Bio-surveillance Capability Requirements for the Global Health Security: Study on Epidemiological Differences of COVID-19 Cases

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Abbreviations

GHSA: Global Health Security Agenda

IHR: International Health Regulation

COVID-19: Corona Virus Disease 2019

SARS-CoV-2: Sever Acute Respiratory Syndrome by Coronavirus-2

PCR: Polymerase Chain Reaction

RT-PCR: Real Time Polymerase Chain Reaction

NPI: Non-Pharmacological Intervention

PI: Pharmacological Intervention

CDC: Center for Disease Control and Prevention

WHO: World Health Organization

WHA: World Health Assembly

OIE: World Organization for Animal Health

BALF: Broncho-alveolar Lavage Fluid

IVD: In Vitro Diagnostic

POC: Point of Care

PON: Point of Need

AI: Artificial Intelligence

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

FAO: Food and Agriculture Organization

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ABSTRACT

Background: Just eleven months after the first reported COVID-19 infection, the global tally has surpassed 60 million cases with a global death toll standing at 1.4 million. Even though with the launch of the Global Health Security Agenda in 2014, only 67 countries came under the umbrella of this agenda and trying to exchange as well as integrate various strengths to fight against massive threats of multiple infectious diseases. The current Covid-19 pandemic basically exposed the paucity of capacities and capabilities of nations' Bio-surveillance System, even the so-called developed ones.

Method: Cross-sectional study was carried out within the time period of the 16th September - 30th November 2020, taking into account the secondary data of COVID-19 patients up to 22nd April 2020, in South Korea, Australia, & England as sample population. After the extensive analysis of the data-driven from the authorized websites of the three countries - the Incidence Rate (%) and Case Fatality Rate (%) according to age and sex groups were compared along with Crude Incidence Rate, Crude Mortality Rate, Age & Sex-Specific Incidence Rate, Age & Sex-Specific Mortality Rate, Age & Sex Adjusted Incidence rate, Age & Sex Adjusted Mortality rate, by plotting into charts and graphs.

Results: In the case of all three countries, Incidence Rates are increasing with the increase in age of the population. Except for the female of South Korea, the incidence of COVID-19 in both the other two countries were high in case of the male population. the mortality rate of male patients was higher than female patients in all age groups in all three countries. In the case of England, the Incidence Rate (%) and Case Fatality Rate (%) according to age and sex groups along with Crude Incidence Rate, Crude Mortality Rate, Age & Sex-Specific Incidence Rate, Age & Sex-Specific Mortality Rate, Age & Sex Adjusted Incidence rate, Age & Sex Adjusted Mortality Rate all are 30 to more than 100 times higher than Australia and South Korea. Australia shows the lowest in COVID-19 infection and death rates among the countries in all aspects.

Conclusion: This study shows the gaps of currently available bio-surveillance methods leading to an uncontrolled and unprecedented surge of the ongoing COVID-19 contagion and fatality world-wide, driving mankind into an uncertain future. Ameliorating the currently available bio-hazard and disease surveillance system by filling those gaps up along with the help of continuous need-based research and innovations, imply tremendous importance to overcome the current situation and to predict upcoming “Disease-X” threats.

CHAPTER I

INTRODUCTION

Since the starting of the current year, the world is facing the most overwhelming pandemic situation caused by SARS-CoV-2 infecting one tenth of the world population and killing more than one million people worldwide. Pandemic is a circumstance where planning is needed to be done preemptively to get rid of hundreds of thousands of mortalities and morbidities. Even though experts from all over the world were repeatedly warning about such unprecedented global pandemic of emerging diseases along with trying to capacitate the health security by a wide range of prevention, early detection, and response countermeasures, COVID-19 already proved how unprepared we were. From the very early of this pandemic we were in a deficit of strong and integrated enough bio-surveillance system. Lack of laboratory facility, personal protective equipment and critical care equipment facilitate this disease to rampage throughout the globe without any sign to be stopped. Now, while we are going through the 10th month of this COVID-19 pandemic, still there are lot of shortage of integrations in different aspects of prevailing surveillance system which turning all of our efforts in vein to halt the further spread of this contagion day by day. Still we have to focus on evaluation what we have made wrong and where we should indulge our best efforts to improve the system. In this thesis by comparing the current incidence rate and case fatality rate of COVID-19 cases according to different age and sex group of population and by focusing on the available bio-surveillance system of South Korea, Australia, and England, I intended to find out the required steps to be taken for more development in integrating of that in those three countries.

LITERATURE REVIEW

Section 1.1

Global Health Security Agenda

The 58th World Health Assembly (WHA) concurred in May 2005 to reformulate the Regulations for International Health on the verge of increasing events of world-wide infectious diseases outbreaks, like- AIDS, SARS, MARS and a few intentional release of harmful pathogens (like Anthrax in USA) following Twin Tower Attack). It was updated in order to prevent, protect, monitor as well as provide a public health response to the international spread of communicable diseases, so that those become fully compatible in limiting public health threats, and to avoid undue conflict with international trade, traffic and economy. [1]

The IHR (2005) issued additional responsibilities to WHO and the global health community to initiate and integrate the resources for capacity-building and emergency response. Although many countries have reinforced their IHR (2005) capabilities for disease detection and response, just around 20 percent have announced that they have completely fulfilled their requirements by the specified deadline of June 2012. [2]

In this given context, during February 2014, the introduction of the Global Health Protection Agenda (GHSA) was launched to develop new approaches revitalizing capacity-building for improved checking of emerging and re-emerging infectious diseases occurrences, whether natural, accidental or deliberate, endangering not only public health, but the interests of national, regional and global security. The three dimensions in which the GHSA goals are set taking in conjunction with their 11 action packages, prevention, detection and response, undeniably overlap with and strengthen the core capability criteria defined in the IHR agreement to identify, evaluate, report and respond.

In the table below the "Prevent, Detect and Respond" mandate of Global Health Security Agenda the necessary recommendations to achieve the objectives:

Objectives and Recommendations under the "Prevent, Detect and Respond" mandate of GHSA

Objectives under the "Prevention" mandate of GHSA		Actions Recommended under GHSA Objectives
1	Prevent the emergence and spread of antimicrobial drug-resistant organisms	Reduce factors that enable antimicrobial resistance (AMR); improve surveillance for AMR; promote appropriate and responsible use of antibiotics in all settings.
	Prevent the emergence and spread of emerging zoonotic disease	Reduce factors that enable emergence of zoonotic disease threats; increase surveillance for novel zoonotic diseases; promote safe practices in livestock production and animal marketing
	Strengthen international regulatory frameworks governing food safety	Develop strategies to improve food safety

2	Promote national biosafety and biosecurity systems	Develop multi-sectorial approaches to manage biological materials, including identifying, securing, monitoring, and storing dangerous pathogens in a minimum number of facilities; frameworks to advance safe and responsible conduct of research
3	Reduce the number and magnitude of infectious disease outbreak	Establish effective programs for vaccination against epidemic-prone diseases and nosocomial infection control
Objectives under the “Detection” mandate of GHSA		**Actions Recommended under GHSA Objectives**
4	Launch, strengthen, and link global networks for real-time bio-surveillance	Establish monitoring systems that can predict and identify infectious disease threats
		Establish interoperable, networked information-sharing platforms and bio-informatics systems and networks that link to regional disease detection hubs.

5	Strengthen rapid and transparent reporting in the event of health emergencies of international concern	Strengthen capabilities for accurate and transparent reporting to WHO, OIE, and FAO during emergencies
	Strengthen sample sharing in the event of health emergencies of international concern	Rapid sample and reagent sharing between countries and international organizations
6	Develop and deploy novel diagnostics	Strengthen country and regional diagnostic capacity at the point-of care and point-of-need
	Strengthen laboratory systems	Strengthen laboratory systems capable of safely and accurately detecting dangerous pathogens with minimal bio-risk
	Train and deploy bio-surveillance workforce	Build capacity through trained disease detectives and laboratory scientists

	Objectives under the "Respond" mandate of GHSA	Actions Recommended under GHSA Objectives
8	Develop an interconnected global network of emergency operations centers	Establish emergency operations centers.
	Develop multi-sectorial response to biological incidents	Establish trained, functioning, Multi-sectorial rapid response teams, with access to a real-time information system
		Develop capacity to attribute the source of an outbreak
9	Improve global access to medical and nonmedical countermeasures during health emergencies	Strengthen capacity to plan for, produce or procure, and deploy personal protective equipment, medications, vaccines, and technical expertise and to deploy nonmedical countermeasure

GHSA encourages to build national capacities for early identification of biological hazard, characterization and transparent reporting. GHSA advocates for real-time "bio-surveillance" to be launched, reinforced and linked by global networks, reinforcing the global standard for rapid and open reporting to international actors, rapid sample exchange, developing and deploying new diagnostics, strengthening laboratory systems, and training and deploying workforce of efficient and accurate bio-surveillance. [3]

Section 1.2.

