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Basic Reproduction Rate and Case Fatality Rate of COVID-19: Application of Meta-analysis

Suryakant Yadav*[1], Pawan Kumar Yadav[2], M. Kishore[3], Sayeed Unisa[4], Chander Shekhar[5], Usha Ram[6], Laxmi Kant Dwivedi[7], Preeti Dhillon[8], Neha Yadav[9] and Sourav Dey[10]

Abstract: The outbreak of novel coronavirus disease of 2019 (COVID-19) has a wider geographical spread than other previous viruses such as Ebola and H1N1.This study aims to provide the estimates of the basic reproduction rate (R_0) and case fatality rate (CFR), which applies to a generalized population. The systematic review helped to retrieve the published estimates of reproduction rate and case fatality rate in peer-reviewed articles from the PubMed MEDLINE database with defined inclusion and exclusion criteria in the period 15 December 2019 to 3 May 2020. A meta-analysis, with the inverse variance method, fixed- and random-effects model and the Forest plot, was performed to estimate the mean effect size or mean value of the basic reproduction rate and case fatality rate. We estimated the robust estimate of R_0 at 3.02 (2.42-3.68) persons and the robust estimate of CFR at 2.56 (2.06-3.05) percent after accounting for heterogeneity among studies using the random-effects model. We found that one person is likely to infect two to three persons in the absence of any control measures, and around three percent of the population are at the risk of death within one-and-a-half months from the onset of disease COVID-19 in a generalized population.

Keywords: COVID-19, SARS-CoV-2, Reproduction Rate, Case Fatality Rate, Systematic Review, Meta-analysis.

Introduction

The outbreak and spread of novel coronavirus-2019, particularly identified as Severe Acute Respiratory Syndrome Coronavirus2 (SARS-CoV-2), in Wuhan City, Hubei Province, China, was first time reported to World Health Organisation (WHO)China Country Office on 31 December (WHO, 2020). On 7 January 2020, Chinese authorities confirmed the SARS-CoV-2 virus as the causative agent , and on 12 January 2020, WHO confirmed it (Tang et al., 2020b; You et al., 2020). The epidemics of Severe Acute Respiratory Syndrome (SARS) and Middle East Acute Respiratory Syndrome (MARS) in the past (Kwok et al., 2019)and the recent outbreaks of infectious diseases like Ebola and H1N1 influenza (Chowell et al., 2004; Nishiura and Chowell, 2014) make us conscientious about comprehending the spread of such viruses and consequences regarding life losses, morbidity, economic burden, and political

* Corresponding author
[1] Assistant Professor, Department of Development Studies, International Institute for Population Sciences (IIPS), Mumbai, India, Email: suryakant_yadav@iips.net
[2] Research Scholar, Department of Development Studies, IIPS, Mumbai.
[3] Researcher, Department of Development Studies, IIPS, Mumbai.
[4] Professor and Head, Department of Mathematical Demography and Statistics, IIPS, Mumbai.
[5] Professor, Department of Fertility Studies, IIPS, Mumbai.
[6] Professor, Department of Department of Public Health & Mortality Studies, IIPS, Mumbai.
[7] Assistant Professor, Department of Mathematical Demography and Statistics, IIPS, Mumbai.
[8] Assistant Professor, Department of Mathematical Demography and Statistics, IIPS, Mumbai.
[9] Research Scholar, Centre of Social Medicine and Community Health, JNU, New Delhi.
[10] Researcher, Department of Development Studies, IIPS, Mumbai.

instability. It is of utmost crucial to control the spread and outbreak in the very first case of the disease (Lv et al., 2020). It is a highly transmittable zoonotic coronavirus disease.

The first step for academicians and government agencies, beforehand, is to study the basic reproduction rate (R_0), which is the average number of secondary infectious cases produced by an infectious case(WHO, 2003) that provides the plausibility of the spread, outbreak, and severity of an epidemic in a short time available to them. The value of R_0 greater than one indicates that the transmission of disease from one person to other persons is likely to increase, and the value of R_0 less than one indicates that the transmission is likely to die out. R_0 determines the potential for an epidemic spread in a susceptible population in the absence of specific control measures (Kucharski et al., 2020).For understanding the transmissibility of SARS-CoV-2 in population, every country had made efforts to estimate the R_0.Numerous studies have shown that the recovery rate has remained more or less the same, but still, reproduction rate and case fatality rate (CFR) varied across the regions (Fanelli and Piazza, 2020; Guan et al., 2020). The case fatality rate is defined as the percentage of individuals with symptomatic or confirmed diseases who die from the disease. The case fatality rate is currently in the range of 2-8 percent but has varied across the age groups– higher at old ages and lower at child and adult ages. The estimates of CFR based on hospital records lies in the range of 8-28 percent (Verity et al., 2020). These estimates are evidence of the severity of coronavirus in a short time of its outbreak.

