Summer Training Project

Submission of Report#1

Research on COVID-19 in India

Submission of Report#2

Online Course on Systematic Review & Meta-Analysis

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INTRODUCTION

The novel Coronavirus disease, COVID -19 has found its way to all parts of the world. It is spreading globally at a brisk pace and becoming a cause of worry for the people and the governments. The major cause of concern is that being a novel infection, there is no formidable treatment or intervention to cure the disease. Hence in that scenario, the focus of the governments across the world and India has been to slow down the spread of the disease through the implementation of 'non-pharmaceutical measures'- which include social distancing, maintenance of personal hygiene and protection norms. The pandemic has called upon governments to give holistic institutional support to the general public, in developed and developing countries alike. In this regard, this research has touched upon the trends of Covid-19 in India with respect to the gender, age and morbidity. It also includes a comprehensive analysis of the health systems of the various states of India.

METHODOLOGY

The major sources for this report are the publicly accessible COVID-19 datasets, along with the regular updates from the various government websites like that of 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.

The primary focus of this report was to undertake a broad analysis of the trends of cases and fatalities across various States and Union territories in India, with a focus on the age-gender and comorbidities datasets of the deaths due to Covid-19. The various data available through news reports, statistical websites and other Indian databases created through the various crowd sourcing channels primarily dedicated to COVID-19 outbreak were analysed. The publically available reports pertaining to the health care infrastructure, workforce, and patient data were collated 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. The daily bulletins published by the respective state governments were incorporated for the analysis. Also, the data provided by the state health agencies and ministries and the various health care consulting firms for the containment policies of the Government of India and the State governments towards tackling the corona virus pandemic were analysed and presented.

AN OVERVIEW OF THE SITUATION OF COVID-19 ACROSS INDIA

The most noted phenomenon in the present world is the emergence and spread of the novel Coronavirus disease, Covid-19. After originating in the Wuhan district of China, it has found its way to all the countries of the world. India reported its first case on 30th January, 2020 in Thrissur district of Kerala. Presently, all of the Indian states and Union Territories have been affected by this pandemic and have deployed different strategies to tackle it. Kerala, in particular, has been the pioneer in 'flattening the curve' and demonstrating an impressive recovery rate. Other states have shown mixed results, with the situation becoming seemingly pessimistic in a few.

The pandemic has cut across all aspects of the society, impacting communities, individuals, markets and businesses in an unprecedented manner. 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 stringent ten week long nation-wide lockdown ordered in March was the primary reaction from the Union Government, which 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. This, however, took a toll on the economy and ultimately as parts of India reopened, the cases continue to grow.

Number of days taken to add each additional one lakh cases

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

The 8 states which include Maharashtra, NCT of Delhi, Tamil Nadu, Gujarat, Uttar Pradesh, West Bengal and Andhra Pradesh have contributed to more than 85% of the total active corona virus caseload and have also been responsible for more than 87% of the total number of deaths due to the virus.

States contributing to maximum caseload

Top 8 states contribute 85.5% of active caseload and 87% of total deaths in India