Bio-surveillance

Bio-surveillance is a complex concept characterized as active data collection, adequate analysis and interpretation of data from the biosphere that may be linked to the activity of diseases and threats to human or animal health, whether contagious, poisonous, metabolic or otherwise, irrespective of their deliberate or natural origin, with a view to early warning of health threats, health event detection and overall circumstantial awareness of disease activity.[4] It encompasses all attempts by public health authorities to collect and analyze information on hazards and risks of importance to public health, including disease outbreaks that occur naturally, reportable ailments and syndromes, zoonotic disease events, environmental exposures, natural disasters, and terrorism-related malady. [5]

The four essential functions of basic surveillance include [6] –

1) Detecting and documenting cases of disease in particular populations;
2) Reviewing and verifying the reported data with case information for the identification of outbreak
3) prompt provision of appropriate responses at local / regional level and to allow for reasonable national-level disease prevention and control from outbreaks.
4) Epidemiological Knowledge along with epidemilogical intelligence to help with long-term public policy, regulation and services on health and health care.

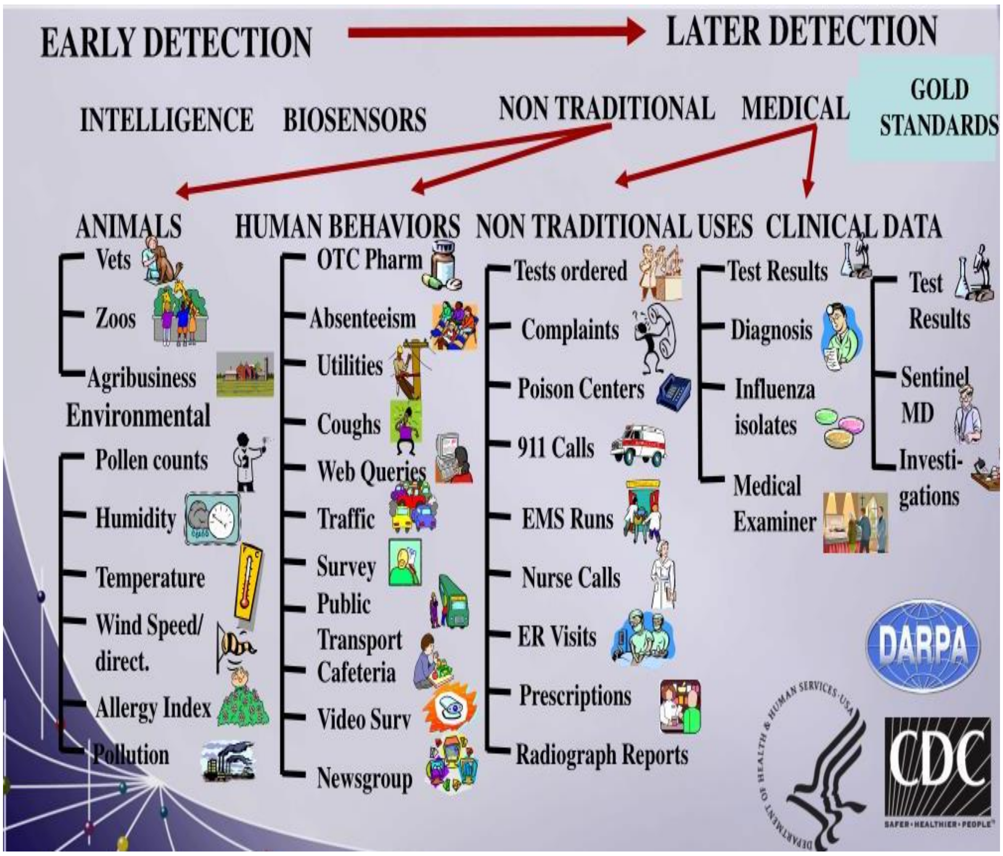
Health care surveillance refers to the continuous systematic compilation, review, interpretation and relaying of data.

Passive surveillance which is the crucial element of global biosurveillance, is much more convenient as well as easy to incorporate and free of technical hurdles. It is preeminently used with other approaches to point out a treatment quickly and implement steps to safeguard public health, for instance prophylaxis, immunization, and quarantine. Even so, this sort of surveillance is also contingent on health care providers reporting actively as well as the collection of data, which can result in substantial time gaps between the occurrence of an incident and the knowledge that there has been a public health problem, such as an outbreak of an infectious disease. These time-lags can mean that public health initiatives, such as steps to isolate people from society, can not be served successfully to reduce disease transmission. [5] Since it is presumably not prompt and precise enough to be used alone in tackling deliberate spread of bio-agents too.

On the otherhand, much more effort, efficiencies and public health resources are obligatory for active surveillance to be effective. This surveillance includes outreach to particular organizations, such as sentinel health-care facilities or hospitals, to systematically collect disease information; thus it is usually conducted to look for a particular ailment like emergence, re-emergence or resurgence of a contagion. [4]

However, if accurately planned and used, robust and real-time or near real-time bio-surveillance methods, can reliably pinpoint the situations preceding the public health issue as it happens, enabling relevant authorities to safeguard and protect the population. In order to better comprehend the cause, mode of transmission, dose-response relationship, and other features of diseases or other health conditions, bio-surveillance systems can also provide potentially useful data for the study. Formulating a bio-surveillance systems with the potency to rapidly gather, evaluate and share diverse data types through key stakeholders is not beyond pragmatic, technical, political, ethical and legal issues. [5]

A total integration of surveillance and alert system of any biological incident or accident can be achieved by following schematic diagram:



Biosurveillance Data Space Novel data sources explored by BioAlirt [8]

For enhancing this vigilant system of disease-surveillance, a total combination of knowledge-based careful searching and sensing of upcoming diseases-events prior the occurrence of disease with concurrent bio-protective measures as well as national integration is indispensable. [9, 10, 11] Those capacities reflect the resources that a public health system needs to draw on: facilities, policies and practices, response systems, competent and skilled workers. These include legal, economic, and organizational dimensions as well as the intangible relationships between people and organizations that studies indicate are vital to efficient implication of crisis-plans and community resilience. Capacities are important but not sufficient to ensure optimum functioning of a technical

process. Whereas capabilities for bio-surveillance identify the activities that a public health system is competent of taking to efficiently detect, categorize and respond appropriately to crisis situations: surveillance, epidemiological investigations, prevention and control of diseases, expanded capacity for health care, communication of threats to the public, and integration of dynamic response through an effectual incident management system. [12]
Despite the huge rise in financial resources and expertise that our ability to improve biosurveillance has been propelled throughout the last decade, there have been many problems that need to be tackled, all over the globe When many systems are used combinely, the importance of disease monitoring systems to public health officials is highest. Restricted integration and miscommunication between the different private and public surveillance systems is the of disease surveillance at this point. [12]

Section 1.3.

Coronavirus and COVID-19

Being first discovered in 1965 by Tyrrell and Bynoe during research on human embryonic tracheal organ cultures obtained from the respiratory tract of an adult with a common cold, [13] an extensive research on Coronavirus were performed till date. These are single-stranded, positive-sense RNA viruses and belong to the order Nidovireales, family Coronaviridae and subfamily Corovirinae. Coronavirus has the largest genomes among all RNA viruses that ranges from 26 to 32 kilobases in length, with G + C contents varying from 32% to 43%. These type of virus are predominantly associated with enteric and respiratory diseases in animals and humans. Subfamily coronavirinae further diverges into three major generas or groups-the alpha-Coronavirus (group 1), the beta-CoVs (group-2), and the gamma-CoV (group 3) characterized by varying genetic mkeup and antigenic cross-reactivity. Delta-CoVs, representing a novel genus of Coronaviruses were also later found in birds and pigs. Out of these, only alpha-CoV strains (HCoV-229E and HCoV-NL63) along with beta-CoVs s (HCoV-HKU1, HCoV-OC43, severe acute respiratory syndrome coronavirus [SARS-CoV], and Middle East respiratory syndrome coronavirus [MERS-CoV]) have been identified as human pathogenic strains. Swine acute diarrhea syndrome (SARS-CoV), porcine transmissible gastroenteritis virus, and porcine enteric diarrhoea virus (PEDV) are a few examples of alpha alpha and beta-CoVs that hold the potential to pose heavy disease burden on livestock. [14]

Currently, an ongoing pneumonia outbreak caused by a novel Coronavirus strain named SARSCoV2 belonging to the beta-coronavirus genera is an emerging threat to public health all over the world. Ongoing extensive research has suggested that bats are the natural reservoir and pangolins are probably the potential intermediate host of the virus, as 99% homology was found between SARS-CoV2 and coronavirus strain isolated from pangolins. [14]

On January 8 2020, the pathogen of severe unexplained viral pneumonia was identified by sequencing as tentatively named the novel (new) coronavirus 2019 (2019-nCoV). On February 12, 2020, International Committee on Taxonomy of Viruses declared that 2019-nCoV was officially named as SARS-CoV-2, and at the same day, World Health Organization declared the disease caused by SARS-CoV-2 was officially named as coronavirus disease 2019 (COVID-19). Till now, about 6 million of cases have been confirmed in 211 countries and territories such as the USA and Southeast Asia, including severe and death cases.

