



Meta-analysis and comprehensive study of coronavirus outbreaks: SARS, MERS and COVID-19



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ABSTRACT

Background: Zoonotic coronaviruses have caused several endemic and pandemic situations around the world. SARS caused the first epidemic alert at the beginning of this century, followed by MERS. COVID-19 appeared to be highly contagious, with human-to-human transmission by aerosol droplets, and reached nearly all countries around the world. A plethora of studies were performed, with reports being published within a short period of time by scientists and medical physicians. It has been difficult to find the relevant data to create an overview of the situation according to studies from accumulated findings and reports. In the present study we aimed to perform a comprehensive study in the context of the case fatality ratios (CFRs) of three major human Coronavirus outbreaks which occurred during the first twenty years of 21st century.

Methods: In this study, we performed meta-analyses on SARS, MERS and COVID-19 outbreak events from publicly available records. Study analyses were performed with the help of highly reputable scientific databases such as PubMed, WOS and Scopus to evaluate and present current knowledge on zoonotic coronavirus outbreaks, starting from 2000 to the end of 2020.

Results: A total of 250,194 research studies and records were identified with specific keywords and synonyms for the three viruses in order to cover all publications. In the end, 41 records were selected and included after applying several exclusion and inclusion criteria on identified datasets. SARS was found to have a nearly 11% case fatality ratio (CFR), which means the estimated number of deaths as a proportion of confirmed positive cases; Taiwan was the country most affected by the SARS outbreak based on the CFR analysis. MERS had CFRs of 35.8 and 26 in Saudi Arabia during the 2012 and 2015 outbreaks, respectively. COVID-19 resulted in a 2.2 CFR globally, and the USA reported the highest mortality ratio in the world in the end of first year of COVID-19 pandemic.

Conclusion: Some members of the *Coronaviridae* family can cause highly contagious and devastating infections among humans. Within the last two decades, the whole world has witnessed several deadly emerging infectious diseases, which are most commonly zoonotic in nature. We conclude that pre-existing immunity during the early stages of a pandemic might be important, but case control and management strategies should be improved to decrease CFRs. Finally, we have addressed several concerns in relation to outbreak events in this study.

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Introduction

Severe acute respiratory syndrome coronavirus (SARS) is considered the first pandemic of the 21st century, but coronavirus

disease 2019 (COVID-19) will be remembered as the most devastating outbreak in human history [1]. COVID-19 hugely affected the global economy as well as the health of people [2]. To date through the end of the first year of pandemic, around 1 million people have lost their lives, and more than several million have lost their jobs; nearly all countries stopped their international and domestic movements including trading, which has, in turn, severely affected the economy of the developing world. The world is beginning to enter an eclipse period of human activities [3]. It will take several decades

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to restore the economic losses and other socioeconomic damages caused by the pandemic [2,4].

COVID-19 is caused by a coronavirus, formerly called novel coronavirus 2019 (2019-nCoV). The International Committee on Taxonomy of Viruses (ICTV) announced the virus as SARS-CoV-2 due to the virus genome being closely related with the SARS virus, which also caused an outbreak in 2002 in China [5]. A similar respiratory illness that caused an outbreak occurred in Saudi Arabia in 2012; the disease was called Middle East respiratory syndrome (MERS) and is also caused by a coronavirus [6]. MERS almost affected the entire Middle East region during the outbreak. A common feature of SARS, MERS and COVID-19 is the causative agent—the coronavirus originates from animals [6]. Coronaviruses are zoonotic in nature likely because of the nature of the virus' molecular genomic organization, such as longer genomic RNAs, which allow various mutations and recombination at the gene level to occur more randomly and frequently. Sub-genomic RNA organizations also allow new coronavirus strains to emerge during virus replication in the host cell [7,8]. Direct contact with infected wild animals and with their products is suspected to be a primary virus source for initiating human transmission. Transmission and spreading of viruses from human to human is rapidly accelerated by aerosol droplets and threatens human health, with mortality ranging from 2.5 to 35% [9]. Common signs of COVID-19 are associated with respiratory failure and high body temperature along with severe coughing. The severity of infection is characterized by the development of pneumonia, acute respiratory distress syndrome (ARDS) and accumulated infiltrating exudates in the lower respiratory tract, kidney failure and even death at the final stage of infection [10–12].

Seven human coronaviruses (H-CoVs) have been identified to date. Four coronaviruses have been identified as common coronaviruses including alpha CoVs-NL63, 229E, beta-CoVs OC43 and HKU1. Three of them have been identified as deadly coronaviruses as follows: SARS-CoV, MERS-CoV and SARS-CoV-2. The last one, SARS-CoV-2, is responsible for the disease known as COVID-19 [13].

In this study, we summarize and report meta-analyses on outbreak events of SARS, MERS and COVID-19 with comprehensive study in the context of case fatality ratios. The objectives of this study are as follows: to extract the numbers of human cases and mortality numbers from SARS, MERS and COVID-19 outbreaks in terms of their emerging time periods and place where outbreaks occurred; to identify CFR in relation with magnitude of each infection; to find a connection between outbreak sources and spread; to summarize underestimated measurements to control of disease spread around human population. Finally we have also addressed the occurrences and ratios of coronavirus infections among male and female genders. To identify and select the outbreak reports and studies from databases, we have followed Preferred Reporting in Systematic reviews and Meta-Analyses (PRISMA) guidelines along with flow chart diagrams. Data were sorted by searching specific keywords of diseases in order to collect published records during the outbreaks. Only outbreak events were included in the meta-analysis and results were evaluated with their respective originating countries in their given timelines. Medline/PubMed, Scopus and Web of Science (WOS) were the main data sources of this analysis. Meta-data searches and analysis were restricted from 1 June of 2000 to the last week of December 2020.

Meta-analysis results of SARS, MERS and COVID-19 showed that coronaviruses gradually caused pandemics, starting from epidemics that originated from animals and spread to humans. Comprehensive analysis showed that COVID-19 has the highest transmission ratio with the lowest fatality rate among humans, and MERS has the highest fatality ratio but is limited geographically.

Methods

Protocol for the literature search

This protocol followed PRISMA guidelines and recommendations to address meta-analysis studies from epidemic and pandemic outbreaks [14,15]. For meticulous identification and selection of records from databases, PRISMA flow charts were followed during the collection of relevant data in order to draft this meta-analysis study (Fig. 1).

Database search strategy for meta-analysis

Published records were obtained from the PubMed, Scopus and WOS databases. “Outbreak” AND “SARS” for SARS events; “Outbreak” AND “MERS” for MERS events; “Outbreak” AND “COVID-19” or “SARS-CoV-2” or “2019-nCoV” keywords were searched through the search boxes of the database websites without excluding any information in order to identify the study materials for this literature search.

Screening, inclusion or exclusion criteria

Report and study searching activities were divided into three groups for SARS, MERS and COVID-19 and time interval restriction criteria were applied after keywords searching. Search strategies for time restrictions were decided when outbreaks emerged and stopped or infections were no longer being recorded except COVID-19. Currently, as of early 2021, vaccines had been developed and introduced for COVID-19. We only included data from pre-vaccine era for COVID-19, as we did for SARS and MERS infections, to compare CFRs from each outbreak. Selected time intervals were obtained from the World Health Organization (WHO) and ProMED or the European Centre for Disease Prevention and Control (ECDC) databases. The following time intervals were restricted for screening of published records: 2002–2004 for SARS; 2012–2019 for MERS; and 2019–present (27 December 2020) for COVID-19 outbreaks. To determine the eligibility criteria, we sorted and excluded duplicated records that were collected from different databases. Full-text availability and records written in English language were included as eligibility criteria. Studies were included after deciding the quality of synthesis and assessment of quantitative analysis based on information provided in the title, abstract and text of the identified studies and records. Finally, records were included in meta-analysis studies after excluding irrelevant and biased studies (Table 1). Additionally, for the selection of COVID-19 records, a meta-analysis study search was applied to sort records due to the huge, accumulated number of studies. Current data and latest numbers were obtained from <https://www.worldbank.org/>, <https://www.ecdc.europa.eu/> and <https://globalhealth5050.org> for human population, COVID-19 cases, and deaths and gender ratio, respectively, to build various graphs and tables.