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

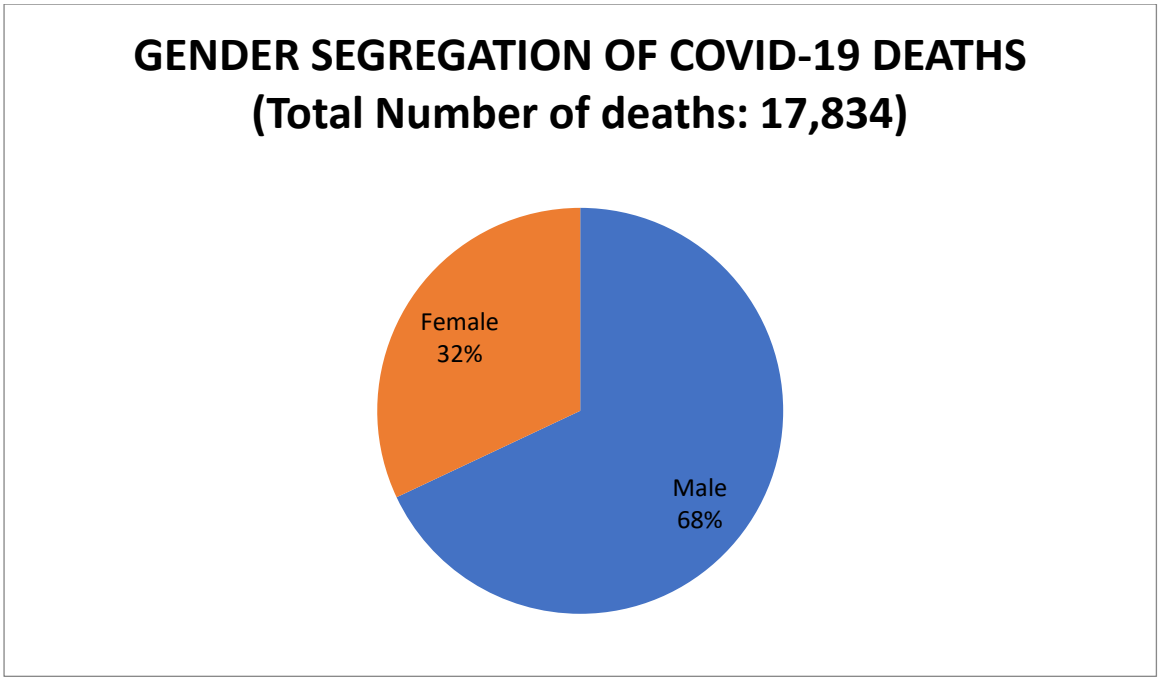
India's total active caseload : 217,780

Total Deaths – 11,883

DISTRIBUTION OF THE COVID-19 DEATHS BETWEEN GENDERS

Case fatality ratio is the percentage of deaths from among all reported cases or 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. Infection fatality ratio, however, takes into account undiagnosed cases at the population level too. India's case fatality rate at present is around 3%. According to the analysis by IDSP- Integrated Disease Surveillance Program, there is a clear segregation of Covid-19 deaths in India with respect to gender. 68% of all deaths related to Covid-19 in India were among Males.

This disparity in the gender segregation of the case load and fatality is seen in other parts of the world as well. In most of the other countries grappling with high cases and deaths due to Covid-19, more men have been infected by the disease than women and also a higher percentage of men suffer fatalities than women in the population.



Similar to the pattern observed with other diseases, the various epidemiological and demographical theories have been cited as the reasons for a higher caseload and subsequent fatalities in men than women:

a) The naturally more robust immune system of females than males.
b) Women are more particular about personal hygiene and adopt habits like hand washing more when compared to men.
c) Across societies, males have been observed to indulge more in greater health-risk behaviour than women like smoking or may be due to their occupational hazards
d) Consequently, males have higher chances of comorbidities or pre-existing health conditions such as cardio-vascular diseases, hypertension, respiratory diseases etc. compared to women.

However, a peculiar feature has been pointed out by a study done by a group of scientists on India's Covid-19 patterns. According to it, though it may seem that fatality is more in males when compared to females, but if we see the Case Fatality of females in India then it is higher than men which are surprisingly uncommon across the world. In other words, this research points out that females are more susceptible to succumb from corona virus, compared to males. It asserts that that around 3.3% of the total cases in the women were dying as

compared to 2.9% of the cases who were men. These figures correspond to the cumulative data available as on 20th May,2020 in India.

Among the females also, it has been observed that those in the age group of 40-49 years or more, 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). Another surprising revelation has been that there has been no fatality in males in the age bracket of 5-19 years and that only females have had the fatalities due to Covid-19.

Such deviations in the fatality rates between men and women from the global trends point out to a very serious conclusion that though generally females have advantage in terms of a stronger immune system, they do not have a distinct advantage of survival as compared to men in case of Covid-19. This may be due to a variety of reasons. Firstly, the opportunities to get tested by men and women are not uniform 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. Secondly, there are more aged women in than men in India as they have higher life expectancy than their male counterparts. Thirdly, 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. This stems from the poor health-seeking behaviour of females in the Indian society. Lastly, more women in India's lowest socio-economic strata live in unhygienic, ill-ventilated and clogged households having higher chances of contracting the disease than men who invariably stay outside their homes for the greater part of the day.

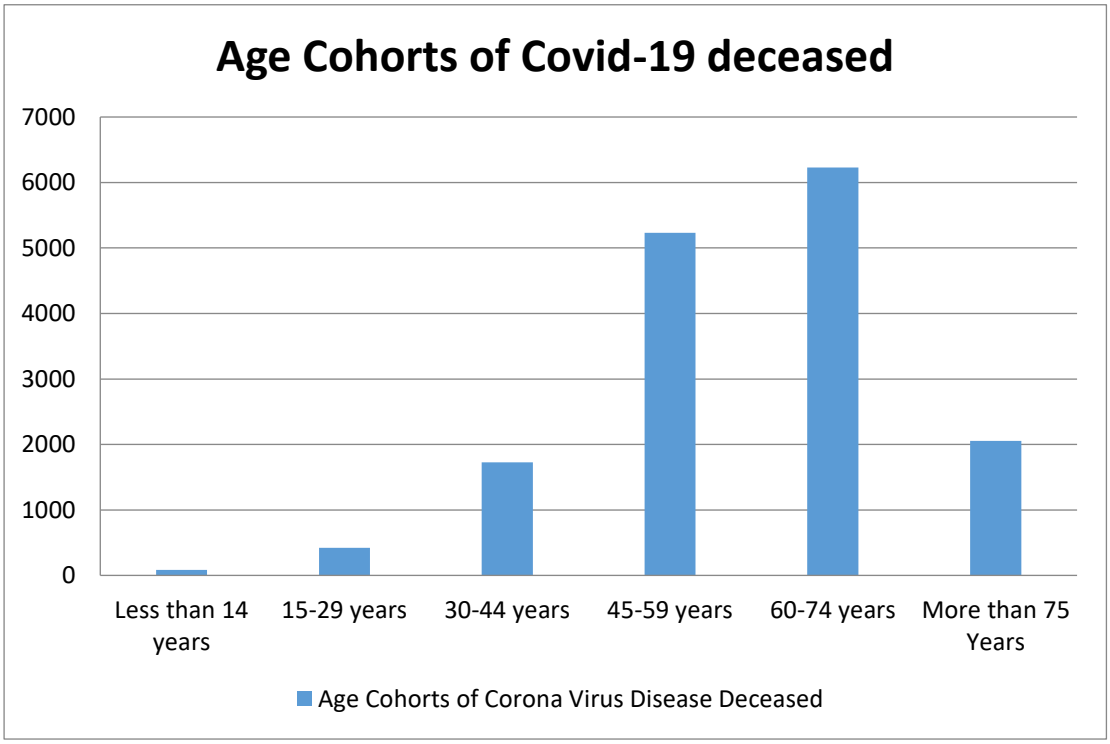
This analysis could have been more concrete if the respective state governments had shared age-specific data of COVID-19 cases and fatalities. It would also have led to the development of holistic estimates of Covid-19 deaths and guided policy decisions at the grassroots level.