An abundance of research is being conducted globally on this Novel Coronavirus strain to gain knowledge about its origin, evolutionary history, phylogeny, along with the transmission pattern with clinical symptoms and sequelae of this disease. This thesis is an effort to affirm requirements for capacitating the bio-surveillance system for prevention of this public threat as an agenda of Global Health Security.

Section 1.4.

COVID-19 Coronavirus Real Time PCR Kit

Currently WHO authorized COVID-19 Coronavirus Real Time PCR Kit is an In Vitro Diagnostic (IVD) reagent that relies on fluorescent PCR technology with the aim to qualitatively detect SARS-CoV-2 from both upper and lower respiratory tract-specimens. Specimens collected from upper respiratory tract include throat swab and nasopharyngeal swab and those from lower respiratory tract include sputum. Sampling objectives focus on suspected cases infected by SARS-CoV-2, suspected cases due to overcrowding, other cases needed to be diagnosed with SARS-CoV-2, and other suspected environmental and biomaterials (for traceability analysis, for example). Sampling should be carried out by well trained professionals with biosafety and experimental skills. Typically, SARS-CoV-2 RNA could be detected from upper and lower respiratory tract specimens if a person is infected. Positive result suggests SARS-CoV-2 infection but bacteria and other virus induced co-infection could not be excluded. SARS-CoV-2 test result is not the only confirmation evidence of suspected cases and all positive results have to be reported to Centers for Disease Control (CDCs) and authorities. However negative result cannot straightforwardly exclude SARS-CoV-2 infection as well as the only decision-making evidence for treatment and patient management. Since negative result should be correlated with medical history, clinical observation and epidemiological information. The test is only available to equipped and certificated clinical laboratories and PCR laboratories and the technicians carrying out SARS-CoV-2 nucleic acid testing should be well trained with laboratory biosafety and PCR experimental skills. [15]

As broncho-alveolar lavage fluid (BALF) samples are not practical for the routine laboratory diagnosis and monitoring of the disease, collection of other samples such as sputum, nasal swab, and throat swab is rapid, simple, and safe; even though, detection of viral RNAs in BALF is much dependable for the diagnosis and monitoring of viruses in severe cases, since gathering of BALF needs both a suction tool and an expert operator, in addition to being painful to the patients.

An important issue with the real-time RT-PCR test is the risk of eliciting false-negative and false-positive results. It is reported that many 'suspected' cases with typical clinical characteristics of COVID-19 and identical specific computed tomography (CT) images were not diagnosed. [16] Thus, a negative result does not exclude the possibility of COVID19 infection and should not be used as the only criterion for treatment or patient management decisions. It seems that combination of real-time RT-PCR and clinical features facilitates management of SARS-CoV-2 outbreak. Several factors have been proposed to be associated with the inconsistency of real-time RT-PCR. [17]

CHAPTER II

Section 2.1.

Methodology

Study Design: Cross-Sectional Study

Study Period: 16th September - 30th November 2020

Sample Population: COVID-19 patients in South Korea, Australia, & England.

Sample Size: Total COVID-19 patients in South Korea, Australia, & England extracted from the database of bellow sources.

Data Collection Tool: Data collection sheet

Data Management & Analysis Plan: Data will be checked and edited after collection.

- Chart by spreadsheet of window 7.
- Cross tabulation will be prepared and a comparison will be made between the data driven about three countries from above sources.
- Graphical representation and interpretation of data.

Quality Control and Quality Assurance: All effort will be made to reduce the likelihood of important errors which compromise the essential integrity of the research data. Data will be collected by principal investigator as a result there will be minimum bias on the research and PI will also monitor all the steps in the study.

Expected Outcome / Impact:

1) People of certain age-groups in given countries are more vulnerable to get COVID-19 infection.
2) People of certain age-groups in given countries have higher death rate due to COVID-19 infection
3) Male sex are more vulnerable than Female sex to be infected and dead in COVID-19.

Site of study: Graduate School of Public Health, Yonsei University, Seoul, South Korea.

Section 2.2.

Types of Data: Secondary

Source of Data: Secondary data of COVID-19 patients in South Korea, Australia, & England (UK).

Total COVID-19 patients in South Korea, Australia, England (UK) extracted from the database of following sources:

1) Coronavirus Infection-19 Outbreak Status in Korea (Domestic Occurrence Status) Update: 22 April 14:08 page: 31 https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030
2) Coronavirus (COVID-19) current situation and case numbers, Department of Health, Australian Government https://www.health.gov.au/sites/default/files/documents/2020/04/coronavirus-covid-19-at-a-glance-22-april-2020.pdf
3) Weekly Coronavirus Disease 2019 (COVID-19) Surveillance Report, Summary of COVID-19 surveillance systems, Year: 2020, Week: 28, Public Health England. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/880848/COVID19_Weekly_Report_22_April.pdf

Total population by Age and Sex in South Korea, Australia, England (UK) extracted from the database of following sources:

4) https://worldpopulationreview.com/countries/south-korea-population
5) https://worldpopulationreview.com/countries/australia-population
6) https://worldpopulationreview.com/countries/united-kingdom-population

Section 2.3.

Calculation of Incidence rate and Case fatality ratio (CFR)

Incidence rate of COVID-19

COVID-19 *Incidence Rate in a specific* ***Age & Sex group*** *population (in 100,000 population)*

$$\frac{number\ of\ total\ COVID{-}19\ {+}ve\ cases}{number\ of\ total\ population\ of\ that\ group} \times\ 100{,}000$$

Case fatality ratio (CFR) [18]

COVID-19 *Case fatality ratio (CFR, in %) among specific* ***Age & Sex group*** *of Patient* =

$$\frac{number\ of\ death\ from\ disease}{number\ of\ confirmed\ cases\ of\ specific\ group} \times\ 100$$

CHAPTER III

RESULTS

1. Incidence rates of COVID-19 Infection in South Korea, Australia, and England in different Age and Sex group

Table -1

Age Group in years	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
S. Korea									
M	3.63	12.3	36.77	13.46	10.61	15.19	18.13	19.67	28.15
F	2.86	11.53	27.72	18.44	23.69	31.07	25.52	21.21	28.15
Australia									
M	2.08	6.09	35.62	29.59	29.65	33.87	43.89	45.41	25.77
F	2.7	6.59	46.25	27.48	21.65	35.42	41.09	34.99	17.14
England									
M	7.83	6.71	54.72	91.71	142.47	210.37	251.92	378.17	819.2
F	9.01	16.26	148.09	168.02	195.05	192.2	169.44	244.08	796.08

As we see from the table: 1

In **South Korea** male patients of age group 0-9, 10-19 and 20-29 years are found more infected than their female counterparts while the female patients of after 30 years of age were infected more than males of those age groups. The males of 20-

29 years and females of 50-59 years got COVID-19 infection higher than the other age and sex group of people.

On the other hand, **Australia** saw higher cases of confirmed contagion in males of 30-39, 40-49, 60-69, 70-79, 80+ age group of people than women of those categories. Similar to South Korea Australia has higher cases in higher age groups of both genders except the age group of 20-29 years of population.

Aside from above two countries, **England** experienced a sky rocketed cases in each age group of population and the infection among the higher age categories were soared in both sexes. Incidence rate of COVID-19 infection in female were exorbitant than their male counterpart from the age group of 0-49 years; the opposite scenario is seen in the age groups from 50 years and onwards while the gap between male and female incidence rate came shorter at the age above 80 years.