The incubation period of $R_0$is in the range of 5 to 14 days(Linton et al., 2020),which may be followed by death in without treatments or in no control measures. The severity of this disease remained suspicious because the onset of the disease is often unknown, and crude CFR is heavily underreported (Kobayashi et al., 2020; Zhao et al., 2020a). Therefore, in the absence of control measures and no vaccination, this disease for an infected person shows higher risk for comorbidities and other underlying health conditions (CDC COVID-19 Response Team 2020)–the high immunity level to protect a person is an assumption in this case. The effect of MARS and SARS are known in the past; however, the variants of SARS or MARS are acute killer diseases (Malik et al., 2016; WHO, 2003).

The effective reproduction rate (R_t), which is the potential for epidemic spread at a time ‘t’ under the control measures(You et al., 2020), is a function of R_0 and proportion of the susceptible population (Cao et al., 2020). Since the incidence of new cases of SARS-CoV-2, the R_0 is crucial to understand the mechanism as well as the implementation strategies (Ferguson et al., 2005) to reach an effective value of R_t, which should be less than one for containing the outbreak (Heffernan et al., 2005; Wallinga and Lipsitch, 2007).The epidemic is considered to be under control when R_t is less than one. The CFR is quite easily measurable and less sensitive to censoring and bias (Ge and Sun, 2020)as compared to R_0. The moments of the distribution of death and mortality patterns are most useful for calculating adjusted CFR (Lazzerini and Putoto, 2020; Onder et al., 2020); however, R_0 is quite sensitive to the onset of diseases and the number of days to get a prediction (Zhao et al., 2020c). In other cases, it is R_t, which is time-variant and mathematically, a limiting case of R_0. Nevertheless, R_0 is the most warranted statistics of the epidemiological model for COVID-19.

This study aims to provide, from a systematic review and a meta-analysis, a summary statistic of $R_0$and CFR which has the best applicability for other regions or countries as well as the lower level of geography districts and towns/village at the point of the onset of disease in a susceptible population. This summary statistics of $R_0$and CFR would be of immense utility to government authorities for the practical implementation of strategies or control measures at the very initial phase of the COVID-19disease transmission at any level of geography as well as regardless of the low R_t values at a higher level of geography or in the past. This study aims to fulfil two specific objectives (1) to summarise the characteristics of studies specific to the basic reproduction rate and case fatality rate of COVID-19 and (2) to access and compute the basic reproduction rate and case fatality rate among the confirmed cases of COVID-19 across the countries.

Materials and Methods

We accessed the works of literature from the PubMed MEDLINE database. Based on the terms “coronavirus” in All Fields in PubMed MEDLINE search, the search in the database showed a 3536number of articles. With “COVID-19” in the field Title/Abstract, it showed 2248 number of articles. The preliminary basic search showed significant works of literature that are available to allow work on the systematic review of overall COVID-19.