AGE COHORTS OF CASES IN INDIA

An IDSP study conducted the analysis of age-wise split of deaths and the following trends were observed:

- 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



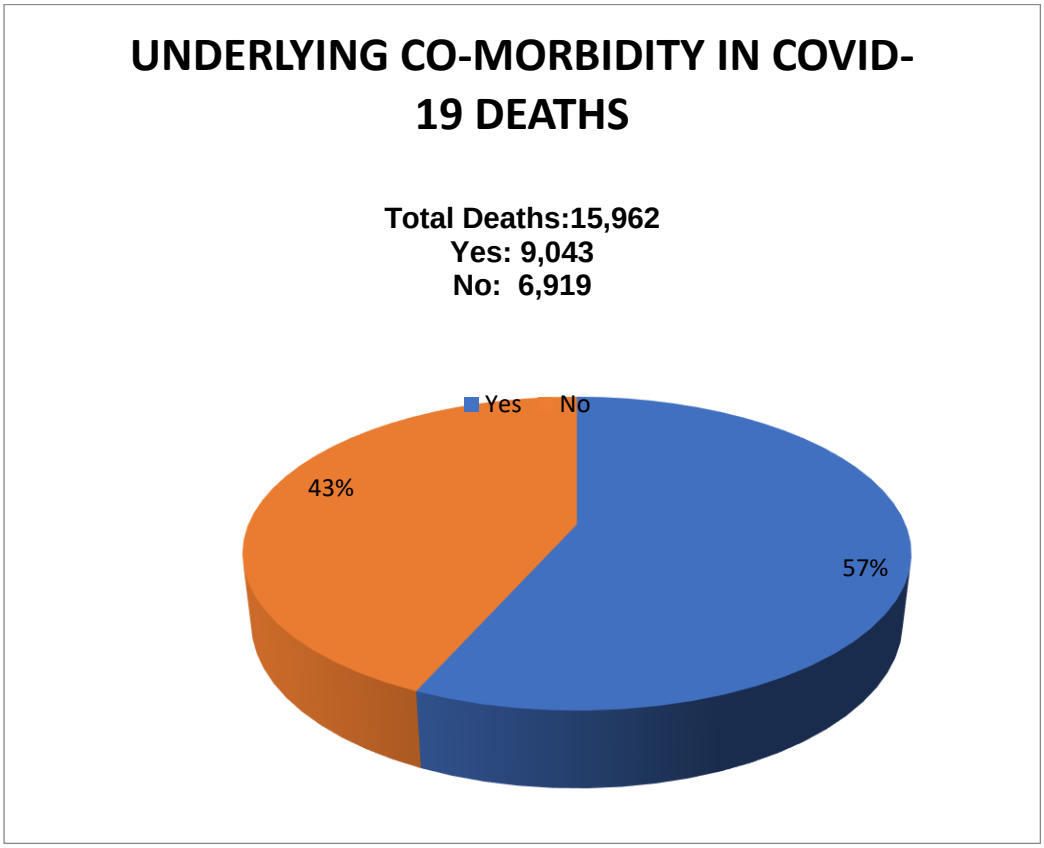
Source: Integrated Disease Surveillance Program Analysis

The same study has also reported that 57% of the patients in our country who had succumbed to Covid-19 had pre-existing health conditions or comorbidities which made their risk to the disease more pronounced. However, 43% of them had no pre-existing health conditions co-occurring with Covid-19 and yet resulted in deaths.

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.

COMORBIDITIES

The Covid-19 pandemic has also shed light on the seriousness of the burden of NCDs or Non Communicable Diseases. The increased susceptibility of the Covid-19 affected patients has been a matter of concern across the globe and poses challenges to the health providers as well. Though 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 Covid-19 patients at a greater risk of fatality.



Thus, elderly people and those with co-morbidities are advised to stay indoors as otherwise the management of the infection in those patients becomes extremely difficult. Recent reports also suggest that diabetes in particular poses a serious threat when it occurs in the Covid-19 patients. Also, higher the number of comorbid conditions in a patient, the more chances are of the patient succumbing to the infection.