2. Comparison between Male & Female Crude Incidence Rate / 100,000 in South Korea, Australia, and England

Table – 2

Country	South Korea	Australia	England
Male	156.26	251.95	1963.10
Female	190.18	233.32	1938.26

As we see from the table: 2

The Crude Incidence Rate of COVID-19 in Female is more than that of Male in South Korea which is opposite to that of both Australia and England. Yet The Crude Incidence rate of both sexes in South Korea is lower than that of Australia and England. Data of England shows, for both sexes CIR is more than ten times higher than that of South Korea and more than seven times higher than that of Australia.

3. Comparison between Male & Female Adjusted Incidence Rate (IR) / 100,000 in South Korea, Australia, and England

Table – 3

Country	South Korea	Australia	England
Male	17.83	26.88	164.58
Female	22.30	25.93	171.29

As we see from the table: 3

The Sex Adjusted Incidence Rate of COVID-19 in Female is more than that of Male in South Korea which is opposite to that of both Australia and England. Yet Adjusted Incidence Rate of both sexes in South Korea is lower than that of Australia and England. Data of England shows, for Male, Sex Adjusted Incidence Rate is more than nine times and six times higher than that of South Korea and Australia respectively, while for female, that is >7 times and >6 higher than that of Korea and Australia respectively.

4. Comparison among the Case Fatality Rate (CFR) of COVID-19 Infection in South Korea, Australia, and England in different Age and Sex group

Table: 4

Age Group in years	**0-9**	**10-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80+**
S. Korea									
M	0%	0%	0%	0%	1%	2%	5%	14%	30%
F	0%	0%	0%	0%	0%	0%	1%	7%	20%
Australia									
M	0%	0%	0%	0%	0%	0%	1%	4%	20%
F	0%	0%	0%	0%	0%	0%	1%	3%	15%
England									
M	0%	3%	1%	2%	4%	7%	19%	29%	41%
F	0%	0%	0%	0%	1%	5%	15%	30%	28%

As we see from the table: 4,

While examining the data extracted to interpret the Case fatality rate (CFR) of those three countries, 0% CFR was found for both sexes of 0-19 years of patients for all countries except England as it saw 3% CFR in males of 10-19 age categories. The female patients of South Korea and Australia along with male patients of Australia also have 0% case fatality rate up to 59 years of age. At the same time males of South Korea and females of England of up to 49 years of age experienced

CFR of 0%. In all three countries male patients had higher mortality rate than female patients which increased significantly with the increase of age while England experienced the highest CFR in both age and sex categories of COVID-19 patients. The patients of 80+ age group of both sexes had much higher case fatality rate than any other age group which ranges from 1%-41%, except the female patients of England for which CFR decreased in 2% from age group of 70-79 years to 80+ years.

5. Comparison between Male & Female Crude Mortality Rate (MR) from COVID-19 Infection per 100,000 population in South Korea, Australia, and England

Table – 5

Country	South Korea	Australia	England
Male	11.86	7.45	516.21
Female	7.7	3.87	338.6

As we see from the table: 5
The Crude Mortality Rate of COVID-19 in Male is more than that of Female in all three countries. Yet the Crude Incidence rate of both sexes in Australia is lower than that of South Korea and England. Data collected from England shows, for male, CMR is more than 43 times higher than that of South Korea and more than sixty nine times higher than that of Australia. At the same time CMR for Female in England is >43 times and >87 times higher than that of South Korea and Australia, respectively.

6. Comparison between Male & Female Adjusted Mortality Rate (AMR) from COVID-19 Infection per 100,000 population in South Korea, Australia, and England

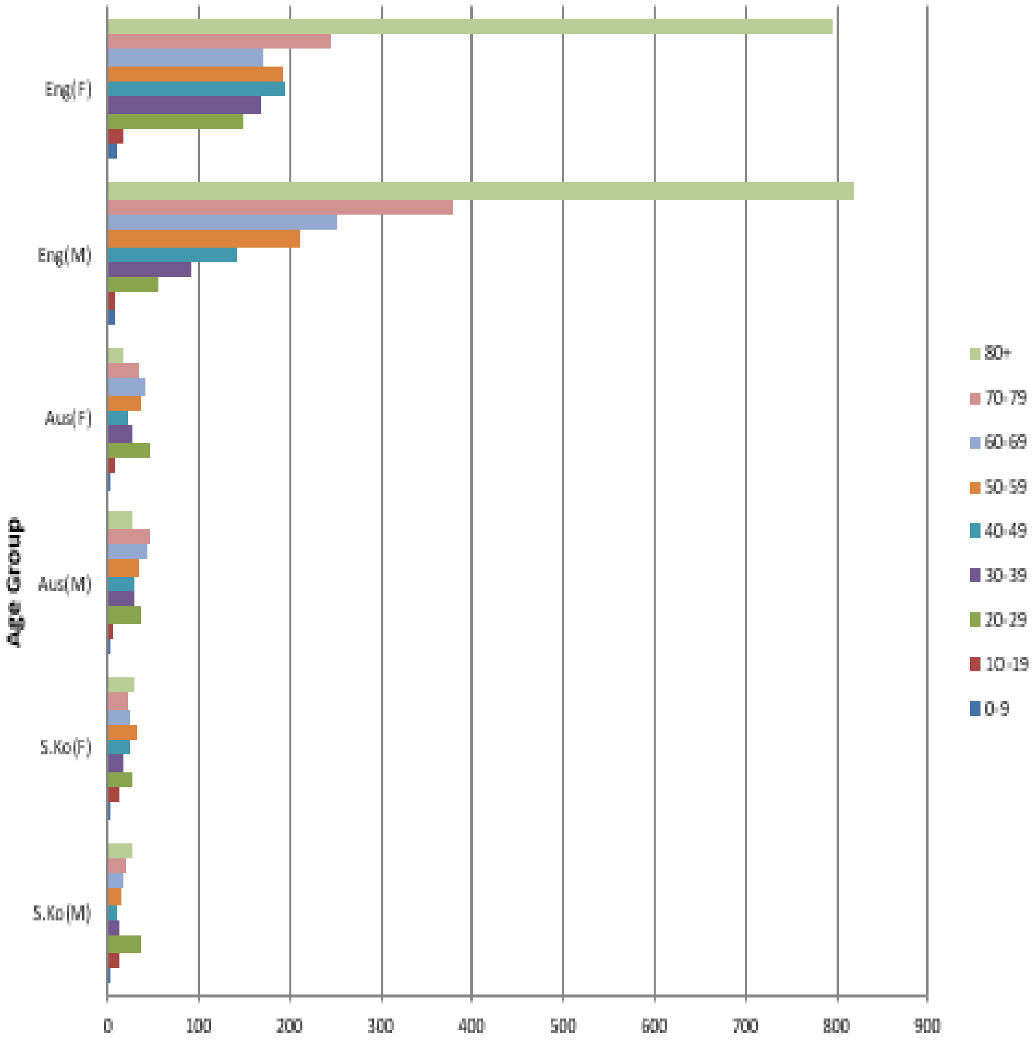
Table – 6

Country	South Korea	Australia	England
Male	0.58	0.39	34.01
Female	0.34	0.21	22.01

As we see from the table: 6

The Adjusted Mortality Rate of COVID-19 in Male is more than that of Female in all three countries. Yet the Adjusted Mortality Rate of both sexes in Australia is the lowest of all. Data collected from England shows, for male, AMR is more than 58 times higher than that of South Korea and more than 87 times higher than that of Australia. At the same time AMR for Female in England is >64 times and >104 times higher than that of South Korea and Australia, respectively

1. Comparison of Incidence rate (%) of COVID-19 Confirmed Cases among South Korea, Australia and England according to age group and sex



Infection rate

<u>Figure: 1</u> Comparison of Incidence rate (%) of COVID-19 Confirmed Cases among South Korea, Australia and England according to age group and sex

From the **Figure: 1** it is clear that the percentage of COVID-19 incidence is huge in the elderly population in England than those of South Korea and Australia. At the same time, it is obvious from the graph that in England people of all age and sex groups had a huge incidence rate of infection when compared to other two countries. In South Korea the male of 20-29 years are more prone to infection among the all other age and sex groups followed by female of 50-59 years and 20-29 years of age. Conversely, in Australia, Female of 20-29 years had higher incidence rate than their Male counterparts; here this group was followed by males from 60-79 years of age.

