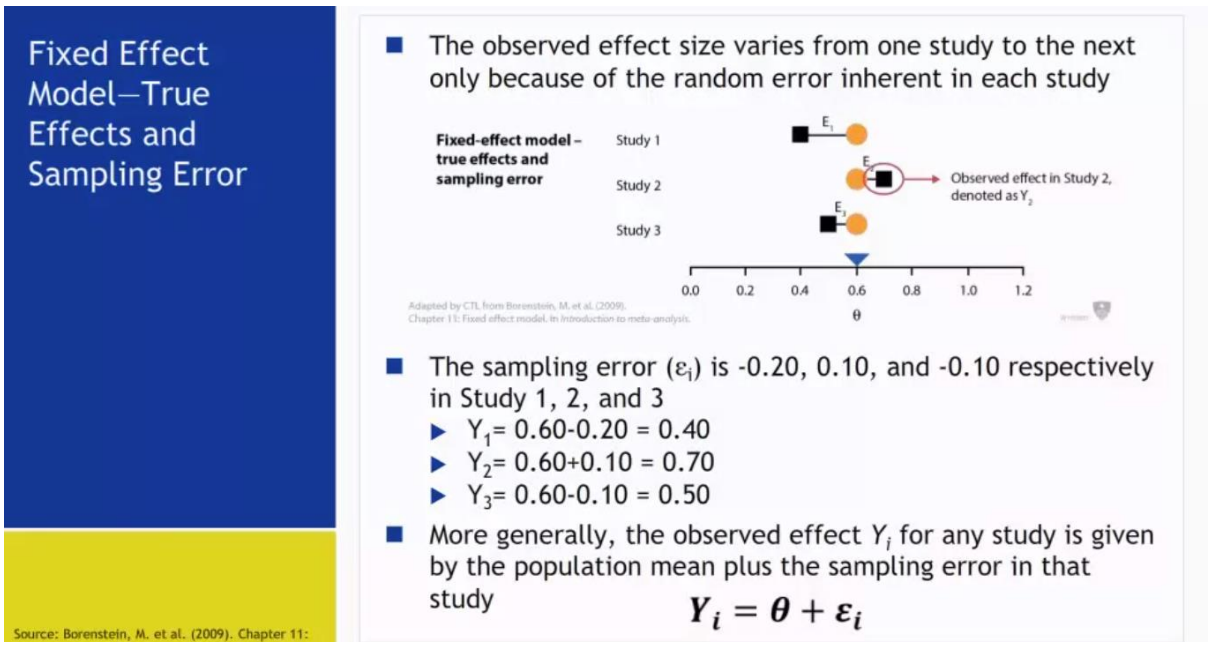
1. **Fixed effect model**
2. **Random effects model**

1. **Fixed Effect Model**: Under the fixed effect model, we assume that all studies, one is including in one's meta-analysis are measuring the same, common (true) effect size. It means that, if it's not for random or sampling error all results in those individual studies would be identical. Under the fixed effect model, we assume that each individual study estimated a true common effect size.