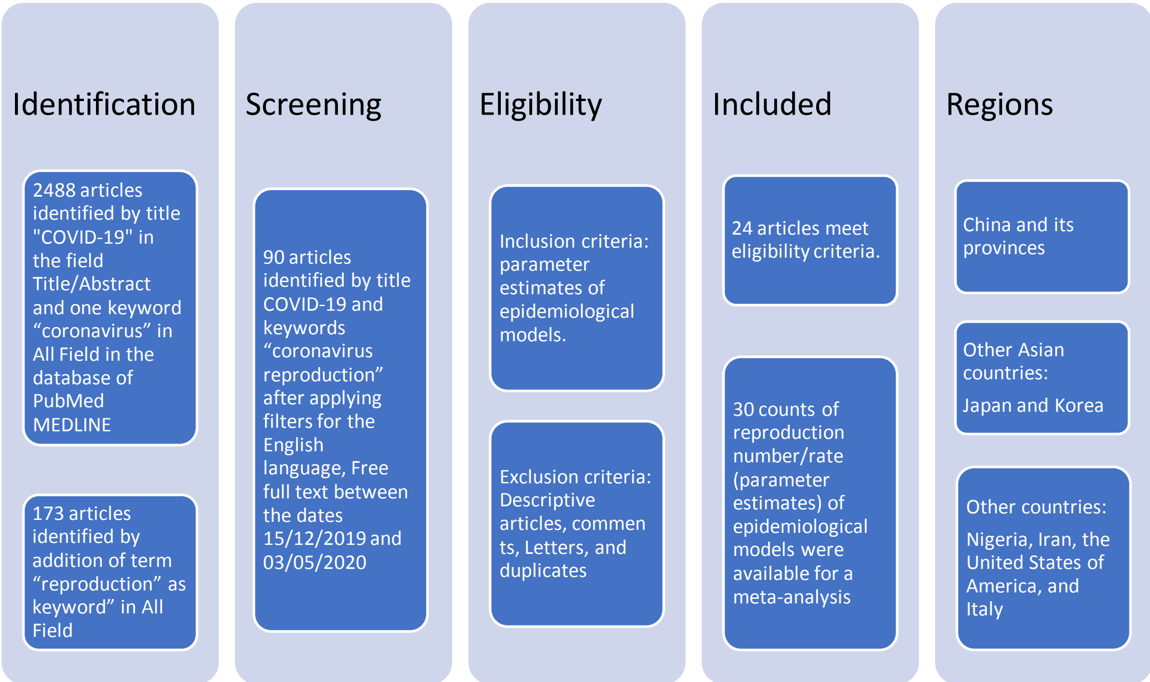
A systematic review of R_0

From this broad set of works of literature, we searched for research articles with description on reproduction number/rates, based on the terms ‘coronavirus reproduction’ in All Fields AND ‘COVID-19’ in the field Title/Abstract. The search gave an output of173 articles. After applying filters for the English language, Free full text, and between the dates 15/12/2019 and 03/05/2020, it gave an output of 90 number of research articles that are peer-reviewed only for screening, so that we consider the complete works of literature. After reviewing the keywords and abstracts of these articles, we come to know that many of these works of literature have not worked on estimation of the parameters, such as reproduction rate, case fatality rate, transmission rate, of epidemiological models. As the focus of this paper is a meta-analysis of reproduction rate and case fatality rate, we extend our search of articles that solved the reproduction rate and case fatality rate from epidemiological equations. We intend to look for articles in which reproduction rate or case fatality rate is estimated or calculated using some methods or methodology. Making our search more extensive, for reproduction rate, we searched based on terms ‘coronavirus reproduction estimation’ in All Fields AND ‘COVID-19’ in the field Title/Abstract. This search in PubMed MEDLINE gives output for29articles to explore the parameter estimates of reproduction rates as well as the methodologies and epidemiological models. We reviewed title, keywords, abstracts, data and methods or methods/methodology, and references in these articles. We found three research articles that were based on a systematic descriptive review or general discussion focused on reproduction rates. Another two research articles were based on a systematic review, and only one research article was based on a meta-analysis of R_0. Out of 29 articles, we found 24 research articles that provided 30 counts of R_0values with related statistics for a meta-analysis (Flowchart 1).

A systematic review of CFR

Similarly, for case fatality rate, considering 2488 numbers of research articles as the starting point of a systematic review, we searched with terms ‘coronavirus and mortality’ in All Fields AND ‘COVID-19’ in Title/Abstract that gave an output of 118 research articles, and with terms ‘fatality’ in All Fields AND ‘COVID-19’ in the Title/Abstract gave an output of 220 articles, and with terms, ‘fatality estimation risk’ OR ‘fatality estimation model’ OR ‘coronavirus mortality model parameter’ in All Fields AND ‘COVID-19’ in the Title/Abstract gave an output of 35 articles. Then, we applied the filters of the English language, Free full text, and between the dates 15th December 2019 and 3rd May 2020, which gave an output of 24 articles. We reviewed these research articles searching for titles, abstracts, and keywords, methodology, and references. Out of these 24 articles, only 17 qualified for quantifying parameter values of CFR (Flowchart 2). These 17 articles provided 29 counts of CFR for a meta-analysis.