2. Comparison of CFR (%) of COVID-19 Confirmed Cases among South Korea, Australia and England according to age group and sex

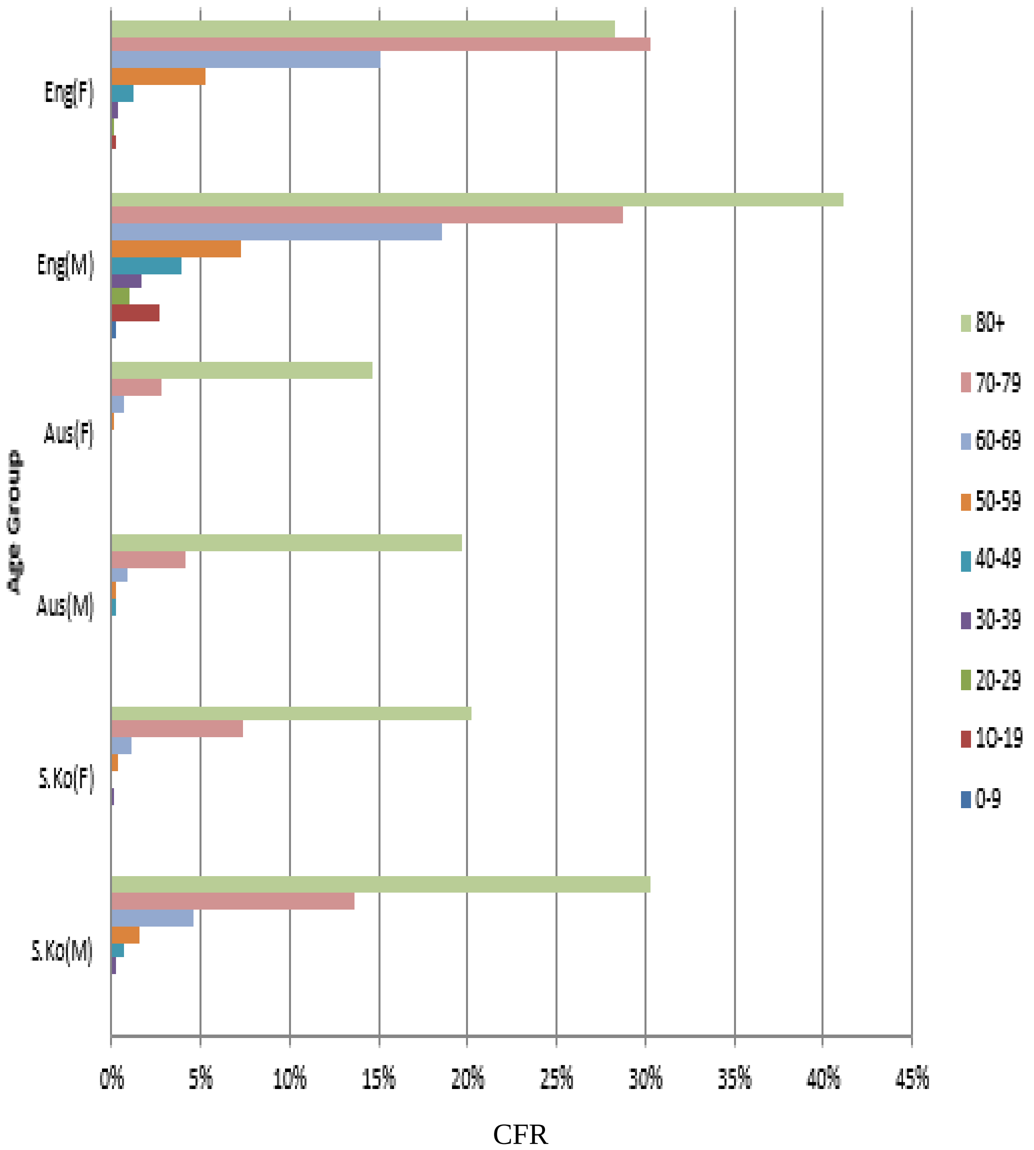
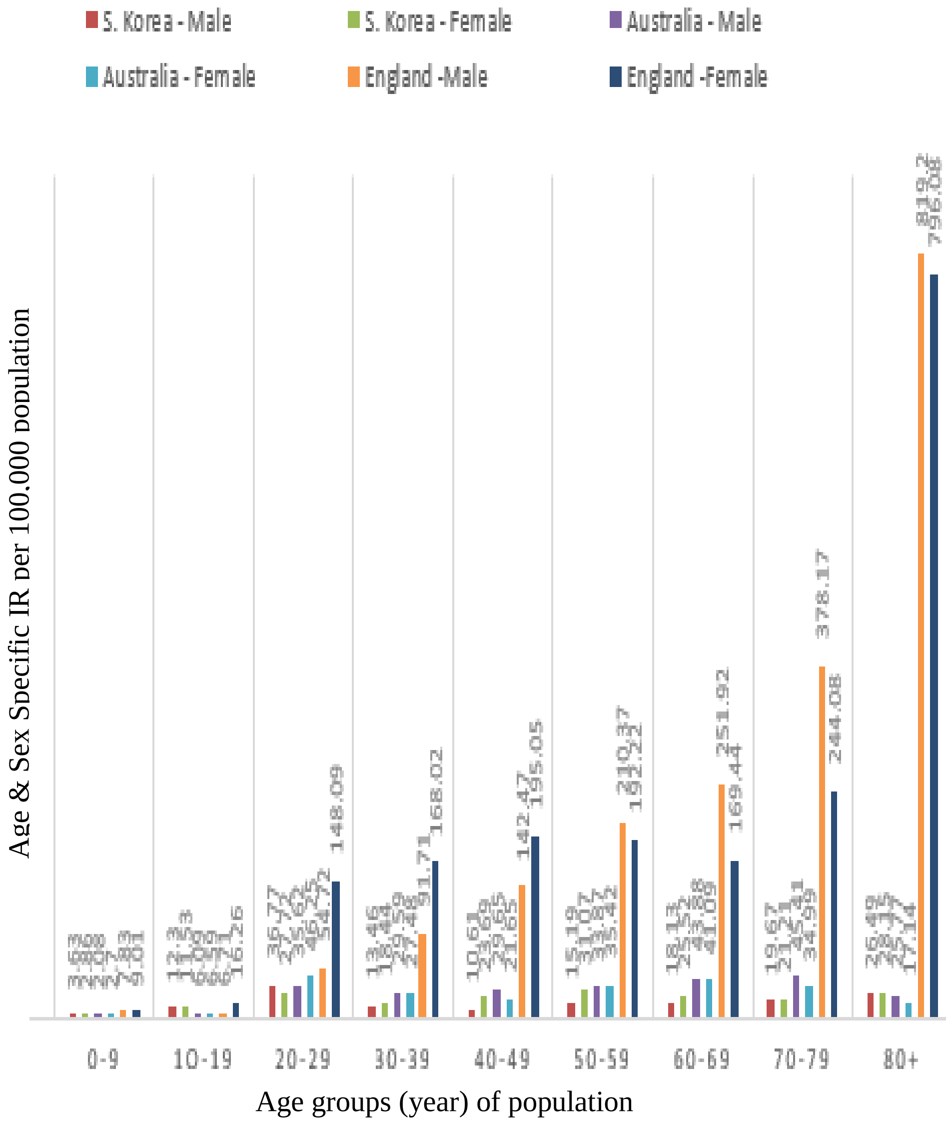


__**Figure 2**__ **Comparison of CFR (%) of COVID-19 Confirmed Cases among South Korea, Australia and England according to age group and sex**

From the **Figure: 2** it is clear that the Case Fatality Ratio (%) of COVID-19 is huge in the elderly male population in all three countries amongst which England saw the most deaths. At the same time, it is obvious from the graph that in England people of all age and sex groups had a huge CFR when compared to their counterparts of other two countries.