Graphics and illustrations

Bar graphs were produced using the GraphPad Prism 7 (Graph Pad Software, San Diego California, USA) statistical software after importing the data from Tables 2, 3 and 4. Calculations of CFR, case or death per million populations were done using Microsoft Excel 2016 (Microsoft Corporation, USA). Virus transmission and spread (Fig. 2) and outbreak timeline info-graphs (Fig. 3) were produced by the authors for this meta-analysis using BioRender, a web-based scientific illustration database.

Table 1
Characteristic and summaries of the included studies in meta-analysis.

Study included	Infection	Year	Publisher	Country	Study/report comment
Donnelly et al. [18]		2003	LANCET	Hong Kong	Study investigated case numbers and admission times to hospital during the SARS outbreak. Study also evaluated patient characteristics in relation to infection.
Chau et al. [24]	SARS	2003	Journal of Epidemiology and Community Health	Hong Kong	Study evaluated daily SARS cases during a period and reported success of effective control measurements such as quarantine of close contacted suspected or persons and describe the importance of sanitation at contaminated environment.
Hsieh et al. [27]		2004	Emerging Infectious Diseases	Taiwan	Study investigated epidemic growth of SARS among the hospitalized patients during the period observed.
Lee et al. [72]		2003	Morbidity and Mortality Weekly Report by Centers for Disease Control and Prevention	Taiwan	This report present first SARS outbreak data and numbers along with patient characteristics in Taiwan.
Chowell et al. [87]		2003	Journal of Theoretical Biology	Ontario, Hong Kong and Singapore	This study presented a global and regional data about SARS from the mentioned areas (Ontario, Hong Kong and Singapore). Study suggest that the epidemic dynamics differ in different region.
Puthuchearry et al. [88]		2004	Archives of disease in childhood	Singapore	Current report provide clinical presentation of SARS in pediatric patient.
Hsu et al. [89]		2003	Emerging Infectious Diseases	Singapore	This study provided clinical, laboratory and radiologic presentation findings of first SARS infected cases along with lab test results.
Wallington et al. [90]		2003	Morbidity and Mortality Weekly Report by Centers for Disease Control and Prevention	Canada	This report provide information of first case of SARS in Canada and its spread to 257 people and also reported second wave after 4 weeks mainly in person such as recovered patients, visitors, and health-care workers.
Nie et al. [91]		2003	World Journal of Gastroenterology	China	This report provides general information of characteristic, mortality, morbidity, therapy and control of SARS in China and adjoining areas.
Zhong et al. [92]		2003	LANCET	China	Serological, molecular test was performed on sample from SARS infected people of Guangdong region. Genetic and Phylogenetic analysis on isolated virus was also done.
Xiaodong et al. [93]		2004	Health Education Research	China	This study provides data about people awareness and change in the daily routine due to SARS. Results indicated that farmers were having lowest information about SARS and hand washing activity enhanced among people.
Memish et al. [94]		2014	International Journal of Infectious Diseases	Saudi Arabia	Epidemiological, genomic and clinical based analysis of all MERS-CoV related cases from Hafr Al-Batin region were reported in this report.
Kronbichler A et al. [95]		2020	International Journal of Infectious Diseases	–	This meta-analysis reviewed the role of asymptomatic patents in COVID-19 in a systematic way from published studies.
Alsahafi et al. [96]	MERS	2016	International Journal of Infectious Diseases	Saudi Arabia	Risk factor analysis of 939 MERS-CoV infected patients was carried out and results revealed that 57.3% of patients with age above 40 died.
Cowling et al. [97]		2015	Euro Surveillance	South Korea	Study was done on 166 MERS-CoV infected patients and it was revealed that incubation period and mean serial interval was 6.7 and 12.6 days respectively.
Yang et al. [98]		2020	Scientific Reports	South Korea	Current report provides information about spreading of MERS in a short period of time and role of super spreader in infection of large population.
Oh et al. [99]		2018	The Korean Journal of Internal Medicine	South Korea	Current review provides information related to clinical presentation, epidemiological investigation along with preventive measure of MERS-CoV.
Korea Centers for Disease Control and Prevention [100]		2015	Osong Public Health and Research Perspectives	South Korea	This study provides us the epidemiological information related to MERS in July 2015 by doing interview with patient and analyzing the medical record. They also studied other information such as interval periods, serial interval etc.
Al Hammadi et al. [101]		2015	Emerging Infectious Diseases	United Arab Emirates	Provided a link between the MERS infected camels and humans.
Khudhair et al. [102]		2019	Emerging Infectious Diseases	United Arab Emirates	Study characterize of high-risk exposure of MERS among the animal slaughterhouse workers.
Ng et al. [103]		2016	The American Journal of Pathology	United Arab Emirates	Current report provided an autopsy report of MERS infected person and provided detailed histopathological, immunohistochemistry, and ultrastructural observation.
Al-Tawfiq et al. [104]		2014	Infection and Drug Resistance	Jordan	This review provide information related to epidemiological situation along with some seasonality patterns in the region. Study also discuss some control measures related to MERS infection.
Mackay et al. [105]		2015	Virology Journal	Jordan	This review paper discussed about various aspect of MERS mainly related to diagnostics, epidemiological and transmission.

Table 1 (Continued)