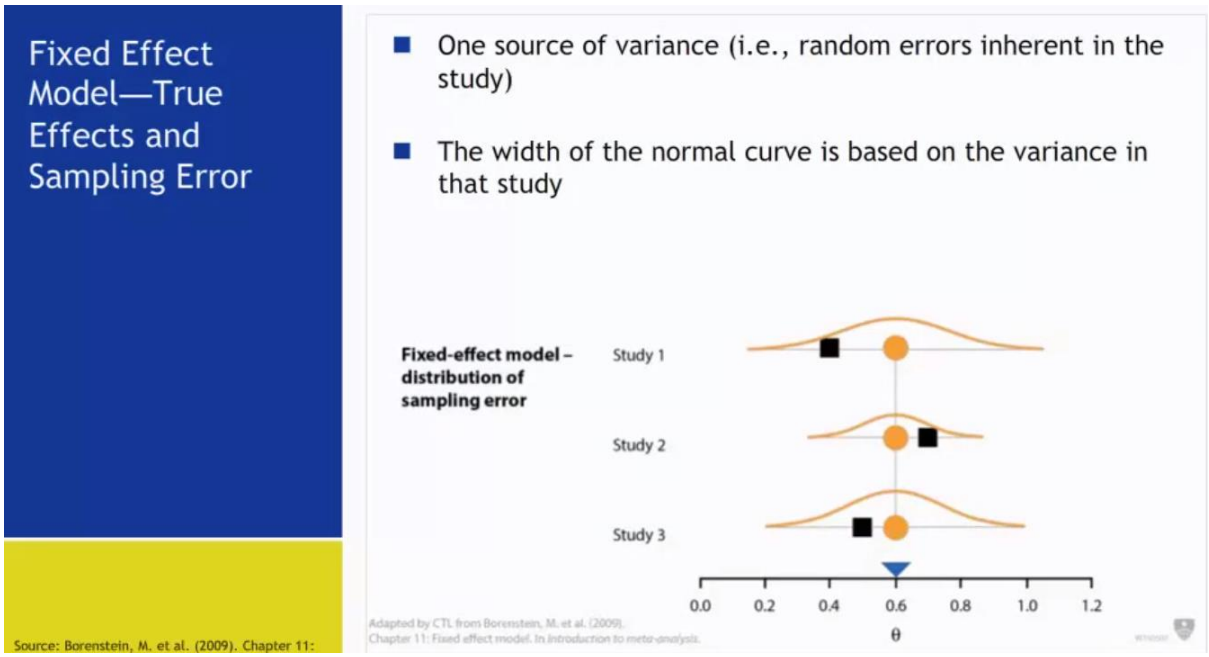


In this example, we have three studies. Each circle on the figure represents the true effect in each study. And again, under the fixed effect model, we assume all the circles coincide with each other, and we're trying to estimate that combined true effect. Well, the problem is, if we already know the true effect size in each study, we don't have to do any research at all, because we just take where that circle is and go with it. Again, the true effect we denoted use theta, and in this particular example, the theta is 0.6. So we don't know the true effect size in each study. What we have from one's data is the observed effect size. And it usually varies from one study to the next. And under the fixed effect model, we assume that there's only one source of variation which is the random errors inherent in each study.

If you look at the second figure on the plot, where we have the black square which represents the observed effect size from each study.Let's say we're comparing vitamin D versus placebo to prevent fracture, and you have three studies.We may observe the effect size of 0.4 in Study 1, effect size of 0.7 in Study 2, and effect size of 0.5 in Study 3.The purpose of doing a meta-analysis is trying to use those observed effect size to make the best guess of where the common combined true effect size is. Again, here for example, the observed effect in Study 2 is circled on the figure, and it's 0.7 in this example. The observed effects size varies from one study to the next only because of the random error inherent in each study. This is the assumption for the fixed effect model meta-analysis. And the sampling error, which is denoted as epsilon in this example, is -0.2, 0.1, and -0.1 respectively in Study 1, 2, and 3.



Just to summarize, under a fixed effect model, there is only one source of variance. And that is the random errors inherent in the study.



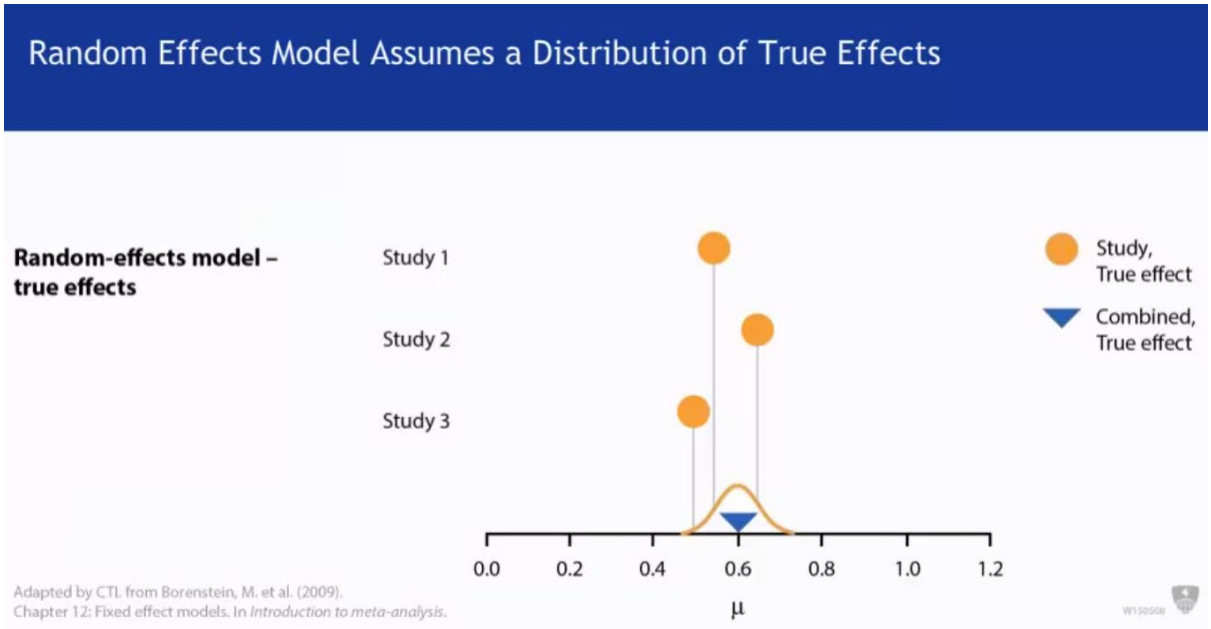
Here, if you look at this figure, we have the distribution of the random errors inherent in the study. Each normal curve on the figure reflects the amount of variance in that study. Comparing Study 1, 2, 3, which study has the largest variance? Well it's the first study because the normal distribution has the widest spread. And the study two is the most precise because the normal curve has a shorter distribution.