IMPACT OF COVID-19 ACROSS STATES

Similar to 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 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 have been responsible. 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.

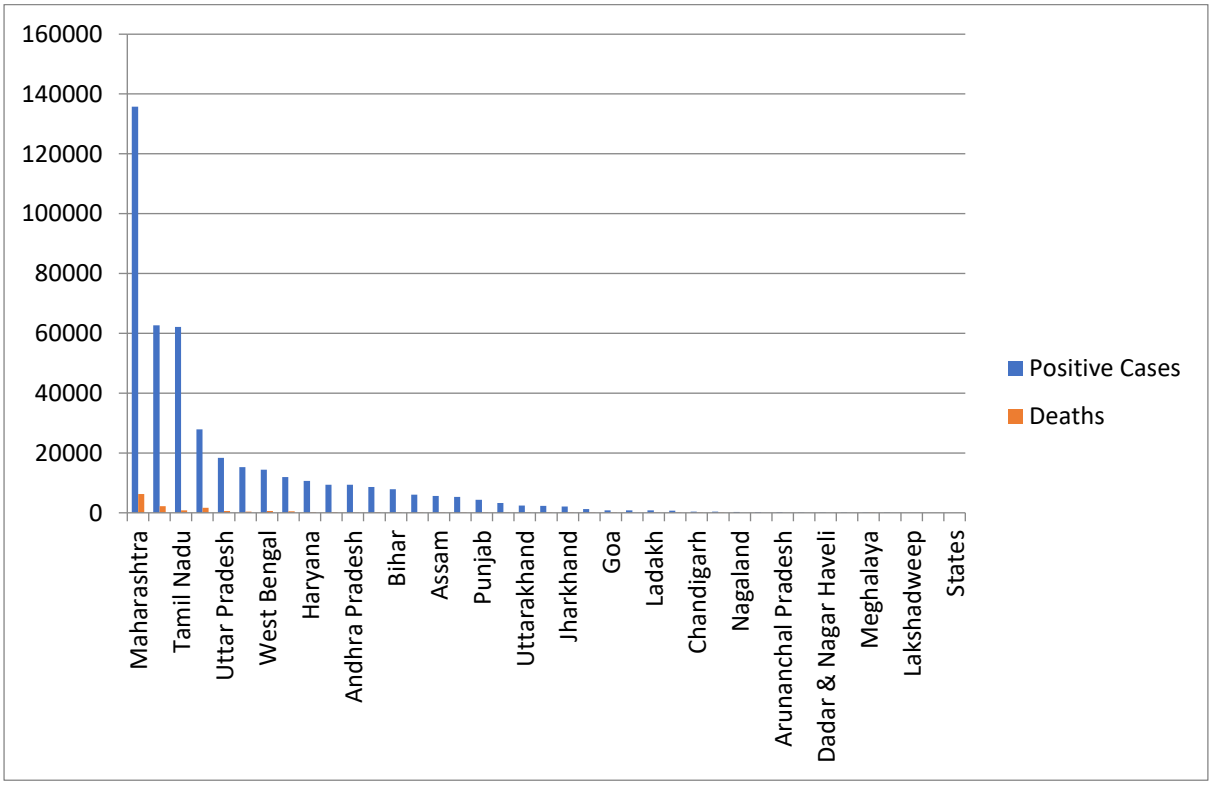
The data of distribution of cases within the different wards of Mumbai conforms to the trend of higher number of cases in areas of greater population density, as follows:

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%

State / UT	Total population	Rural population	Urban Population	% urban population	Area (km^2)	Population density
Maharashtra	112374333	61556074	50818259	45.22	307,713	365/km2
Tamil Nadu	72147030	37229590	34917440	48.39	130,058	555/km2
Gujarat	60439692	34694609	25745083	42.59	196,024	308/km2
Delhi	16787941	419042	16368899	97.50	1,484	11,297/km2

Source: 2011 Census data

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.



Case load across select Indian states/UTs

- 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:

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%

Recovery rates of select Indian states / UTs

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.

The lessons learnt from this differential impact of Covid-19 across states have led to the focus on the following priority areas. Firstly, the testing capacity must be expanded. 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 of 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.

Secondly, 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.

Thirdly, the importance of essential heath care services must not be ignored. 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.

Next, 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.

Lastly, the importance of effective data management cannot be stressed enough. There must be 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.

THE 'R_O' VALUE TRENDS IN INDIA

The R value, or the reproduction number, is a means of understanding the ability of the infectious agent to spread. It is the average number of people to whom an infected person will spread the infection. A variant of it, the R_o is used for novel infections as it assumes that the entire population is susceptible to it. A value above one indicates that the infection is spreading exponentially and is a cause of worry. Hence, the condition is deemed stable when the value reaches unity. Bringing down this number is the whole idea behind imposing a lockdown. It is however based on certain assumptions and might also mask local variations for a country as big as India. Also, there must be rigorous testing to give a concrete estimate for the value. Historically, measles has been observed to have among the highest R value known. Initially, this value for the novel Covid-19 was estimated to be around three globally.