Study included	Infection	Year	Publisher	Country	Study/report comment
Lamers et al. [106]		2015	Emerging Infectious Diseases	Jordan	This study characterized MERS outbreak caused viruses from Jordan and reported some deletion variants in the region.
Al-Romaihi [107]		2019	PLOS One	Qatar	This report provide a comprehensive insights and analyzed the respiratory influenza like infection from Qatar which is revealed that 0.2% cases related to MERS.
Du Toit [108]		2020	Nature Reviews Microbiology	–	This research highlights and provide an importance related to novel coronavirus infection and outbreak.
Zhao et al. [109]		2020	Journal of Clinical Medicine	China	Epidemiological based curve analysis for COVID-19 was done from 1 December 2019 to 24 January 2020 in China. Estimation of the number of unreported cases was performed.
Thompson et al. [110]	COVID-19	2020	Journal of Clinical Medicine	China	This report describe a mathematical modeling to estimate the probability of COVID-19 transmission from one location to another. Study also estimated time of hospitalization in persons.
Yang et al. [111]		2020	Journal of Medical Virology	–	This study provide the commentary about the fast spreading rate of SARS-CoV-2.
Jernigan et al. [112]		2020	Morbidity and Mortality Weekly Report	USA	Current study provide information related to steps taken in the USA by different government agency to control COVID-19 and used information such as traveling history etc to slow down the transmission rate. This report provided by CDC COVID-19 response team.
Rothan et al. [113]		2020	Journal of autoimmunity	–	Review study provide an information related to pathogenesis and epidemiological situation, transmission of COVID-19 outbreak to understand of newly emerged infection.
Dey et al. [114]		2020	Journal of Medical Virology	Worldwide	This report analyzed various information related to COVID-19 from different data sources such as Johns Hopkins University, WHO, Chinese Center for Disease Control and Prevention, National Health Commission to visualize case reports around the globe.
Al-Mandhari et al. [115]		2020	Eastern Mediterranean Health Journal	Eastern Mediterranean Region	This editorial provide information related to preparation made in Eastern Mediterranean region to control COVID-19 pandemic and suggested to implementation of international health regulation (2005).
Lupia et al. [116]		2020	Journal of Global Antimicrobial Resistance	–	This paper performed literature search and summarize the common clinical features of COVID-19 disease and provided therapeutic interventions to whom needed antimicrobial treatment.
Wells et al. [117]		2020	PNAS	Worldwide	This study shows the importance of international travel and border restriction on COVID-19 control. They reported that Chinese administration averted 70% case by these approaches.
Ammad Ud Din et al. [118]		2020	American Journal of Infection Control	Outbreak report from worldwide	This report provides information and brief report update related to COVID-19 and suggest to take precautions against airway transmission route.
Wu et al. [119]		2020	International Journal of Infectious Diseases	–	This study provides epidemiological, clinical finding, diagnosis, treatments and preventions of COVID-19.
Arshad Ali et al. [120]		2020	Journal of Infection And Public Health	–	It provide an outbreak and update related to case of COVID-19 alert.
Grant et al. [121]		2020	PLOS One	Worldwide	This report provide data COVID-19 infected (>16 years old) individuals and provided information related to hospitalized care facility in terms of determine the prevalence of symptoms associated with COVID-19 worldwide.
Khalili et al. [122]		2020	Epidemiology and infection	Worldwide	This meta-analysis provide information related to epidemiological characteristics of COVID-19 infection from worldwide published studies.
Rafiq et al. [123]		2020	Reviews in Medical Virology	–	This paper is perform meta-analyses from COVID-19 cases during three months of pandemic.

Table 2

Case reports and fatality ratio of SARS outbreaks by countries including sex within the given-infected population.

Country	Population of countries during the outbreak ^a (n)	Total Cases (n)	Cases Per million (n/1 million)	Total Death (n)	Deaths per million (n/1 million)	Case–Fatality Ratio CFR (%)	Sex			
							Female (n)	(%)	Male (n)	(%)
Hong Kong	6,730,800	1755	261	300	45	17.1	777	44.3	978	55.7
Singapore	4,114,826	238	58	33	8	13.9	77	32.4	161	67.6
Canada	31,644,028	361	11	41	1	11.4	210	58.2	151	41.8
China	1,288,400,000	5327	4	349	0	6.6	2722	51.1	2605	48.9
Taiwan	22,603,000	674	30	180	8	26.7	325	48.2	349	51.8
Total	1,353,492,654	8355	6	903	1	10.8	4112	46.84	4243	53.16

^a Data and information were provided from <https://www.worldbank.org/> [124].

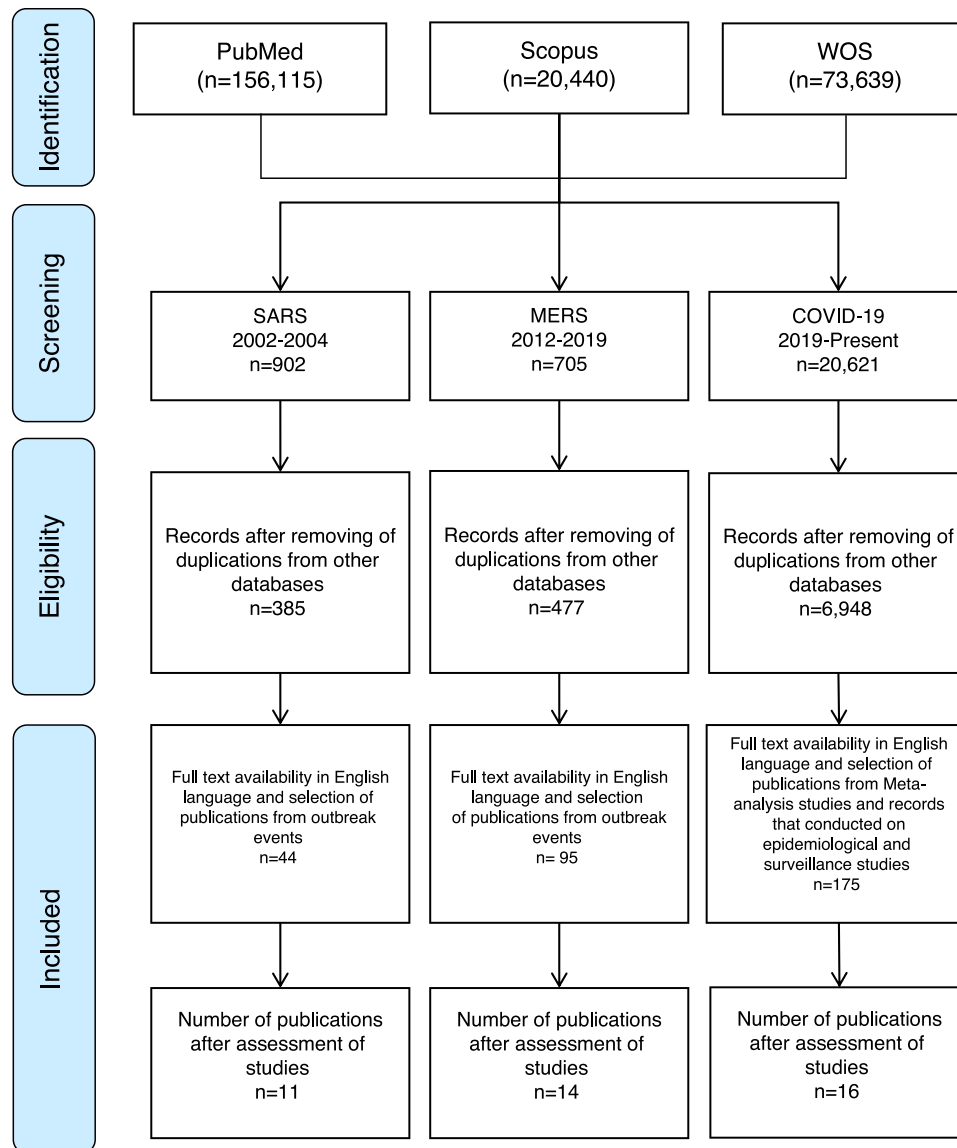


Fig. 1. PRISM Flow diagram showing identification and selection of publications for review of outbreaks by meta-analysis.

Table 3
Case reports and fatality ratio MERS outbreaks by countries including sex within given-infected population.

Country	Population of countries during the outbreak ^a (n)	Total Cases (n)	Cases Per million (n/1 million)	Total Death (n)	Deaths per million (n/1 million)	Case–Fatality Ratio CFR (%)	Sex			
							Female (n) (%)	Male (n) (%)		
Saudi Arabia-2012	29,160,000	1586	54	567	19	35.8	552	34.8	1034	65.2
Saudi Arabia-2015	31,720,000	543	17	141	4	26	142	26.1	401	73.9
South Korea	51,010,000	186	4	39	1	21	76	40.9	110	59.1
United Arab Emirates	9,263,000	91	10	10	1	11	–	N/A	–	N/A
Jordan	9,267,000	28	3	6	1	21.4	12	44	16	56
Qatar	2,566,000	22	9	4	2	18.2	–	N/A	–	N/A
Total	132,986,000	2456	18	767	6	31.2	895	36.45	1561	63.55

^a Data and information were provided from <https://www.worldbank.org/> [124].