3. Age & Sex Specific Incidence Rate (IR) of COVID-19 Infection per 100,000 population in South Korea, Australia, and England in different Age and Sex group

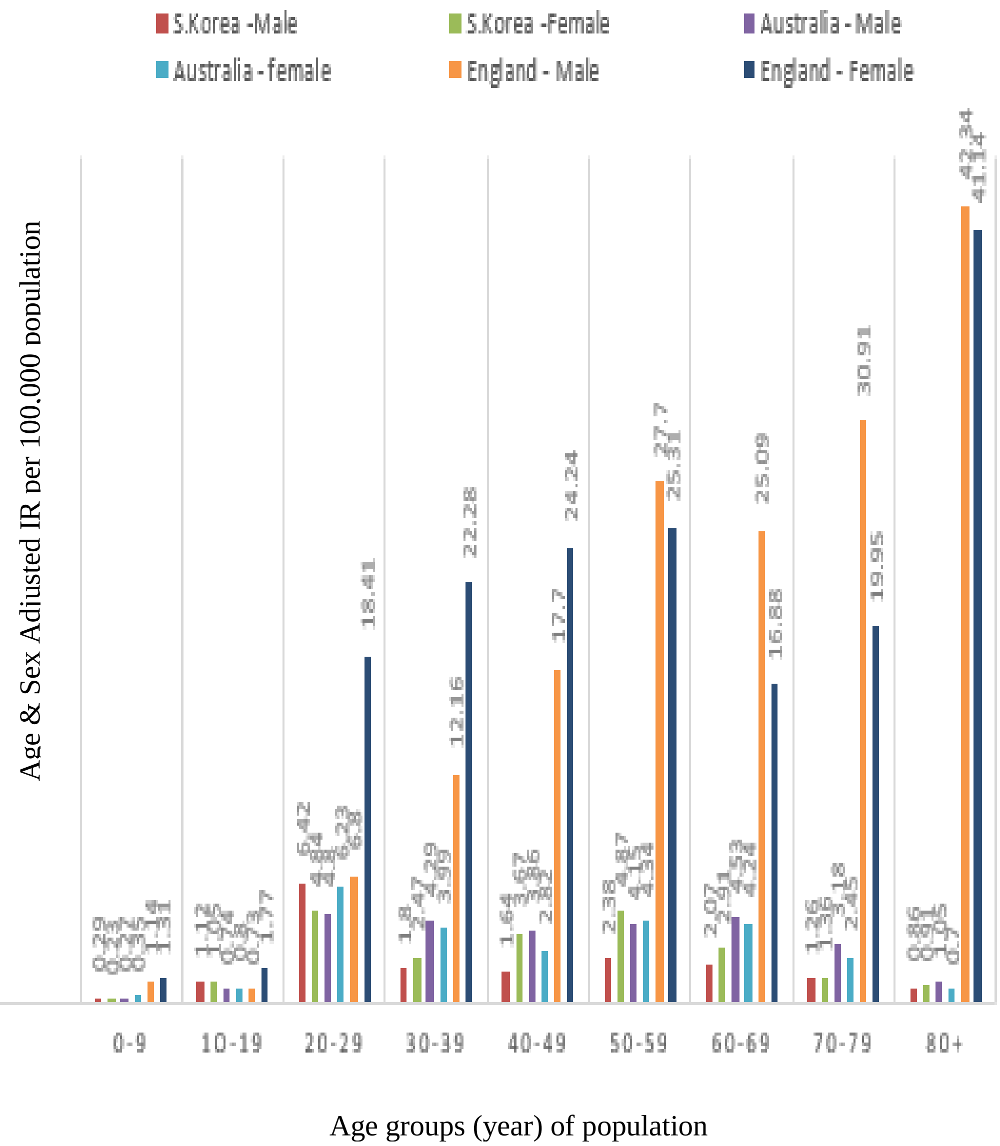


<u>Figure: 3</u> Age & Sex Specific Incidence Rate (IR) of COVID-19 Infection per 100,000 population in South Korea, Australia, and England in different Age and Sex group

As we see in graph,

in all three countries, Age & Sex Specific IR per 100,000 population, increase with the increase of ages in both sexes. However, in case of England, Age & Sex Specific IR of Male of more than 80 years of age-group, gets more than 30 times higher than that of both South Korea & Australia. On the other hand, Age & Sex Specific IR of Female of more than 80 years of age-group gets >28 times higher and >46 time higher than that of South Korea & Australia Respectively. In all other age & sex groups of population, England shows highest Age & Sex Specific IR per 100,000 population. And South Korea shows the lowest of that.

4. Age & Sex Adjusted Incidence Rate (IR) of COVID-19 Infection per 100,000 population in South Korea, Australia, and England in different Age and Sex group

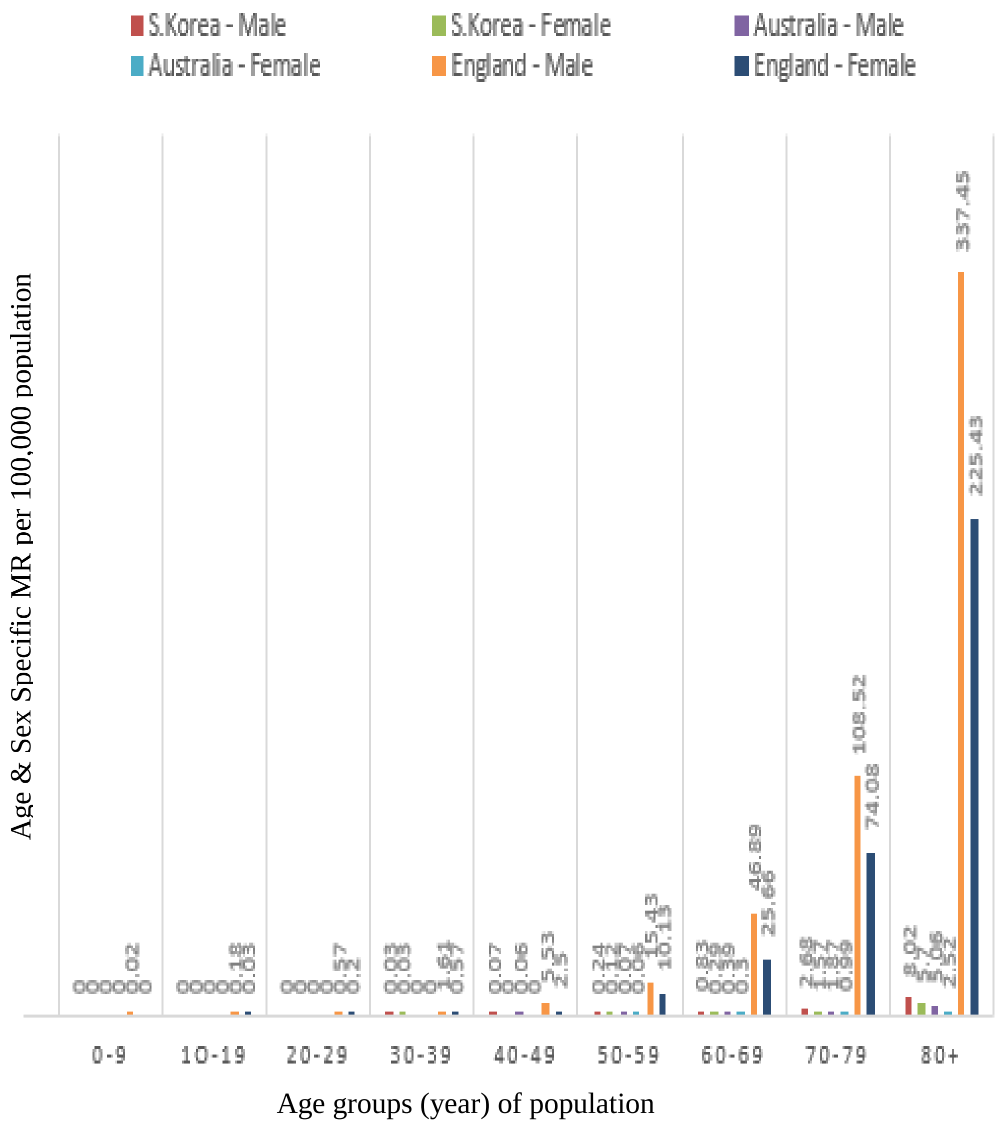


<u>Figure: 4</u> Age & Sex Adjusted Incidence Rate (IR) of COVID-19 Infection per 100,000 population in South Korea, Australia, and England in different Age and Sex

As we see in graph,

in all three countries, Age & Sex Adjusted IR per 100,000 population, increases with the increase of ages in both sexes. However, in case of England, Age & Sex Adjusted IR of Male of more than 80 years of age-group, gets more than 49 times higher than that of South Korea & 40 times higher than that of Australia. On the other hand, Age & Sex Adjusted IR of Female of more than 80 years of age-group gets >45 times higher and >58 time higher than that of South Korea & Australia respectively. In all other age & sex groups of population, England shows highest Age & Sex Adjusted IR per 100,000 population. And South Korea shows the lowest of that.