In India, it was estimated to be between two and three initially. However, by the first week of July, it came down to 1.14 after being around 1.22 in the initial days of June. Studies show

that as of July first week, it is worst for Haryana, where it is around 1.72. This is followed by Delhi, where the value is 1.26. The situation is no better for states like Uttar Pradesh, Tamil Nadu, West Bengal and Andhra Pradesh where the value is marginally higher than the national average.

State	R_0 value in June end
Telangana	1.69
Maharashtra	1.19
Delhi	1.26
Tamil Nadu	1.26

For Maharashtra, it was as high as 1.49 during April, and declining to 1.27 by May end. For Delhi, it was 1.4 during the first week of June, and eventually rose to 1.15 by mid-April. For Tamil Nadu, the R value was above 2 in early May, and reached 1.56 by mid-May. It was 1.31 in early June and further declined to 1.26 by June end.

By early June, the R value stood high at 1.9 for Haryana, while it was 1.68 for Assam. Though it has declined since then, it is still 1.56 for Haryana and 1.31 for Assam by late June. States like West Bengal, Jammu and Kashmir and Gujarat are showing sub-exponential trends. However, the value can only be substantiated when coupled with robust testing.

GOVERNMENT'S RESPONSE TO COVID-19

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. 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.

19. Private practitioners can now prescribe Covid-19 tests in addition to Government affiliated doctors.

20. Private Laboratories are free to test any individual as per the ICMR guidelines.

21. 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.

THE PANDEMIC THROUGH HEALTH SYSTEMS PERSPECTIVE

The inadequate public health spending in developing countries has long been recognised, which is often deemed to be the root cause of the poor health indicators. In India, less than 1.5% of the GDP is spent by the government for healthcare. Also, there is variation in the health spending across states, as heath is a state subject. The average spending by all the states and UTs for FY 2019-20 remains at 5.2%.

State	% of GDP spent on healthcare in 2019-20
Gujarat	5.8%
Tamil Nadu	5.1%
Maharashtra	4.2%
Delhi	13.8%
Kerala	5.1%
Assam	7.4%
Bihar	4.6%
Haryana	5.4%
Chhattisgarh	5.4%
Himachal Pradesh	6.4%
Karnataka	4.6%
Jharkhand	5.6%
Madhya Pradesh	4.9%
Rajasthan	6.2%

Telangana	4.0%
Uttar Pradesh	5.5%
West Bengal	5.1%
Odisha	5.1%

As it can be seen, apart from a very few states / UTs, the public health spending is dismal. It is generally believed that urbanisation is synonymous with economic prosperity. This might be true purely from the perspective of income but such approach often masks the issues peculiar to the urban settings, particularly where the urbanisation has largely been unplanned. It ultimately leads to environmental degradation and most evidently in the form of poor urban health, arising due to the socio-economic reasons. One might be tempted to think that urban areas house the best of the health facilities and state-of-the-art hospitals. However, they are out of reach of the majority of the population in terms of accessibility and affordability. This further increases the out of pocket spending.

The disease burden in the urban areas was also thought to be non-uniform. 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 on-going Covid-19 pandemic.

Urban health has not got its due in the public discourse and is often ignored under the presumably more severe rural health issues. 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.

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**

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	3822000	76	0	76	100
28	Uttar Pradesh	53100000	1062	624	438	41
29	West Bengal	3424700	685	448	237	35

		0				
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	**453576000**	**9072**	**5190**	**4026**	**44.4**

It is high time that decision making is strengthened at the local level, combined with increased autonomy. The situation caused by the current pandemic has only reiterated the need to address the issues in the public health system, starting from spending to manpower. The lessons must be learnt in time, so that we are better equipped to handle the current situation as well as the future challenges.

CONCLUSION

The novel Coronavirus- covid 19 will continue to shape the world for the coming years. After originating in the Wuhan district of China, it has found its way to almost all the countries of the world. It has tested the resilience of the health systems across the world and even the most developed countries are struggling to contain the spread and mitigate its effects. Developing countries are finding it even more difficult because of the dismal public health spending by their governments. In this regard, the situation in India has been relatively better in terms of the number of people affected per million population. However, owing to the fact that we are a densely populated country, with significant rural population only increases the challenges for us. This pandemic has brought many issues to the surface like the need to strengthen the public health infrastructure.

In spite of continuous efforts taken by various state and central governments, they have not been able to prevent damage. It is time that we realise the importance of strengthening the public health system and leverage the technology at its best. We must be willing to adapt to the ‘new normal’ which the current situation demands and adhere to the preventive measures till a concrete cure for the infection is obtained.