Results

A total of 250,194 studies were identified with specific keywords and synonyms for the three outbreaks in order to cover all published outbreak events and evaluate the outbreak cases. In total, 22,228 records were screened and 7,810 records were found to be eligible after applying the time restrictions for each outbreak and

removing duplicated studies. A total of 314 studies were included for overview of the cases, which were reported in the English language with full-text availability as inclusion criteria for quality assessment. Finally, a total of 41 studies were selected and included to evaluate the outbreak events for this study after applying several exclusion and inclusion criteria on identified datasets from SARS, MERS and COVID-19 outbreaks (Fig. 1 and Table 1).

Table 4
Case reports and fatality ratio of COVID-19 outbreaks by countries including sex within given-infected or not infected population.

Region	Country	Population of countries during the pandemic*	Total Cases ^ϕ	Cases per million	Total Death ^ϕ	Death per million	Case–Fatality Ratio	Sex [¥]			
		(n)	(n)	(n/million)	(n)	(n/million)	CFR (%)	Female (n)	(%)	Male (n)	(%)
Asia	India	1,366,417,750	10,055,560	7359	145,810	107	1.5	3,563,690	35.44	6,491,870	64.56
	Iran	82,913,906	1,152,072	13,895	53,448	645	4.6	495,391	43.00	656,681	57.00
	Bangladesh	163,046,161	500,713	3071	7280	45	1.5	145,207	29.00	355,506	71.00
	Indonesia	34,268,528	664,930	19,404	19,880	580	3.0	333,795	50.20	331,135	49.80
	Iraq	39,309,783	584,145	14,860	9181	234	1.6	261,288	44.73	322,857	55.27
	China	1,397,715,000	95,050	68	4764	3	5.0	46,479	48.90	48,571	51.10
	±Sub-total	4,641,054,775	17,238,546	3714	297,828	64	1.7	7,219,216	41.88	10,019,330	58.12
Africa	South Africa	58,558,270	921,922	15,744	24,691	422	2.7	535,268	58.06	386,654	41.94
	Morocco	36,471,769	417,125	11,437	6957	191	1.7	196,049	47.00	221,076	53.00
	Egypt	100,388,073	125,555	1251	7098	71	5.7	–	N/A	–	N/A
	Ethiopia	112,078,730	119,951	1070	1853	17	1.5	46,541	38.80	73,410	61.20
	Tunisia	11,694,719	121,718	10,408	4199	359	3.4	65,728	54.00	55,990	46.00
±Sub-total	1,340,598,147	2,511,635	1874	59,157	44	2.4	1,242,380	49.47	1,269,255	50.54	
Europe	Russia	144,373,535	2,762,668	19,136	49,151	340	1.8	–	N/A	–	N/A
	Spain	47,076,781	1,819,249	38,644	49,260	1046	2.7	965,657	53.08	853,592	46.92
	France	67,059,887	2,473,354	36,883	60,549	903	2.4	1,299,500	52.54	1,173,854	47.46
	United Kingdom	66,834,405	2,040,147	30,525	67,401	1008	3.3	1,101,679	54.00	938,468	46.00
	Italy	60,297,396	1,953,185	32,393	68,799	1141	3.5	1,003,546	51.38	949,639	48.62
	Turkey	83,429,615	1,189,947	14,263	17,851	214	1.5	583,074	49.00	606,873	51.00
±Sub-total	747,636,026	23,081,330	30,872	516,257	691	2.2	12,002,292	52.00	11,079,038	48.00	
America	United States	328,239,523	17,844,839	54,365	317,670	968	1.8	9,313,221	52.19	8,531,618	47.81
	Brazil	211,049,527	7,263,619	34,417	187,291	887	2.6	3,185,097	43.85	4,078,522	56.15
	Colombia	50,339,443	1,518,067	30,157	40,680	808	2.7	764,347	50.35	753,720	49.65
	Mexico	127,575,529	1,325,915	10,393	118,598	930	8.9	654,737	49.38	671,178	50.62
	Argentina	127,575,529	1,547,115	12,127	41,997	329	2.7	771,392	49.86	775,723	50.14
±Sub-total	799,629,413	33,216,866	41,540	820,300	1026	2.5	16,318,118	49.13	16,898,748	50.87	
Oceania	Australia	25,364,307	28,198	1112	908	36	3.2	14,440	51.21	13,758	48.79
	French Polynesia	279,287	16,182	57,940	103	369	0.6	–	N/A	–	N/A
	Guam	167,294	7211	43,104	120	717	1.7	2091	29.00	5120	71.00
	New Zealand	4,917,000	1765	359	25	5	1.4	901	51.06	864	48.94
	Papua New Guinea	8,776,109	761	87	9	1	1.2	–	N/A	–	N/A
	±Sub-total	42,952,146	54,342	1265	1169	27	2.2	23,778	43.76	30,564	56.24
World	±Total	7,673,533,970	76,102,719	9918	1,694,711	221	2.2	35,954,882	47.25	40,147,837	52.75

Data and information were provided from * <https://www.worldbank.org/>; ^ϕ ECDC <https://www.ecdc.europa.eu/>; [¥] <https://globalhealth5050.org/> [62,108–125].
N/A: not available; ± Data represent the region not only listed countries.

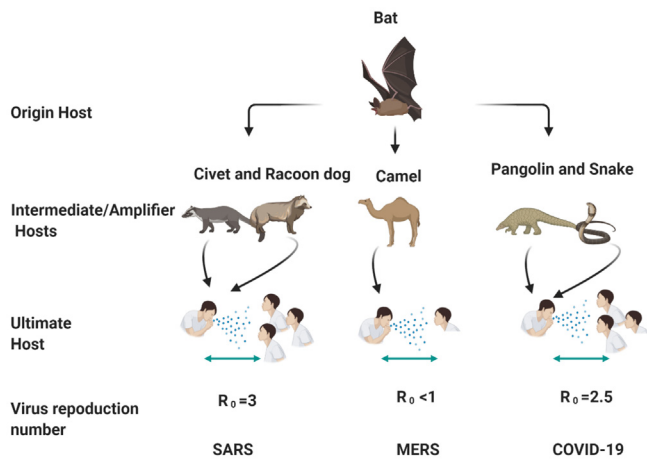


Fig. 2. Info-graphic representation of transmission of SARS, MERS and COVID-19. Host and intermediary host along with R_0 among humans are shown for comparison.

SARS

On November 16th 2002, the first SARS case was reported in Guangdong province, China, with atypical pneumonia (Fig. 3). By the 11th of July 2003, the virus had spread to 29 countries and regions, with confirmed cases at 8355 people and 903 humans dying with virus (Table 2, Fig. 4). The CFR of SARS was estimated to be nearly 11% from all outbreaks around the world in this analysis [13,16]. Outside of China, various regions such as Hong Kong, Taiwan and Singapore were affected most by SARS having the highest CFRs (Table 2, Fig. 4) [17,18]. Hospital workers and frontline health service providers were primarily affected due to aerosol transmission of the virus and close contact with infected patients [19]. Early flu-like symptoms covered the understanding of disease severity and caused an underestimation of protective measurements [20]. Sudden respiratory-related deaths and high spread ratios of the disease created a pandemic alarm situation by the WHO on 12 March of 2003, several months after the first case was reported in China [21,22]. The virus spread to Hong Kong by the travelling of super-spreaders; other countries including Vietnam,

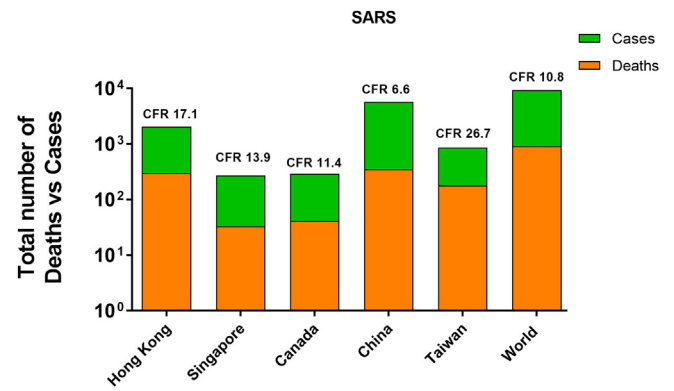


Fig. 4. Graph representing calculated CFRs for SARS during 2002–2004 outbreaks from highly affected countries.