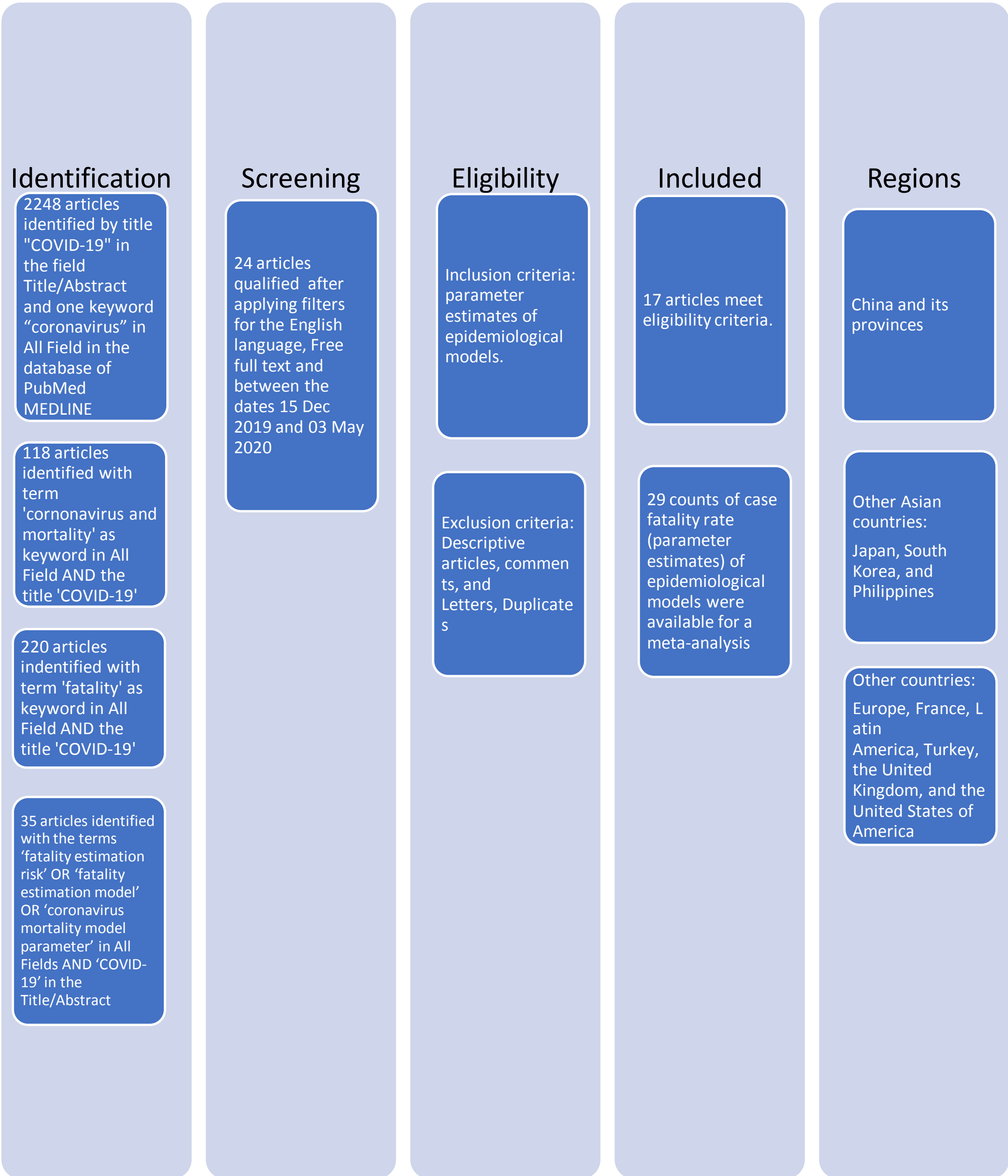
Flowchart 1: Flow diagram for the selected research articles for R_0



Reproduction number/rate (R_0) and Case fatality rate: parameter values of an epidemiological model

The review of methodologies of these 24 peer-reviewed articles for R_0 and 17 peer-reviewed articles for CFR revealed that the studies lacked the control groups. The $R_0$and CFR values were retrieved from these published articles after careful reading and analysing the sections of 'Data and Methods' or 'Methods' or 'Methodology' and the 'Results with tables and figures.' This allowed to extract the date of publication, the period of study, application of methods, confirmed cases, susceptible cases, the R_0 values, the CFR values, and relevant statistics such as confidence interval, standard error, sample size, etc. For every statistic collected, we checked for any references mentioned against the source of statistic to avoid the duplication of estimates in two or more pieces of literature quoted from the same source of the work of literature. In this manner, the statistics of $R_0$and CFR computed in these studies qualified for a meta-analysis. The extracted R_0 values were furthermore examined by the period of study. Many studies have given an effective reproduction rate (R_t) along with R_0 values; nevertheless, we consider the initial period of analysis and R_0 values from the first phase of the evolving epidemiology of the disease. A few of the studies have given several R_0 values starting from the onset of the diseases until the end of the study. In such cases, we included the R_0 values of the very onset period of the disease. The initial period or the first phase in these studies ranged between~5 days to ~12 days. Analysing CFR, we included only adjusted case fatality rate standardized for age and sex distributions or censored cases. Crude case fatality rates were excluded for a meta-analysis. Although several values of CFR were shown in a study, we included only those estimates based on deaths that comprise the sample of an epidemiological model. Two or more estimates of R_0 and CFR were considered from the same study if it belonged to different regions or periods or were estimated from the different method(s).