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://app.datawrapper.de/map/qbomz/publish#export-image
    e. https://coronavirus.jhu.edu/map.html
    f. https://www.grainmart.in/news/coronavirus-covd-19-live-cases-tracker-john-hopkins/
    g. https://www.deccanherald.com/national/coronavirus-india-update-state-wise-total-number-of-confirmed-cases-deaths-on-june-28-854607.html
    h. 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
    i. https://www.hindustantimes.com/india-news/eight-states-account-for-87-of-covid-deaths-85-active-cases/story-hJw0DGuddowJCmY4ySMvJP.html
    j. https://public.tableau.com/profile/anuj.arora#!/vizhome/Covid-19_15852241513720/MapMobile
    k. https://theprint.in/health/telangana-has-highest-covid-r-value-of-1-69-indias-overall-figure-now-1-11/451089/

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

Submission of Report#2

Online Course on Systematic Review & Meta-Analysis

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COURSE NAME : INTRODUCTION TO SYSTEMATIC REVIEW AND META-ANALYSIS

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 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.

- **<u>Key learnings:</u>**
- 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 timepoint.
- 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 METABIAS

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: Metabias 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.

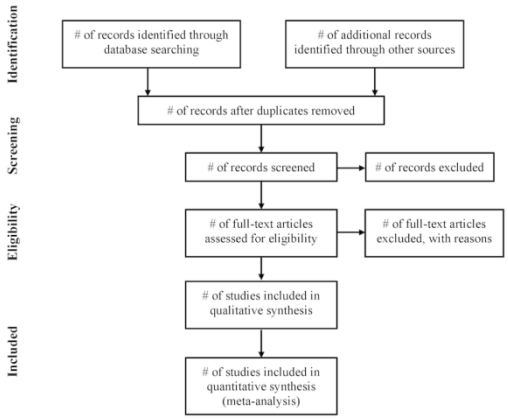
Other areas of concern are when the data is deduced from a graph or short report- it may sometimes not give the complete picture about the study. Next, the impact of abstractor experience may also influence the aggregate data gathered at the end of the process. Lastly, published data cannot be relied 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. Reporting Transparently: 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'.

- Metabias 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.

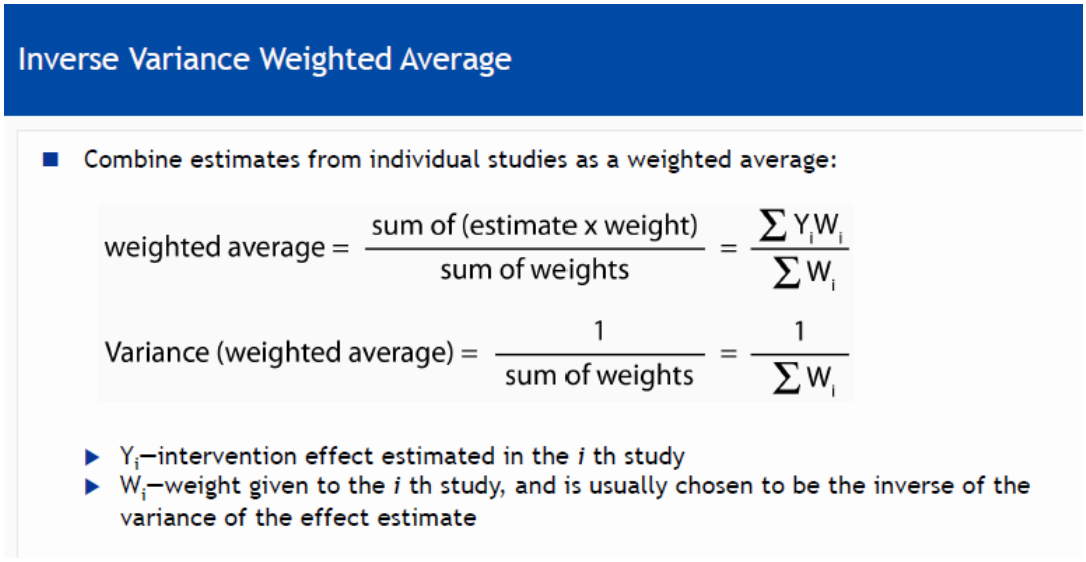
   A general framework for doing the meta-analysis involves answering the following questions: what is the direction of the effect/association? What is the size of the effect? Is the effect consistent across studies? What is the strength for the evidence?

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.