Singapore and Canada also became outbreak epicenters for SARS disease [23,24]. The Center of Disease Control (CDC) announced that the human to human transmission wave was broken, and there have been no SARS cases reported since 2004 [25]. Interestingly, the CFR and number of people affected by SARS were found to be higher outside of its country of origin (Table 2). China, which was the outbreak zone for SARS, had the lowest CFR (6.6%), while the median of the CFR was estimated to be 10.8% from this meta-analysis report (Table 2, Fig. 3). Taiwan was found to be a highly affected country from the SARS outbreak. A rapid increase within one month was noticed in Taiwan among hospitalized patients and people who had been in contact with infected or probable suspected individuals. It was also estimated and discussed that the highest increase in CFR and number was directly related to the lack of testing for the disease, poor management of the outbreak event, mismanagement of hospitals, and underestimation of infection during patient transfer to other hospitals, leading to inadequate isolation and quarantine procedures [26]. These results indicate that, to prevent the outbreak wave from the hospital and break the transmission chain, rapid testing, quarantine, and increasing awareness about infection among healthcare community members are important measures to take [26,27]. Susceptibility or risk factors for SARS were also evaluated from these studies; people who were older than 51.2

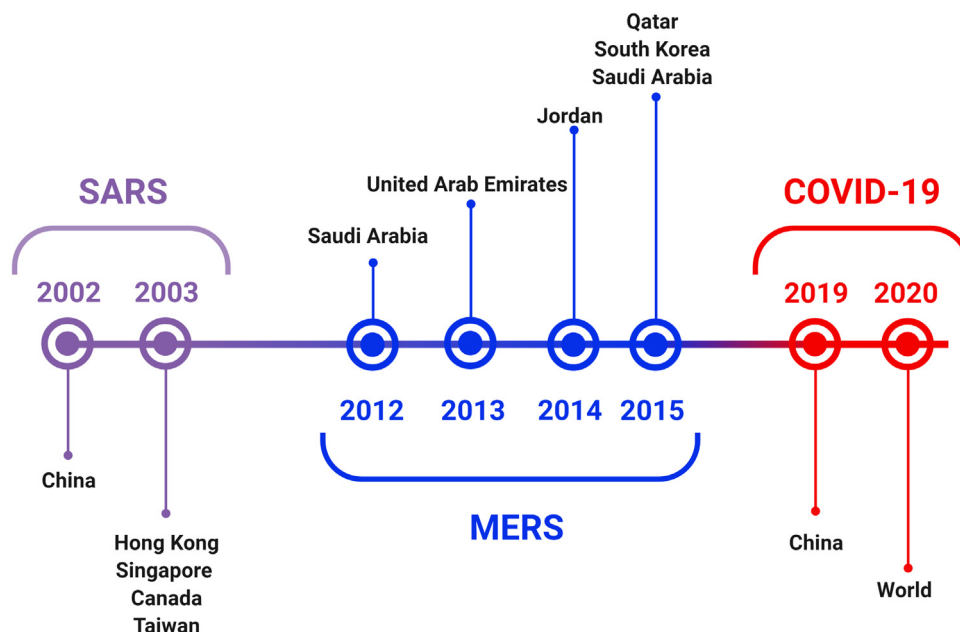


Fig. 3. Info-graphic illustration of coronavirus (SARS, MERS and COVID-19) outbreak events in respective originating countries and dates of first occurrences.

years of age, with one or more pre-existing conditions such as diabetes and cardiovascular or pulmonary problems, could contribute to or increase the severity of SARS [28–30]. The gender of infected patients (male 53.16% vs. female 46.84%) was also suspected to be a risk factor associated with SARS (Table 2).

Early investigations suspected that civet cats and raccoon dogs spread the virus to humans during butchering and consumption activities; however, soon after, it was molecularly discovered that SARS-like coronavirus-carrying bats were natural reservoirs of SARS outbreaks, and other animals more likely played a role in spreading the virus to humans by acting as an intermediate amplifier host (Fig. 2) [31–33]. The expected number of secondary cases produced by a single viral case, defined as the reproduction number (R_0), was estimated to range between 2 and 4 for SARS [34]. Therefore, the average number of secondary infectious cases produced by SARS was estimated to be 3 by CDC [17].

Since SARS is also a potential bioterrorism agent, several strategies have been attempted to develop an effective vaccine including an inactivated vaccine, a live-attenuated SARS-CoV vaccine, a viral vector such as adenovirus or vaccinia virus expressing SARS-CoV genes, bacterial vectors, recombinant SARS-CoV proteins or DNA vaccines [35]. Within these candidates, an inactivated SARS-CoV vaccine (ISCV) developed by Sinovac Biotech Co. Ltd. was authorized by China's State Food and Drug Administration (SFDA) to enter phase I trial for the first time. In total, 36 healthy individuals volunteered for the safety and immunogenicity study of this vaccine. Lin et al. documented and published clinical trial results and the ISCV is considered as a generally safe vaccine and can elicit a considerable amount of neutralizing antibodies [36]. A DNA-based vaccine named VRC-SRSDNA015-00-VP has also reached phase I trials in the USA. The vaccine has been developed by researchers working at the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), and National Institutes of Health (NIH) in Bethesda, Maryland. A phase study was conducted with 10 healthy volunteers, with local and systemic reactogenicity assessed as well as immunogenicity. The vaccine is considered as safe and induced both neutralizing antibody responses in all subjects [37]. However, sudden disappearance of SARS affected vaccine development strategies and some of the vaccine candidates were either withdrawn or discontinued because of the lack of a sustainable global market for the products being developed [38].

MERS

The first MERS case was reported on 13 June 2012 in Jeddah, Saudi Arabia (Fig. 3). A 60-year-old Saudi man with history of fever, cough and shortness of breath was admitted to a private hospital. The causative agent was isolated and reported as a sixth coronavirus that apparently may infect humans [6,39]. Three months after the first patient was identified, a second case was reported in Qatar with previous travelling history from Saudi Arabia [6,40]. To date, at least 27 countries have reported human MERS-CoV infections and according to the World Health Organization (WHO), epicurves of most cases were seen in Saudi Arabia and the Republic of Korea. In the Middle East region, the disease had spread to 11 countries, including Bahrain, Egypt, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Tunisia, UAE and Yemen. Amongst these countries, especially cases from Egypt, Lebanon, Tunisia and Yemen, the spread was associated with travel history. Since 2012, a total of 2456 laboratory-confirmed cases have been reported with 767 deaths (CFR is 31.2%) across the highly affected countries (Table 3). The vast majority of these cases occurred in Saudi Arabia between 2012 and 2015 and in total, 2129 cases were recorded, including 708 deaths with, on average, a 33.5% CFR from both outbreaks (Table 3, Fig. 5) [41,42].