Flowchart 2: Flow diagram for the selected research articles for CFR



Data extraction

We extracted the following variables: author, publication date, year, co-authors, sample size, mean statistics of R_0, confidence interval, methods applied, standard deviation, and any other relevant statistics. All the studies, 24for R_0 and 17for CFR, were retained in the present study. These selected studies provided 30 counts of R_0 and 29 counts of CFR for a meta-analysis. Table 1 and Table 2 show respectively for R_0 and CFR, from the list of works of literature, the estimates of published R_0 and CFR by authors applying different methodologies.

Analyses

We performed the meta-analysis to estimate the mean effect size and its precision. The meta-analysis can be performed using the inverse variance method, fixed-effects model, and random-effects model with an assumption of the presence of heterogeneity among the studies. The Higgin's and Thompson's I^2 statistic, Tau-squared (τ^2), and Cochran's Q test were applied to test statistical heterogeneity among the selected studies. The test of heterogeneity was applied for understanding the application of the random-effects model versus the fixed-effects model in a meta-analysis. We plotted Forest plot using the random-effects model with prediction values of 95 percent confidence interval. We plotted Funnel plot at 95 percent, 97.5 percent, and 99 percent confidence intervals to testify the publication bias in this meta-analysis of COVID-19.

Results

A meta-analysis of published $R_0$and CFR values

The average R_0 value and CFR value was computed ata value of 3.65 (3.36- 3.98) persons (Table 1) and 3.96 (3.67- 4.27) percent (Table 2), respectively, based on inverse variance method. We performed a test of heterogeneity to check whether these works of literature stem from the same population or a universe of a population. The applied test of heterogeneity is shown in Table 3. The Higgin's & Thompson's I^2 statistic, which is the percentage of variability in effect sizes not caused by sampling errors, greater than 75 percent indicates a presence of high heterogeneity among these works of literature. The high value of 99.9 percentI^2statistic confirms that these studies did not stem from the same population. The other two statistics which are tau-squared (τ^2) statistic, the between-study variance in a meta-analysis, and Cochran's Q-statistic, the difference between the observed effect sizes and fixed-effects model, are significant for R_0 as well as for CFR (Table 3).These tests of heterogeneity were quite crucial for deciding the application of fixed-effects or random-effects models for a meta-analysis. The fixed-effects model assumes that the studies stem from the same population, whereas the random-effects model is based on the fact the studies stem from the universe of population. Results from the tests of heterogeneity suggest for applying the random-effects model rather than for applying the fixed-effects model for a meta-analysis. We computed the mean R_0value and mean CFR value (mean effect sizes), using the random-effects model in a meta-analysis.

The estimates of $R_0$and CFR were computed using the random-effects model based on data shown in Table 1 and Table 2. We have summarised the estimates of R_0 in Table 4 and CFR in Table 5 from meta-analysis, using all data and data excluding outliers. We estimated mean value of R_0 and CFR, after excluding outliers, at 3.02 (2.42-3.68) persons (Table 4: column (f)) and 2.63 (2.18-3.08) per cent (Table 5: column (f)), respectively, based on the pieces of evidence available across the countries. These estimates are accounted for heterogeneity among the studies. These estimates of R_0 and CFR lies within a narrow confidence interval. Hence, these estimates of R_0 and CFR qualify as a high precision estimates. The estimated R_0value based on the random-effects model is slightly lower than that of based on the inverse variance method.