5. Age & Sex Specific Mortality Rate (MR) of COVID-19 Infected cases per 100,000 population in South Korea, Australia, and England in different Age and Sex group

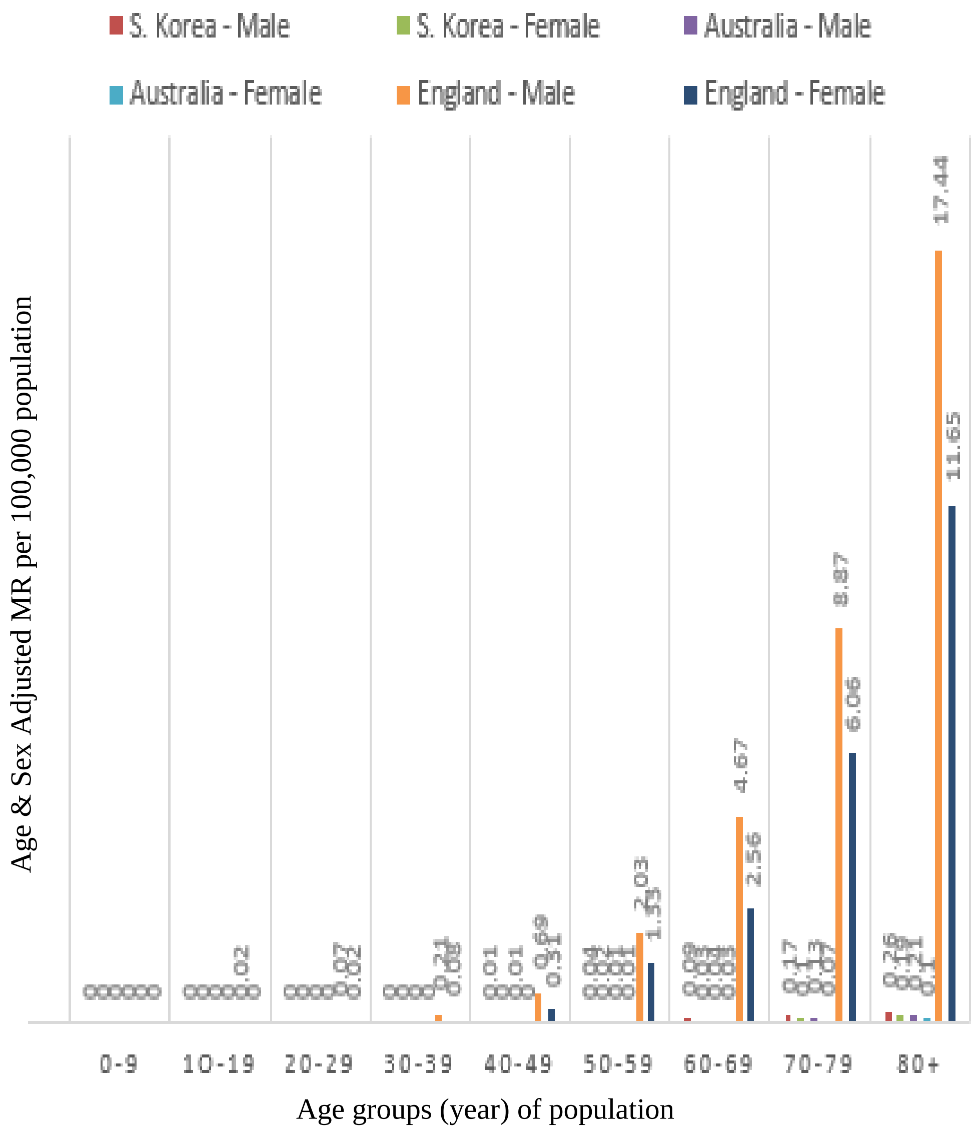


<u>Figure: 5</u> Age & Sex Specific Mortality Rate (MR) of COVID-19 Infected cases per 100,000 population in South Korea, Australia, and England in different Age and Sex group

As we see in graph,

in all three countries, Age & Sex Specific MR per 100,000 population, increases with the increase of ages in both sexes. However, in case of England, Age & Sex Specific MR of Male of more than 80 years of age-group, gets more than 42 times higher than that of South Korea & 66 times higher than that of Australia. On the other hand, Age & Sex Specific MR of Female of more than 80 years of age-group gets >39 times higher and >90 time higher than that of South Korea & Australia respectively. In all other age & sex groups of population, England shows highest Age & Sex Specific MR per 100,000 population.

6. Age & Sex Adjusted Mortality Rate of COVID-19 Infected cases per 100,000 population in South Korea, Australia, and England in different Age and Sex group



<u>Figure: 6</u> Age & Sex Adjusted Mortality Rate of COVID-19 Infected cases per 100,000 population in South Korea, Australia, and England in different Age and Sex group

As we see in graph,

in all three countries, Age & Sex Adjusted Mortality Rate per 100,000 population, increases with the increase of ages in both sexes. However, in case of England, Age & Sex Adjusted Mortality Rate of Male of more than 80 years of age-group, gets more than 67 times higher than that of both South Korea & 83 times higher than that of Australia. On the other hand, Age & Sex Adjusted Mortality Rate of Female of more than 80 years of age-group gets >61 times higher and >116 times higher than that of both South Korea & Australia respectively. In all other age & sex groups of population, England shows highest Age & Sex Adjusted Mortality Rate per 100,000 population.

CHAPTER IV

DISCUSSION

The detection of probabilistic SARS-CoV-2 infection symptoms, separately or collectively, is important for the search for well-classified recommendations of screening and self-isolation to stop transmission. 92 percent reported cases having at least one symptom of fever, cough and dyspnea in the large population-based study including HCW in the United States, and this symptom triad has been reported as the hallmark symptoms of COVID-19 infection. [19, 20, 21, 22] While fever in this study was one of the most common symptoms of seropositive HCW, anosmia and ageusia were the most predictive symptoms of SARS-CoV-2 infection. Of these, anosmia appears in COVID-19 as a main symptom. [23]

In line with the recent major multinational population-based cohort study examining possible COVID-19 symptoms, the findings of the current study report a clear correlation between anosmia, ageusia and COVID-19. [24] In additament, a straightforward correlation was established between the combinations of symptoms of anosmia and/or ageusia, malaise and fever along with anosmia and/or ageusia, malaise and cough and seroprevalence, signifying that these symptoms should be included in the guidelines for regular screening. Similar to many other studies, during analysis of the secondary data from South Korea, Australia, and England, the incidence rate and the fatality rate both were found the least among the children below 10 years of age. In less than 10% cases pediatric population were identified as index case. [25] In addition to that, unlike most other respiratory viruses, children do not appear to be a major vector for transmission of SARS-CoV-2, rather most pediatric cases reported in family clusters. Most children usually have milder or atypical presentations such as headache and nasal discharge, and anosmia and abdominal symptoms. Sometimes these symptoms might be de-emphasized due to underreporting since the infants and children of younger age may not be able to express them. [26] However, in some studies it is observed that in the gastrointestinal tract of infected children, SARS-CoV-2 may live for a longer period than in the respiratory system.

The recurrent shedding of SARS-CoV-2 into the stools of infected children suggests the capacity for fecal excretion to spread the virus. At all levels, major efforts should be made to prevent the spread of infection among children after resuming the elementary school. [27]

For Australia and England, the exact number of total cases disaggregated by sex was not provided in anywhere of the websites of government. In addition to that, although every type of categorization and graphical representation poses separate importance for data analytic process, it is important to enhance the inclusiveness of data acquisition and data types. For genders, it would be useful to include a third alternative, outside the stereotypical, to address the inaccurate values. Sex-disaggregation in an inclusive manner as well as data harmonization is undeniably a prerequisite for strengthening the capacity of global surveillance system. [28]

Among men, susceptibilities toward COVID-19 diseases and the corresponding mortality rates are higher in all countries which may be caused by influence of male endocrine system to their immune system. At the same time endocrine alteration enhances immunosenescence effects contributing postmenopausal women more vulnerable to the infection along with imposed severity. Regular monitoring and evaluation of these vulnerable population category through organized biochemical and endocrine investigations as well as restoring central well-classified database accordingly are needed to be emphasized on. [29]

Both Care-givers to sick in family setting and health-care stuffs are appear to be overwhelmingly female, a factor that would have influenced to higher infection rates for females than males in South Korea and England, as well as made them a potential source of infection during their asymptomatic or pre-symptomatic stage of ailment. During the sub-clinically infected they themselves became potential source of infection to other comorbid patients both male and female and as due to endocrine related cause males are more vulnerable to non-communicable diseases their mortality rate becomes higher. [30]

In addition to that, most of the worshiping places are frequently visited by females of all ages and male of particularly higher ages exposing them to extremely transmissible COVID-19 disease. [31] To overcome the dreadful outcome from spreading of this infection, diagnosis in the earliest possible time is “the must” through the combination of proper contact tracing and rapid detection method.