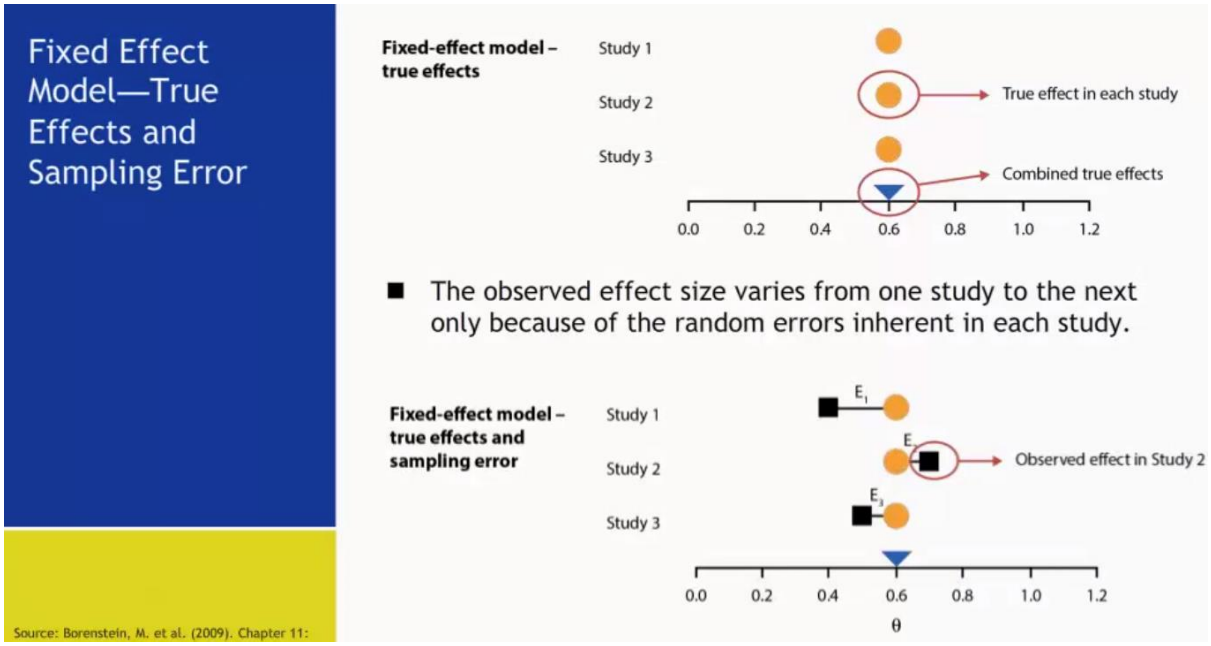
Meta-analysis is the statistical analysis which combines the results of several independent studies considered by the analyst to be combinable hence a systematic reviewer has to make the decision whether the studies are similar enough to be put together in a meta-analysis. So for meta-analysis, we including 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

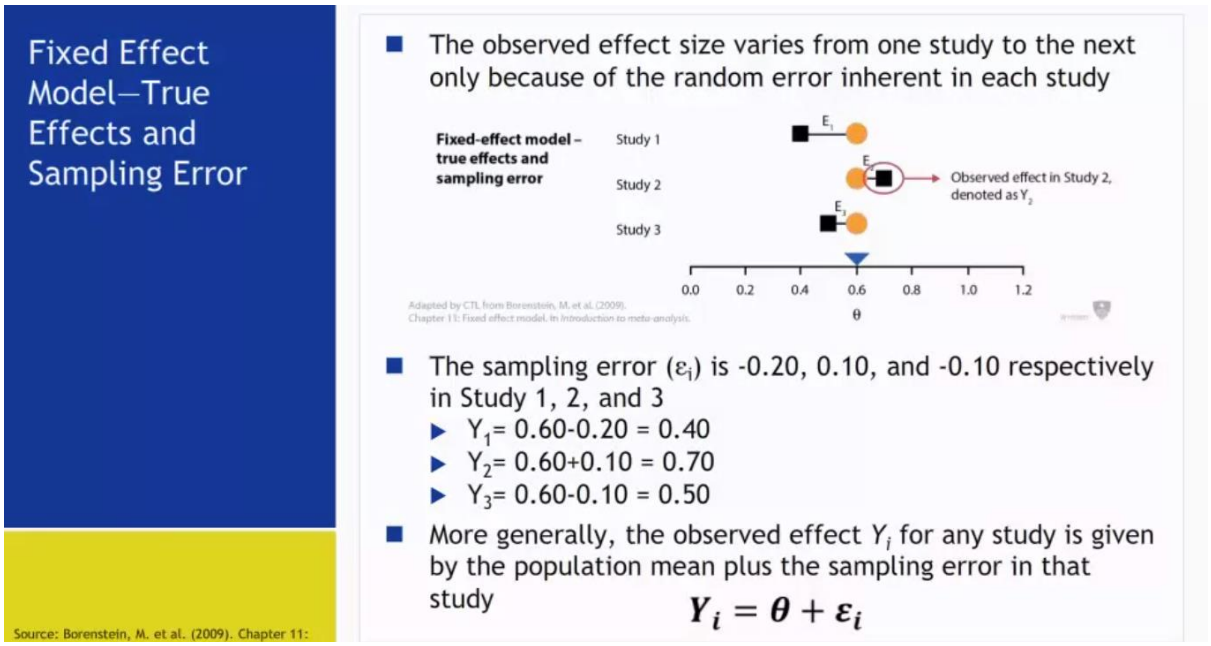
1. Fixed Effect Model: Under the fixed effect model, we assume that all studies, one is including in one's meta-analysis are measuring the same, common (true) effect size. It means that, if it's not for random or sampling error all results in those individual studies would be identical. Under the fixed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