Table 1: Characteristics of included studies in the meta-analysis of R_0

Author/ Study	Region/ Time period (Date/Month/Year)	Methodology	Basic Reproduction Number/rate (R0)	95% Confidence Interval (CI)	Confirmed (C) and Susceptible (S) cases
Adegboye et al., 2020	Nigeria 27/02/2020-19/03/2020	Bayesian method (Short-duration)	4.98	2.65-8.41	318(C)
Adegboye et al., 2020	Nigeria 27/02/2020-11/04/2020	Bayesian method (Long-duration)	1.42	1.26-1.58	318(C)
Anastassopoulou et al., 2020	Hubei Province (China) 11/01/2020-20/01/2020	Susceptible, Infected, Recovered and Dead (SIRD) models (Long-duration)	7.09	5.84-8.35	59000000 (S)
Anastassopoulou et al., 2020	Hubei Province (China) 11/01/2020-16/01/2020	Susceptible, Infected, Recovered and Dead (SIRD) models (Short-duration)	4.8	3.36-6.67	59000000 (S)
Boldog et al., 2020	Hubei Province (China) 23/01/2020-31/01/2020	Time-dependent compartmental model, Galton–Watson branching process	2.6	2.1-3.1	-
Choi and Ki 2020	Hubei Province (China) 20/01/2020-17/02/2020	Susceptible (S), Exposed (E), Symptomatic Infectious (I) hospitalized (H) recovered or death (R): SEIHR model	4.028	4.01-4.046	4992000 (S)
Choi and Ki 2020	Korea 18/02/2020-24/02/2020	Susceptible (S), Exposed (E), Symptomatic infectious (I) hospitalised (H) recovered or death (R): SEIHR model	0.555	0.51-0.60	30 (C)
Jung et al., 2020	China 08/12/2019-24/01/2020	Delay distributions, Markov Chain Monte Carlo (MCMC)	3.2	2.7-3.7	20 (C)
Kucharski et al., 2020	Wuhan (China) 29/12/2019-23/01/2020	Stochastic transmission dynamic model, Geometric random walk, Markov Chain Monte Carlo (MCMC)	2.35	1.15-4.77	-
Kuniya 2020	Japan 15/01/2020-29/02/2020	SEIR compartmental model	2.6	2.4-2.8	239 (C)
Lai et al., 2020	mainland China 31/12/2019-28/01/2020	The pooling of estimates from different studies	2.68	2.47-2.86	278 (C)
Muniz-Rodriguez et	Iran 19/02/2020-	Generalized growth model	4.4	3.9-4.9	-

Author/ Study	Region/ Time period (Date/Month/Year)	Methodology	Basic Reproduction Number/rate (R0)	95% Confidence Interval (CI)	Confirmed (C) and Susceptible (S) cases
al., 2020	19/03/2020				
Muniz-Rodriguez et al., 2020	Iran 19/02/2020-19/03/2020	Epidemic doubling time	3.5	1.3-8.1	-
Peirlinck et al., 2020	USA 21/01/2020-04/04/2020	SEIR compertmental model	5.3	4.35-6.25	311357(C)
Riou and Althaus 2020	Wuhan (China) 31/01/2020-29/01/2020	Simulation	2.2	1.4-3.8	5997 (C)
Rocklöv et al., 2020	Japan 21/01/2020-19/02/2020	Compartmental model using Susceptible, Infected, Infectious, and Recovered (SEIR) model	14.8	5.3-19	619 (C)
Distante et al., 2020	Italian regions Up to 29 March 2020	Susceptible/Exposed / Infectious/ Recovered (SEIR) Model/Exponential Growth Rate	2.45	2.19-2.71	11951 (C)
Sanche et al., 2020	China CDC 15/01/2020-30/01/2020	Hybrid deterministic–stochastic SEIR	5.7	3.8-8.9	140 (C)
Shim et al., 2020	South Korea 20/01/2020-06/03/2020	empirical reporting delay distribution and simulating the generalized growth model	1.5	1.4-1.6	6284(C)
Tang et al., 2020a	China 08/12/2019-04/01/2020	Departmental SEIHR model	3.27	2.98-3.58	33 (C)
Tsang et al., 2020	Wuhan 15/01/2020-03/03/2020	Moments of Gamma distribution, Markov Chain Monte Carlo (MCMC)	3.15	2.8-3.5	-
Wang et al., 2020	Hubei Province (China) 17/01/2020-08/02/2020	Exponential growth (EG) method	3.49	3.42-3.58	-
Wang et al., 2020	Hubei Province (China) 17/01/2020-08/02/2020	Exponential growth (EG) method, Maximum likelihood estimation (ML), Sequential Bayesian method (SB)	2.95	2.86-3.03	
Zhang et al., 2020	Japan (Diamond Princess Cruise Ship- UK) 20/01/2020-17/02/2020	Bootstrap sampling method	2.28	2.06-2.52	355 (C) 3711 (S)
Zhao et al., 2020b	China 01/01/2020-15/01/2020	exponential growth model (Long duration)	2.56	2.49-2.63	2066(C)