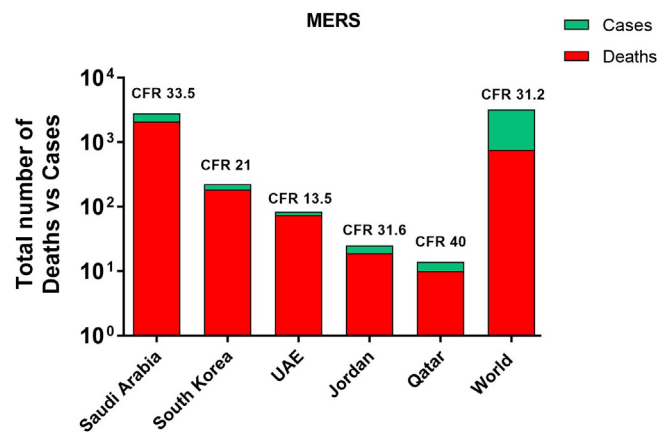


Fig. 5. Graph showing calculated CFRs for MERS outbreaks from highly affected countries.

Arabian camels, also known as dromedary camels, are believed to be a main reservoir and play a critical role as a major source of human infections (Fig. 2). However, the exact role of these animals in transmission of the virus and the exact routes of transmission are still unknown. The virus could be exerted from infected animals by body excretion such as urine [43]. Therefore, close contact with infected animal materials was also considered as a main route of transmission to humans. Like other zoonotic coronaviruses, the virus could have originated in bats and somehow been transmitted to dromedaries in the past (Fig. 2) [44,45].

Human to human transmission had been considered as sub-critical because no evidence of sustained human to human community-based transmission had been reported and humans are considered transient or terminal hosts [46]. Limited household transmission and explosive outbreaks in healthcare settings were reported in Korea. The number of secondary cases resulting from a single initial case or R_0 ranges widely. R_0 was estimated as 0.45 in Saudi Arabia, while it had been calculated from 2.5 up to 7.2 in South Korean outbreaks [46–48].

The 50–59 years age group was at highest risk for acquiring primary infection of MERS. For the secondary cases, the 30–39 years age group was most at risk. Risk factors and outcomes for MERS patients in Saudi Arabia were investigated and a total of 535 cases during the period of March–November 2014 were evaluated considering medical history, travel history and information about animal, food and human exposures. Male as a sex was also noted as a potent risk factor associated with increased susceptibility to MERS, and we have estimated 63.55% of infected patients were male from meta-analyzed studies in this analysis (Table 3) [42,46,49]. A total of 36.46% of these patients had indirect dromedary contact, while 26.88% of them had direct contact. Concerning underlying health conditions, the highest risks amongst patients were reported as having diabetes (55%), current smokers (37%) and heart disease (37%). Emphysema, chronic bronchitis or other chronic lung diseases are also considered as important risk factors, with 13% of patients having these conditions [49].

In relation to vaccine developmental trials, the first human phase I clinical trial for a MERS-CoV vaccine was reported by Modjarrad et al. in the USA. A DNA-based vaccine candidate named GLS-5300 has been tested in 75 healthy individuals aged 18–50 and after three dose injections, and no adverse effects have been reported. Immune efficacy results in vaccinated subjects indicated that the vaccine induced a strong neutralizing antibody response [50]. The S protein-expressing recombinant modified vaccine Ankara (rMVA) candidate named MVA-MERS-S was also investigated in a phase I human trial in Germany. No undesirable effects were recorded after the 3rd dose of the vaccine and

PRNT titers in volunteers showed that 83% of subjects developed neutralizing antibodies against MERS-CoV [51]. A single-dose adenovirus-based vaccine candidate targeting the S protein was also introduced in a phase I trial in the UK. Volunteers received a single intramuscular injection and the vaccine elicited a durable immune response after vaccination. The study results also revealed that there was a moderate neutralizing antibody response that could be detectable even after 12 months [51]. To date, there is no commercially available MERS vaccines for both camels and humans.

COVID-19

The zone of origin of this virus strain was Huanan seafood market of an industrial city in China (Hubei province), named Wuhan, at the beginning of December 2019 (Fig. 3). Huanan seafood market is a wet market and is famous for selling live animals and the meat of various animals, such as bats, frogs, snakes, birds, marmots, rabbits, fish, shellfish, hedgehogs and badgers [52,53]. In its initial stage, the virus had infected about 50 people in China, who were showing signs of pneumonia [54]. When samples from these patients were analyzed, it was confirmed that this pneumonia was related to viral infection; further genomic investigation showed that this virus belonged to the *Coronaviridae* family [53]. At the beginning of the outbreak in China, it was not recorded whether the virus could spread through human to human transmission. Therefore, in Hong Kong, it was confirmed that human to human transmission was present; moreover, it was also confirmed that the transmission route was nosocomial or air-droplets (Fig. 4) [55]. Genetic analysis of SARS-CoV-2 showed that it has more resemblance to two bat-derived coronavirus strains, i.e., bat-SL-CoVZC45 and bat-SL-CoVZXC21; therefore, it is now thought that this virus is of bat origin and pangolins or snakes were suspected to serve as intermediate amplifier hosts to the virus [54–56]. In another study conducted by Chan et al., 2019-nCoV shared nucleotide similarity of 89% and 82% with SARS-like-CoVZXC21 and human SARS-CoV, respectively [57]. As compared to other coronavirus infections, this virus had spread across the world like a fire in a dry forest. The main reason for this could be the genomic modification in the S (spike) protein on the envelope of the virus RBD (receptor-binding domain) area and would be the cause of the high infectivity rate [53]. The prediction or estimation of virus R_0 of COVID-19 among humans still did not resemble the current situation around the world due to there being several outbreaks and epicenters, but some studies predicted R_0 values of 5.7 in Wuhan and others measured the R_0 between 4.0 and 7.1 from some European countries and the USA [58,59]. One report from the CDC estimated virus R_0 with five different scenarios that ranges between 2.0 and 4.0. Currently, R_0 was determined to be 2.5 from a CDC report in August 2020 (Fig. 2) [60].

Outside of China, COVID-19 had been reported earlier by Thailand, Japan, Italy, the USA, France, the UAE, Egypt, and Algeria [61], and the chain of infection extends across the whole world. At the end of the last week of December 2020, more than 235 countries or territories had COVID-19 cases. Across the globe, a total of 76,102,719 cases had been reported and more than 1,694,711 patients had lost their lives (December 2020) (Table 3, Fig. 6A–F). The highest mortality was recorded from the US ($n = 317,670$) followed by Brazil ($n = 187,291$) and India ($n = 145,810$) [62]. In this study, we have calculated the highest CFRs from Mexico (CFR 8.9) in America, Egypt (CFR 5.7) in Africa, and China (CFR 5) in Asia (Table 4). Interestingly, Yemen reported to have a CFR of 29 (<https://www.ecdc.europa.eu/>).