While compared to South Korea and Australia, in England, often ethnic minorities experience significantly excess hospital deaths. Compared with the white British majority so far, official non-hospital deaths can only account for a small part of the difference. Age and place obviously play a part, but they do not reveal the real tale, while seemingly depict substantial disparities between various minority communities. It is possible that underlying health conditions, workplace exposure and a number of other variables are significant, with some more important for specific groups: Bangladeshi males have high rates of underlying health problems, while black Africans and Indian males are especially vulnerable to the virus because of their prevalence in healthcare roles. As further study is done, the significance of every other element for each category might become easier to understand. [32]

Data extracted and interpreted here all have used RT-PCR method to confirm the diagnosis of COVID-19 cases as it is considered as a gold standard according to the guidance of WHO due to its high sensitivity and specificity in detection of infectious agents. Advanced equipment for laboratories and highly qualified technicians are the prerequisite of RT-PCR test. Moreover, it requires long assay reaction time up to 2 hours or more. As a result this method, though gold standard**,** is not suitable for Point of Need (PON) and Point of Care (POC) for case detection following enabling rapid Non-Pharmacological Interventions (NPI) to halt the transmission as well as rapid Pharmacological interventions (PI) to check complications in susceptible population group. So Korea has invented and is still carrying on research for further improvising Rapid Antigen Detection kits with more than 95% sensitivity and specificity. A framework for massive molecular genetic tests, capable of performing 15,000 to 25,000 PCR tests, has already been developed in Korea, and accurate testing takes only about six hours, since KDCA took a decision not to implement Rapid Diagnostic Tests through antigen detection with current prevalence of COVID-19 at this time. [33] Similarly, in Australia, currently available guidance does not approve the use of rapid antigen tests in present situation with low prevalence of cases. [34] On the other hand, with a very high incidence and prevalence of cases in England, RDT became a crucial tool to help monitor this virus and make life more natural. After carrying out mass testing by RDT using antigen detection technology in Liverpool, this virus can be identified faster than ever before, even in people who do not have symptoms. Via applying a nose and throat swab to a special test kit, these tests detect if the virus is present. These lightweight portable tests demonstrate a point-of-care outcome in 15-30 minutes, without the need to be tested in a laboratory, like a pregnancy test. They directly detect the virus without the RT-PCR or LAMP (loop mediated isothermal amplification) amplification steps. An objective review of one test (the SD Biosensor test) showed that it had a 99.3 percent clinical precision and a 76.6 percent clinical sensitivity. [35]

For upgrading the rapidity of such diagnostic capacity innovative diagnostics technology with high sensitivity, specificity, and reliability like CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). [36]

No routine antibody test is done in any of the country among South Korea, Australia, and UK that can provide sero-prevalence data for better understanding of the true extent of COVID-19 infection throughout the country. As a result the age and sex group of population who remain asymptomatic during their active infection period never be addressed in national surveillance system as they become negative in RT-PCR test after a certain period of time. It has been seen in several studies that frontline health care worker who are mostly female of middle aged, found sero-positive albeit 10%-50% of them remain asymptomatic or have very mild symptoms that are not sufficient for clinical diagnosis. [37, 38]

In South Korea, tracing the source of infection from inbound travelers to the people from most remote areas, through quick and accurate epidemiological investigation including quarantine of contacts, central and local governments respond to Suspected and confirmed COVID-19 cases. Necessary information, including the location of confirmed cases, is obtained via an interview with reported cases for epidemiological investigation. Interviews with healthcare workers and family members can also be conducted if appropriate. More objective data (medical records, mobile GPS, CCTV video, credit card records, even tracking through programed wristband etc. can be obtained and checked in the event that the acquired information is inadequate. To attend healthcare education, monitor their symptoms, and remain in self-quarantine, the contacts found during the investigation are needed. In order to avoid any new infections, information on the whereabouts of suspected cases is posted to websites. [39] South Korea has been using this automated contact tracing to monitor the spread of COVID-19, mostly setting the public health safety beyond the personal privacy of individuals, continuous research for improvisation of such technolog ies to safe-guard confidentiality is being carried on, though. [40]

Similarly, like the ‘TraceTogether” app of Singapore, Australia develop its own COVID Safe app, as a cornerstone to its national public health policy early in the crisis. What is particularly fascinating about these cases is the privacy problems posed by the apps, and how they are addressed in each country, as well as the ways in which both the states interweave own immediate future of societal concerns and health policy through such an app. [41]

It is difficult to understand why it took the UK so long to adopt a well privacy maintaining contact tracing app even when Singapore has had efficient track and trace technology in place since March, especially when Singapore's technology was open-sourced and obtainable for use by app developers around the world. Contact-tracing applications are gradually being released across the four nations of the UK about half a year after they entered the Covid-19 lockdown during mid-March. [42]

The most common features throughout these apps are real-time maps and notifications of reported cases as well as their proximity, home isolation with quarantine monitoring and control systems, direct government reporting and self-reporting of symptoms, and COVID-19 education. Some more advanced services include regular physiological status self-physical assessment as well as virtual medical consultations. [43] Even though supporters believe that apps using centralized approach offers prompt and valuable information about the spread of infection to epidemiological investigators, these apps has much more privacy risks. On the other hand, apps that use a decentralized approach are more confidentiality-friendly, since the information remains on the devices of users. [44]

Artificial Intelligence (AI) can quickly analyze uncommon, irregular and alarming symptom; thus beneficial in the diagnosis of the infected cases with the assistance of various medical imaging technologies like Computed tomography (CT), Magnetic resonance imaging (MRI) scan of human body. Thus generate warning to the patients and the healthcare authorities. [45, 46] AI can help analyze the level of infection by this virus identifying the clusters and 'hot spots' and can successfully do the contact tracing of the individuals and also to monitor them. It can predict the future course of this disease and likely reappearance along with projection of cases and mortality by quickly analyzing various data available in its neural platform. Thus strengthening AI based bio-surveillance can impact future patient care and address more potential challenges which reduce the workload of the healthcare staffs providing better outcome not only in prevention but case detection along with treatment. [47, 48]

Moreover, geo-climatic and cluster-distribution of the genetically and /or point mutated unique strains of COVID-19 virus have been identified during research on "disease-severity" and "high-transmissibility" in the European countries. [49] Thus high morbidity and mortality of immune-compromised patients infected by COVID-19 might be explained by the correlation with the disastrous consequences of these newer mutations. [50] Higher transmission potential of any mutant strains creates huge burden for Health Care Facilities resulting rapid surge in death rates. Since health care personnel and care-givers are more vulnerable during treating patients therefore, a huge rampage of the virus is going on in those countries. The most troublesome state is that, till date, six countries, namely Denmark, Spain, the Netherlands, Sweden, Italy and the United States of America have reported SARS-CoV-2 in farmed minks to OIE. This variant is inter-transmissible between human and minks leading minks a potential reservoir of this strain. Preliminary findings from recently identified mink-associated variant indicate that this particular variant in both minks and the human cases shows moderately decreased sensitivity to neutralizing antibodies which poses a threat towards the vaccination failure along with increased incidence of re-infection by SARSCov-2 leading to much more morbidity and fatality. In this regard extensive surveillance, sampling and sequencing of SARS-CoV-2, not only to find out the animal reservoirs in our surroundings but to find out the extension of the variant in human clusters are needed to be identified. Along with it, timely and regular updating and integration of this genetic sequencing data into global initiative on sharing all influenza data (GISAID) is inevitable for strengthening "Bio-surveillance capacity" both nationally and internationally. [51]

CHAPTER V

CONCLUSION

This study is aimed to exhibit the gaps of currently available bio-surveillance strategy that has led the whole world into an unending surge of the COVID-19 contagion and fatality, driving the entire mankind into an apparently unending misery. Ameliorating currently available bio-hazard and disease surveillance system by filling those voids up, along with the help of incessant need-based research and innovations, imply a tremendous importance to overcome the current situation; This effort, at the same time, will enable the nations to exchange own concerns through a robust integration system under the **Global Health Security Agenda**, to become much more efficient in dealing accordingly with any prediction of **"Disease-X"** threats.

CHAPTER VI

LIMITATIONS OF THE STUDY

WITH RECOMMENDATIONS

Integrated bio-surveillance capability building not only requires laboratory improvisation and technical synchronization but also it requires ethical aspects to be considered, so that confidential information are not being leaked from the server or mishandled by third party. In this regard much more intensified research in related fields are still in dire need to be coordinated with a strict view to halt of current pandemic in near future.

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