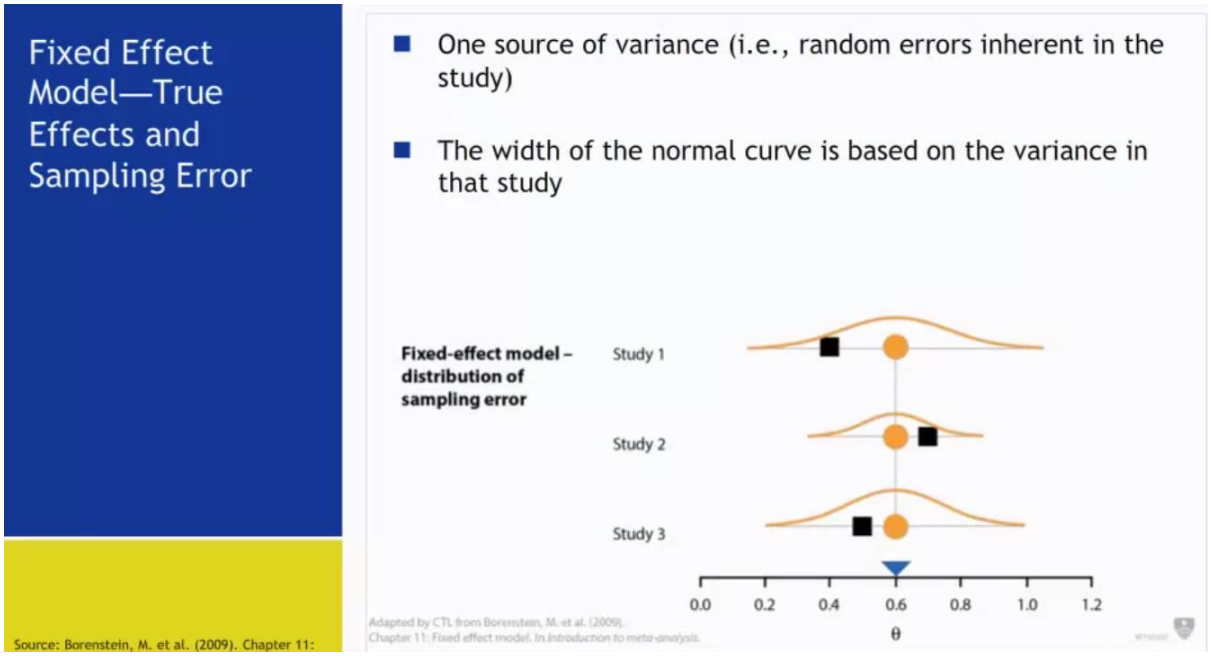
In this example, we have three studies. Each circle on the figure represents the true effect in each study. And again, under the fixed effect model, we assume all the circles coincide with each other, and we're trying to estimate that combined true effect. Well, the problem is, if we already know the 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.



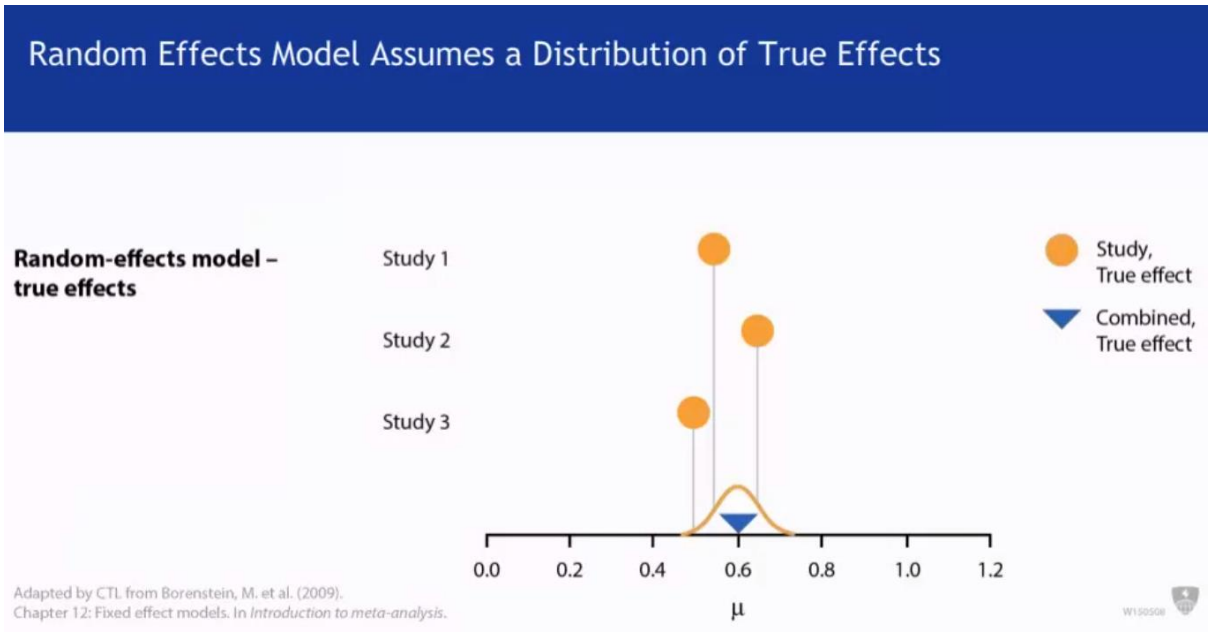
Here, if you look at this figure, we have the distribution of the random errors inherent in the study. Each normal curve on the figure reflects the amount of variance in that study. Comparing Study 1, 2, 3, which study has the largest variance? Well it's the first study because the normal distribution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