Among Asian countries, we estimate that China, where this pandemic emerged, has had fewer than 100,000 infected people and the lowest deaths per million ($n = 3$), whereas its CFR was calculated to be the highest, at 5. We have analyzed all the continents of the

globe, and we have observed that the CFR is the highest in American and African countries (2.5 vs. 2.4; Table 4 and Fig. 6F). Yemen has the highest CFR (29.05) in the world (data not shown; only highest cases were listed by countries), followed by Mexico (8.9). As this pandemic is still ongoing, at present, there are many variations related to risk factor analysis for COVID-19. Generally, epidemiology-based studies conducted with large sample sizes have revealed that age, sex, diabetes, hypertension, obesity, respiratory conditions such as asthma, smoking and heart disease are major risk factors associated with the current pandemic. Different countries have different data on risk factor analysis. In China, it was recorded that out of 2044 patients, 57.58% were over 60 years of age [63]. In relation to sex, out of 3988 patients, 79.9% were male in Italy [64]. In the USA, out of 5700 patients, 33.8%, 41.7%, and 56.6% were diabetic, obese and had hypertension, respectively [65]. In another USA study, out of 2215 patients, 11.6% had asthma and 29.6% were current or former smokers [66]. In relation to heart conditions, out of 3988 patients, 13.3% had heart disease in Italy [64] and from the USA, a study showed that out of 2215 patients, 8.8% had congestive heart failure [66].

More than twelve months have passed since COVID-19 was first identified, and to date, the scientific community has made ceaseless efforts, which has resulted in the development of over 300 vaccine projects. Around 50 of them are undergoing clinical evaluation, and more than 10 candidates have reached phase III trials where half of them have reached completion with positive results [67]. An inactivated vaccine, which is currently available under the CoronaVac brand name and manufactured by Sinovac in China, has elicited varying sera conversion efficacies, estimated between 50% and 91% in phase III trials from different countries, but these data have not been published or peer reviewed yet [68]. As a groundbreaking technology, two different messenger RNA-based vaccines have also completed phase III trials and have been licensed by the European Medicines Agency in Europe and by the WHO in the USA. Frontrunners of these types of vaccines are BNT162b2 (Pfizer-BioNTech; Germany and USA collaboration) and mRNA-1273 (Moderna, USA) and phase trial results indicated that overall, seroconversion results reached more than 90% among the vaccinated human subjects [69,70]. In regard to adenoviral-based vaccine technology, two different vaccines, Ad26CoVS1 (Johnson and Johnson, USA) and ChadOx1 (AstraZeneca-Oxford, UK), also completed phase III clinical studies on humans. These vaccines also elicited a strong immune response against the S1 subunit of viral RBD after two dose applications (Johnson and Johnson have not published results yet) [71].

In summary, a remarkable number of safe and effective vaccines were developed within twelve months, and hopefully, this may result in a decisive end for the pandemic situation.

Sex distribution

We also determined the sex distributions among the outbreak events of the coronaviruses. It was estimated that SARS and COVID-19 had similar infection rates in males (53.16% vs. 52.75%, respectively) and females (46.84% vs. 47.25%, respectively), but the differences between males and females to become infected with SARS or COVID-19 were not statistically significant ($p > 0.05$) when considering overall outbreaks. We found statistical significance ($p < 0.05$) in MERS infection events. We measured that males become infected with MERS (63.55%) more than females (36.45%) (Fig. 7).

Discussion

Coronaviruses have a very wide range of hosts among vertebrates, including humans. Three important coronavirus outbreaks

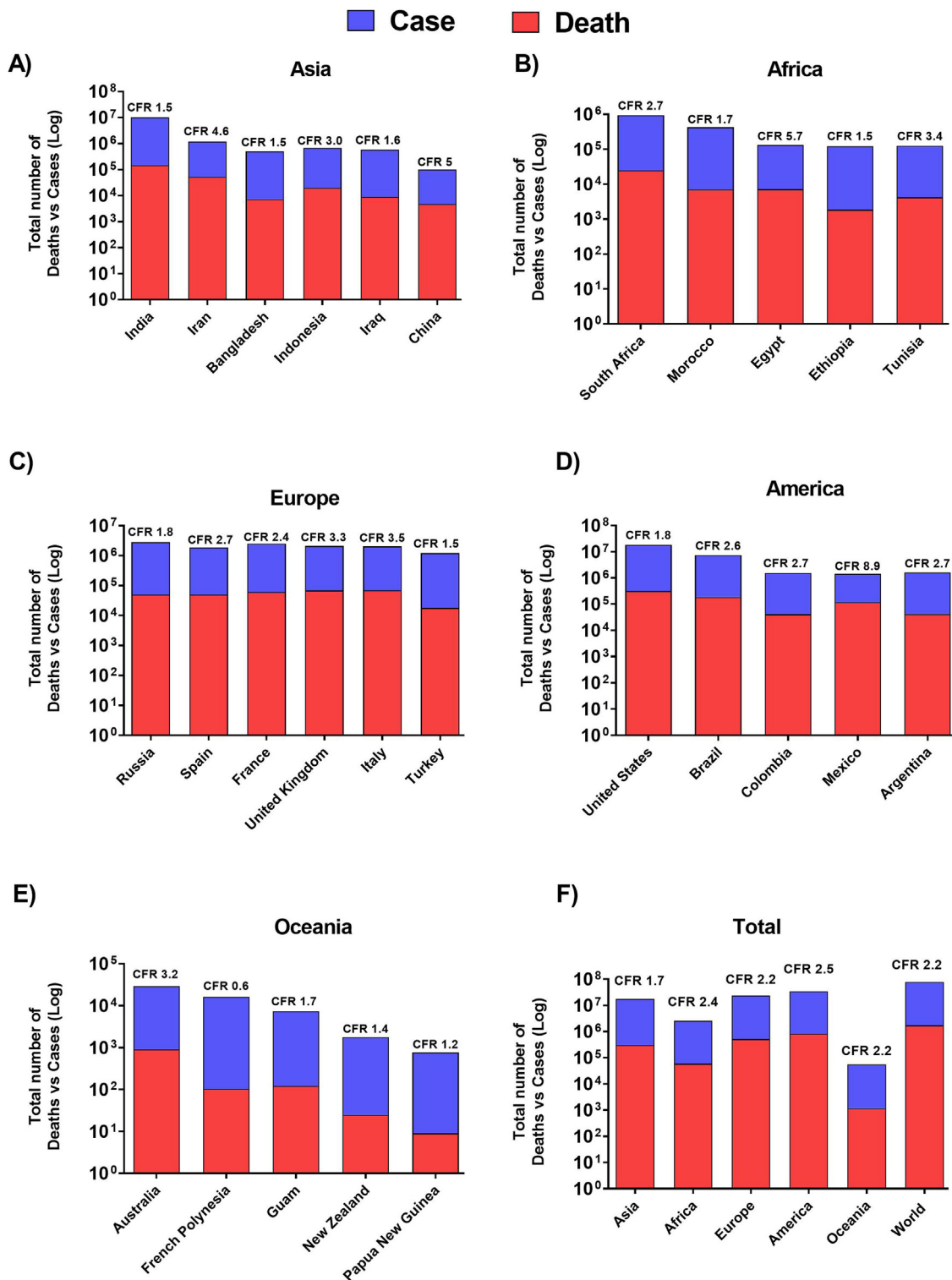


Fig. 6. COVID-19 CFR status up to the last week of December 2020, since the first case was reported. Graphs bars represent continents (A–E) and some and highly affected selected countries with death vs. case numbers around the world. Total case and death numbers along with CFRs are included in the latest graph to summarize current pandemic situation in the world (F).

have occurred in the past two decades. The SARS-CoV outbreak was first identified in Guangdong, China, and spread to many countries in South Asia, North America and Europe by a human-to-human transmission chain. Improved isolation and quarantine responses against the outbreak enabled virus spread to be controlled, and were successfully applied in Canada when virus spread to here; poor management of the outbreak not only resulted in failure to

control the spread of infection but also increased the CFR in Taiwan [26,27,72]. A change in the outbreak center occurred in SARS and some evidence also claimed that existing immunity against low pathogenic prototype strains of SARS virus or SARS-like viruses among the Chinese community might result in them having the lowest CFR during the SARS epidemic [73–76]. The CFR results estimated in this study also indicate that there was a wide CFR range