Author/ Study	Region/ Time period (Date/Month/Year)	Methodology	Basic Reproductio n Number/rate (R0)	95% Confidence Interval (CI)	Confirmed (C) and Susceptible (S) cases
Zhao et al., 2020b	China 10/01/2020-24/01/2020	exponential growth model (Short-duration)	2.24	1.96-2.55	-
Zhou et al., 2020	China 10/01/2020-31/01/2020	Dynamic compartmental model, Basic SEIR model	5.316		118 (C) 11081000 (S)
Zhu and Chen 2020	China CDC 01/12/2019-23/01/2020	MLE estimation, Poisson transmission model	2.54	2.49-2.6	3442 (C) 8348 (S)
Zhuang et al., 2020	Korea 20/01/2020-05/03/2020	stochastic model	2.6	2.3-2.9	6088(C)
Zhuang et al., 2020	Italy 06/02/2020-05/03/2020	stochastic model	3.2	2.9-3.5	3142(C)
Overall Mean R_0 with 95% CI			**3.65**	**3.36-3.98**	**30**

Note: Unit of R_0 is expressed in persons.

Table 2: Characteristics of included studies in the meta-analysis for CFR

Author/ Study	Region/ Period (Date/Month/Yea r)	Methodology	Case fatality rate (CFR)	95% Confidence Interval (CI)	Deaths (D)/ Confirmed cases (C)
Amariles et al., 2020	Europe 06/03/2020-18/03/2020	Stochastic differential evolution algorithm, SIRD model	4.3	0.30-8.30	4664(D) 88850(C)
Amariles et al., 2020	Latin America 06/03/2020-18/03/2020	Stochastic differential evolution algorithm, SIRD model	1.95	0.80-3.10	14 (D) 1510 (C)
Anastassopoulou et al., 2020	Hubei Province (China) 11/01/2020-10/02/2020	Susceptible, Infected, Recovered and Dead (SIRD) models	2.94	2.9-3.0	-/-
Bayham and Fenichel, 2020	USA 15/02/2020-22/03/2020	Infection mortality rate, MCKC simulations	2.3	1.80-2.80	-
Chatterjee et al., 2020	Globally 01/12/2019-28/02/2020	Descriptive: Adjusted fatality rate	3.41	3.29-3.54	2859 (D) 83704 (C)
Fu et al., 2020	Overall --	Systematic review/Meta-analysis	3.6	1.1- 7.2	43 (D)
Geldsetzer 2020)	USA	Rapid online Surveys/compute	5	2.0-15.0	1924 (C)
Geldsetzer 2020	UK	Rapid online Surveys/compute	3	2.00-10.0	1540 (C)
Jung et al., 2020	China (Fixed starting point) 08/12/2019-24/01/2020	Delay distributions with a fixed starting point, MCMC	5.3	3.5-7.5	41(D)
Jung et al., 2020	China (Varying starting point) 13/01/2020-24/01/2020	Delay distributions variable starting point, MCMC	8.4	5.3-12.3	41(D)

Kobayashi et al., 2020	Hubei 31/12/2020-14/02/2020	Descriptive: Adjusted fatality rate	18	11-81	-
Kobayashi et al., 2020	Outside mainland China 31/12/2020-14/02/2020	Descriptive: Adjusted fatality rate	2.5	1-85	-
Kobayashi et al., 2020	Hubei 5 days	Descriptive: Infection fatality risk	0.27	0.19-0.38	
Medina 2020	Philippines 08/03/2020-06/04/2020	simple linear regression model	4.35	4.12-4.55	163 (D) 3000 (C)
Mizumoto and Chowell 2020	China 01/01/2020-11/02/2020	Delay models, MCKC, Bayesian framework	12.2	11.3-13.1	Rolling (D) 1117 (C)
Öztoprak and Javed 2020	Turkey 16/03/2020-31/03/2020	linear regression analysis	1.85	1.51-2.18	314 (D) 13531 (C)
Öztoprak and Javed 2020	France 16/03/2020-31/03/2020	linear regression analysis	1.97	1.79-2.15	48 (D) 2281 (C)
Russell et al., 2020	Japan 05/02/2020-04/03/2020	Age standardisation	2.6	0.89-6.70	7 (D) 705 (C)
Shim et al., 2020	South Korea 20/01/2020-26/02/2020	Generalized growth model	0.7	0.4-1.1	42 (D) 6284 (C)
Verity et al., 2020	China 01/01/2020-08/02/2020	Bayesian Marko-Chain Monte Carlo (Adjusted for censoring)	3.67	3.56- 3.8	24 (D) 70117 (C)
Verity et al., 2020	China 01/01/2020-08/02/2020	Bayesian Marko-Chain Monte Carlo (Demographic adjustment)	1.38	1.23- 1.53	24 (D) 70117 (C)
Wang and Liu, 2020	China 15/01/2020-11/03/2020	binomial probability method	3.9	3.80-4.10	3169 (D) 80793 (C)
Wang and Liu 2020	China outside of Hubei 15/01/2020-11/03/2020	binomial probability method	0.87	0.72-1.00	3169 (D) 80793 (C)
Wang and Liu, 2020	China 15/01/2020-11/03/2020	survival analysis method	4.6	4.40-4.70	3169 (D) 80793 (C)
Wang and Liu 2020	China outside of Hubei 15/01/2020-11/03/2020	survival analysis method	0.92	0.76-1.10	3169 (D) 80793 (C)
Wilson et al., 2020	China 21/02/2020-05/03/2020	Time-delay adjusted case-fatality risk	3.5	3.35- 3.61	2624 (D) 75569 (C)
Wilson et al., 2020	82 countries 21/02/2020-05/03/2020	Time-delay adjusted case-fatality risk	4.2	2.58-6.87	15 (D) 354 (C)
Yang et al., 2020	China 10/01/2020-03/02/2020	Linear regression	2.1	2.05-2.14	-/-