The most important summary points for the fixed effect model are:

1) **All studies in analysis share a common (true) effect.**
2) **The meta-analytic result is our estimate of this common effect**
3) **All the observed variation reflects the sampling error.**
4) **The study weights are assigned proportional to the inverse of within studies variance: The larger the study, the smaller the variance. So the larger study will contribute more information to the meta-analysis results. So it will take up more weight in one's pooled estimate.**

2. **Random Effects Model**: Examples of systematic reviews and meta-analysis are quoted to explain the limitations of the fixed effects model. It has the underlying assumption of homogeneity of studies which cannot hold true in most cases. Hence, the need for an alternate model arises.

Under the random effects model, we assume there's a distribution of true effects. Earlier under the fixed effect model we assume all studies are identical and there's only one true effect. So here, instead, we assume there's a distribution of them.



So again, the circles represent the true effect in studies. We're using the same example. There are three studies, so we have three circles, the true effect. And under the random effects model, these three circles no longer coincide with each other. Now there is a distribution.

Under a random effects model, we have to capture both sources of variance-the within study variance, as well as the between-study variance. Under the fixed effect model, we assume all studies share a common true effect size. That's why all the three circles, lying on top of each other, so there's only one identical common effect size. However, under the random effects model, if you look at the figure on the upper right-hand corner, here's a distribution. The three circles no longer align together. There's a distribution of effect size and because of that distribution, we added one more level of variability, which is the between-study variance. Under the fixed effect model, there's one source of variance which is captured by a normal curve for each study. However, under the random effects model, we actually have one more layer, which is the variance between studies. That's why you have four normal curves instead of three, which still have that within-study variance So while doing a Meta-Analysis either assume the studies are identical, they're the same then, we are going to use a fixed-effect model. If we cannot make that assumption, then we're going to use a random effects model by assuming that the studies are slightly different from one another. We're going to assume the true effect sizes are not the same, but there's a distribution. You have to take

the data you collected from each individual study, and try to make a best guess where the common effect is. And that guess depends on how different or how similar the studies are. If they are identical, then go ahead and use the fixed effects model. If you cannot make that assumption, then you're better off with the random effects model.

The between study variance, from each individual study is referred to as the Tau Square. If the numbers of studies are small then the estimate of the tau square will have poor precision. The confidence interval captures the within study variants. To estimate the between study variance. There are different ways to do it and one of the most popular one in the literature is called the DerSimonian Laird Method or the Method of Moment.

- DerSimonian and Laird Method (Method of Moment)

$$T^2 = \frac{Q - df}{C}$$

$$Q = \sum_{i=1}^{k} W_i (Y_i - M^*)^2 = \sum_{i=1}^{k} W_i Y_i^2 - \frac{(\sum_{i=1}^{k} W_i Y_i)^2}{\sum_{i=1}^{k} W_i}$$

$$df = k - 1$$

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$$

What is a random effects model in summary?