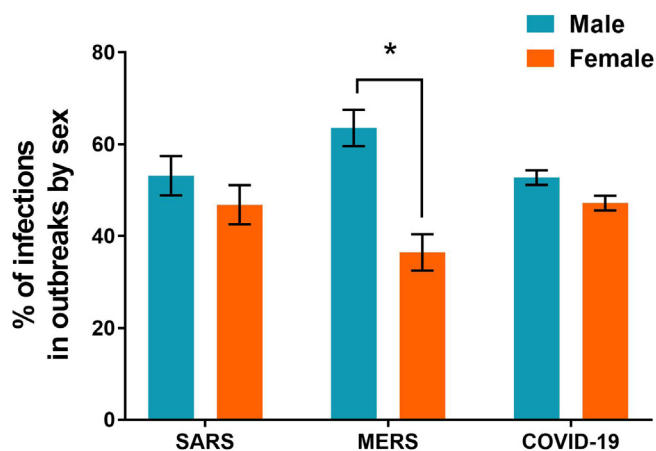


Fig. 7. Schematic presentation of infections by sex distributions among the outbreaks. Error bars represent standard errors of medians, and a two-tailed non-parametric t-test was performed to analyze significant differences with Gaussian distribution (* $p < 0.05$).

(between 6.6 and 26.7) among the countries in which SARS outbreaks emerged. This might also be correlated with the pre-existing immunity theory, but we experienced that case management strategy also affects CFR, such as in Taiwan (CFR 26.7).

Almost nine years later, a second coronavirus infection along with higher mortality appeared in the Middle East and was later named MERS-CoV. It had the highest CFR in Saudi Arabia where it emerged. Most of the cases originated from animal to human transmission, mainly by camels, and human to human transmission was limited with the lowest R_0 ($R_0 < 1$); however, it was also estimated to be between 2.5 up to 7.2 during the outbreak in South Korea [48]. However, virus spread remained and was sustained only with people who were in close contact with MERS-infected patients such as family members and health care providers [77]. Thus, we can conclude that the MERS outbreak mainly emerged by animal to human transmission in zoonotic settings, most commonly by camels; the human to human transmission chain was weak where there was no close contact with infected patients. It should also be underlined that the R_0 increased within a community where pre-existing immunity was absent [78]. Our CFR results were estimated to be 31.2 in the world, and this figure was between 21 and 40 among the outbreak events. Outbreak reports indicate that most of the deadly events were reported from the area where close contact histories with infected animals were documented. It appears that CFR was much higher in patient zero, who had close contact with infected animals, and that mortality begins to decrease when transmitted between human to human. However, the contagious power of MERS was estimated to be less than 1 in Saudi Arabia ($R_0 = 0.45$) while it was measured as high as 7.2 in South Korea [48]. Unfortunately, South Korea suffered more from human-to-human transmission during the MERS outbreak, but this outbreak example was more related with case control management.

In December 2019, a third coronavirus infection spread throughout the world from Wuhan and the globe is still suffering from cases of SARS-CoV-2. Rapid spread of the virus fueled a global pandemic and there are many lessons we need to take from this outbreak.

According to our estimation, almost 1% of the world population (Table 4) became infected with SARS-CoV-2 by the end of the first year of the pandemic. It is evident that human to human transmission exists and the COVID-19 transmission ratio is between MERS and SARS without pre-existing immunity. COVID-19 appears to be the most heavily documented and investigated outbreak in human history. We report that protective measures and social distancing are important to control its spread and transmission. In an estima-

tion model analysis, a study investigated the importance of social distancing. Model analysis results indicate that social distancing is the best pandemic control measure when a vaccine is not available [79].

The sex distribution among the outbreaks was not found to be important for SARS and COVID-19 in this study. However, some studies revealed that there is a strong correlation between sex and death ratio in COVID-19 outbreaks [80] and some studies revealed that it might be correlated with immune landscape differences between the sexes [81]. Whether sex is a considerable risk factor for death or not, our results indicate that male sex has a higher infection rate than females, but to become infected with COVID-19 or SARS is not significantly associated with gender. Males became infected with MERS at a higher rate and with statistical significance compared to females ($p < 0.05$). However, these results could also be gender independent because the presence of males in some areas, such as occupational reasons, was higher than that of females and this could lead to biased results while evaluating the sex factor in infections. In addition, epidemiological studies should be conducted with multivariable factors that affect exposure risks to the agents to study sex factors in infections [82].

At present, the USA and India are highly affected by the pandemic. In these pandemic situations, the hygiene status of the community can also play an important protective role. For example, in India, COVID-19 infection was uncommon in a slum area of Mumbai (Dharavi), and this can be explained with the hygiene hypothesis [83]. These slum areas have lower hygienic living conditions and people are more prone to various infections on a yearly basis, yet show less symptoms or morbidity to emerging infections. An explanation could be that the immune status in these people is high due to repeated exposure to antigens, which can train their innate immunity to newly emerged infections.

As these coronaviruses mainly attack the respiratory tract, those who have respiratory problems should take more protective measures. Moreover, from the analysis of various studies in many developing and developed countries, it is observed that older people should pay more attention to protecting themselves, as they are more prone to infection along with having a reduced recovery rate. People with metabolic diseases such as obesity and diabetes also should be considered carefully and mortality rate in this susceptible society is high as compared to populations with no underlying condition. We and others also reviewed and studied metabolic fitness as a way to control viral infections as well as COVID-19 and some medications that target the metabolism could be beneficial [84–86]. It appears that ensuring vaccinations are delivered all around the world is the only way to wipe out the COVID-19 pandemic; some successful vaccines have already been approved by the health agencies of some countries.

Conclusion

In this meta-analysis study, we analyzed the outbreak events of SARS, MERS and COVID-19 in a comprehensive manner. SARS-CoV affected nearly more than 8000 people in a very wide area and resulted in 903 deaths, while MERS-CoV appeared in a relatively small area with a total of 2456 cases and 903 deaths through a limited transmission level but a higher CFR. CFR was calculated to be between 6.6% and 26.7% for SARS-CoV and from 11% to 35.8% for MERS-CoV, respectively, from total cases during the epidemic. The COVID-19 pandemic is still ongoing (as of January 2021) and has reached 35 million people who have tested positive worldwide. However, the real numbers could be higher than this and rapidly change on a daily basis. The origin host is believed to be bats for all three coronavirus outbreaks, while amplifying hosts are raccoon dogs for SARS, camels for MERS and pangolin for COVID-19. Human

to human transmission has been verified for all three viruses with different R_0 . Their potential effects on healthcare and agricultural industries have made them important public health concerns over the past few decades. Moreover, at present, this COVID-19 pandemic is also hampering the financial statuses of several developing countries worldwide by having a direct impact on international trade.

Overall, the human race should learn from these three pandemics to improve health facilities in hospital settings and reduce human and wild animal interaction to decrease zoonotic outbreak. As wild animals already maintain their own territories in wild natural habitats, their interactions with domesticated animals should also be restricted. Moreover, inter-species animal interaction should also be minimized at wet markets.

Author contribution

EB, DS and NC designed the study and searched the literature from databases. All authors analyzed the results and were involved in producing the tables and figures.

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Competing interests

None declared.

Ethical approval

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