1. **The true effects in the studies have been sampled from a distribution of true effects.**
2. **The summary effect is our estimate of the mean of all relevant true effects, and the null hypothesis is that the mean of these effects is 0(or 1 for ratio)**
3. **The confidence interval for the random effects estimate indicates our uncertainty about the location of the centre of the random effects distribution, not its width a glance, but the idea is the confidence interval from your random effects.**
4. **Our goal is to estimate the mean of the distribution, taking into account two sources of variance (within and between**)

CONCLUSIONS

Fixed Effect Model:

Under the fixed effect model, you assume that the true effect is the same in each study. And that the only reason for variation in estimates between studies is sampling error.

Random Effects Model:

The model is trying to estimate a main effect about which it is assumed that the truest study effect varies. So again, the idea is you assume that all these studies are estimating an effect but there's a variation between studies is different?

COURSE WRAP-UP SUMMARY

- Systematic Review uses pre-specified and rigorous methods to identify, appraise and synthesize all evidences on a given topic
- Systematic Reviews can be used to investigate heterogeneity or the reasons for different results among the studies included for the review.
- Reviewers should minimize bias and errors at each step.
- The most crucial step is framing an answerable question using PICO analysis.
- Searching for studies should be comprehensive through the various search platforms like PubMed, Medline etc.
- Risk of Bias assessment helps determine how trustworthy the evidence is.
- Always conduct a qualitative synthesis in the studies and when appropriate conduct a Meta-analysis which is the Quantitative combinations of individual studies
- Not all Systematic Review would have a Meta-Analysis and Meta-Analysis should not be done when the combined estimates of all the studies included does not give a precise estimate as they may not be addressing the same questions at all.

REFERENCES

The data has been sourced primarily from the World Health Organization (WHO), Government of India and the databases maintained by the respective state governments, till June 30, 2020.

1. The following newspapers were followed on a regular basis which formed the basis of analysis:
    a. The Times of India
    b. The Hindu
    c. The Indian Express
    d. Economic Times
    e. Deccan Herald
2. The following websites were also followed on a regular basis and provided the data for cases:
    a. Ministry of Health and Family Welfare (https://www.mohfw.gov.in/)
    b. Covid dashboard on Government of India (https://www.mygov.in/covid-19/)
    c. https://www.coronatracker.com/country/india/
    d. https://www.mygov.in/corona-data/covid19-statewise-status/
    e. https://www.mohfw.gov.in/
    f. https://app.datawrapper.de/map/qbomz/publish#export-image
    g. https://coronavirus.jhu.edu/map.html
    h. https://www.grainmart.in/news/coronavirus-covd-19-live-cases-tracker-john-hopkins/

i. https://www.deccanherald.com/national/coronavirus-india-update-state-wise-total-number-of-confirmed-cases-deaths-on-june-28-854607.html

j. https://www.hindustantimes.com/india-news/nearly-70-of-india-s-covid-19-cases-come-from-five-states-including-uttar-pradesh-state-tally/story-MQWu7bFFBuxP2upecZhIKK.html

k. https://www.hindustantimes.com/india-news/eight-states-account-for-87-of-covid-deaths-85-active-cases/story-hJw0DGuddowJCmY4ySMvJP.html

l. https://public.tableau.com/profile/anuj.arora#!/vizhome/Covid-19_15852241513720/MapMobile

m. https://theprint.in/health/telangana-has-highest-covid-r-value-of-1-69-indias-overall-figure-now-1-11/451089/

n. https://indianexpress.com/article/explained/india-coronavirus-cases-explained-june-infections-deaths-6484737/

o. https://www.indiatoday.in/news-analysis/story/how-covid-19-picture-changed-for-india-in-june-1695795-2020-070https://www.worldometers.info/coronavirus/countries-where-coronavirus-has-spread/

p. https://thefederal.com/covid-19/covid-19-june-worst-hit-month-as-india-recorded-nearly-4-lakh-cases/

3. The following government reports were referred for statistics:

   a. Ministry of Women & Child Development, Rural Health Statistics report 2018-19

   b. Census of India, 2011

4. https://www.healthpolicy-watch.org/as-coronavirus-spreads-its-time-to-diagnose-treat-our-broken-health-systems/

5. Dikid, T., Chaudhary, S., Goel, K., Padda, P., Sahu, R., Kumar, T., ... & Narain, J. P. (2020). Responding to COVID-19 pandemic: Why a strong health system is required. Indian Journal of Medical Research, 151(2), 140.