Yang et al., 2020	Hubei 10/01/2020-03/02/2020	Linear regression	1.41	1.38-1.45	-/-
Overall Mean CFR (SD) with 95% CI			**3.96**	**3.67-4.27**	**28**

Note: The unit of CFR is expressed in percent.

Table 3: Test of heterogeneity for sample in a meta-analysis

Test of Heterogeneity	R_0	CFR
I^2statistic	99.9% (99.9%- 99.9%)	99.7% (99.6%- 99.7%)
Tau-squared (τ^2)	2.42 (0.82-4.60)	1.22 (1.06- 5.81)
Cochran's Q statistics	22716.05*	7657.4*
n	30	28

Source: Own calculations
*: significant at 95% of confidence interval

Table 4: Overall effect size based on various methods for R_0

Model	All data (n=30)			Excluding outliers (n=28)		
	Inverse variance method	**Fixed-effects model**	**Random-effects model**	**Inverse variance method**	**Fixed-effects model**	**Random-effects model**
	(a)	**(b)**	**(c)**	**(d)**	**(e)**	**(f)**
Overall effect size (persons)	3.65 (3.36- 3.98)	3.36 (3.34- 3.37)	3.13 (2.72- 3.91)	3.13 (2.83- 3.47)	3.36 (3.35- 3.38)	3.02 (2.42- 3.63)

Source: Own calculations.
Note: The unit of R_0 is expressed in persons. The estimates are significant at 1 % level of significance. Random-effects models give the best estimate after accounting for heterogeneity in studies; Estimates from the fixed-effects model and inverse variance method are shown for comparison.

Table 5: Overall effect size based on various methods for CFR

Model	All data (n=28)			Excluding outliers (n=24)		
	Inverse variance method	**Fixed-effects model**	**Random-effects model**	**Inverse variance method**	**Fixed-effects model**	**Random-effects model**
	(a)	**(b)**	**(c)**	**(d)**	**(e)**	**(f)**
Overall effect size (per cent)	3.96 (3.67-4.27)	2.17 (2.15- 2.19)	3.20 (2.76- 3.64)	2.79 (2.58- 3.02)	2.16 (2.14- 2.18)	2.63 (2.18- 3.08)

Source: Own calculations;
Note: Unit of CFR is expressed in percent. The estimates are significant at 1 % level of significance. Random-effects models give the best estimate after accounting for heterogeneity in studies; Estimates from the fixed-effects model and inverse variance method are shown for comparison.

Table 6: Effect size and test of heterogeneity for $R_0$by region and overall

Statistics	**Region**			**Test for Subgroup differences**	**Overall**
	China and its provinces	**Other Asian countries**	**Other countries**		
Effect Size (random-effects model)	3.21 (2.73-3.68)	1.90 (1.06-2.73)	3.41 (2.37-4.44)	7.87 (*p-value* =0.019)	3.02 (2.42-3.63)
I^2statistic	99.7%	99.5%	97.6%		99.9%
Tau-squared	-	-	-		2.42 (0.72- 4.12)
Cochran's Q statistics	-	-	-		22653.9*
n (sample=28)	16	5	7		28

Source: Own calculations (n=28) excluding outliers.

Note: The estimates are based on the random-effects model. The estimates are significant at 1 % level of significance. *: significant at 95% confidence interval; Unit of R_0 is expressed in persons. Other Asian countries include studies based on data from Japan and Korea. Other countries include studies based on data from Nigeria, Iran, Italy, and the USA

Table 7: Effect size and test of heterogeneity for CFR by region and overall

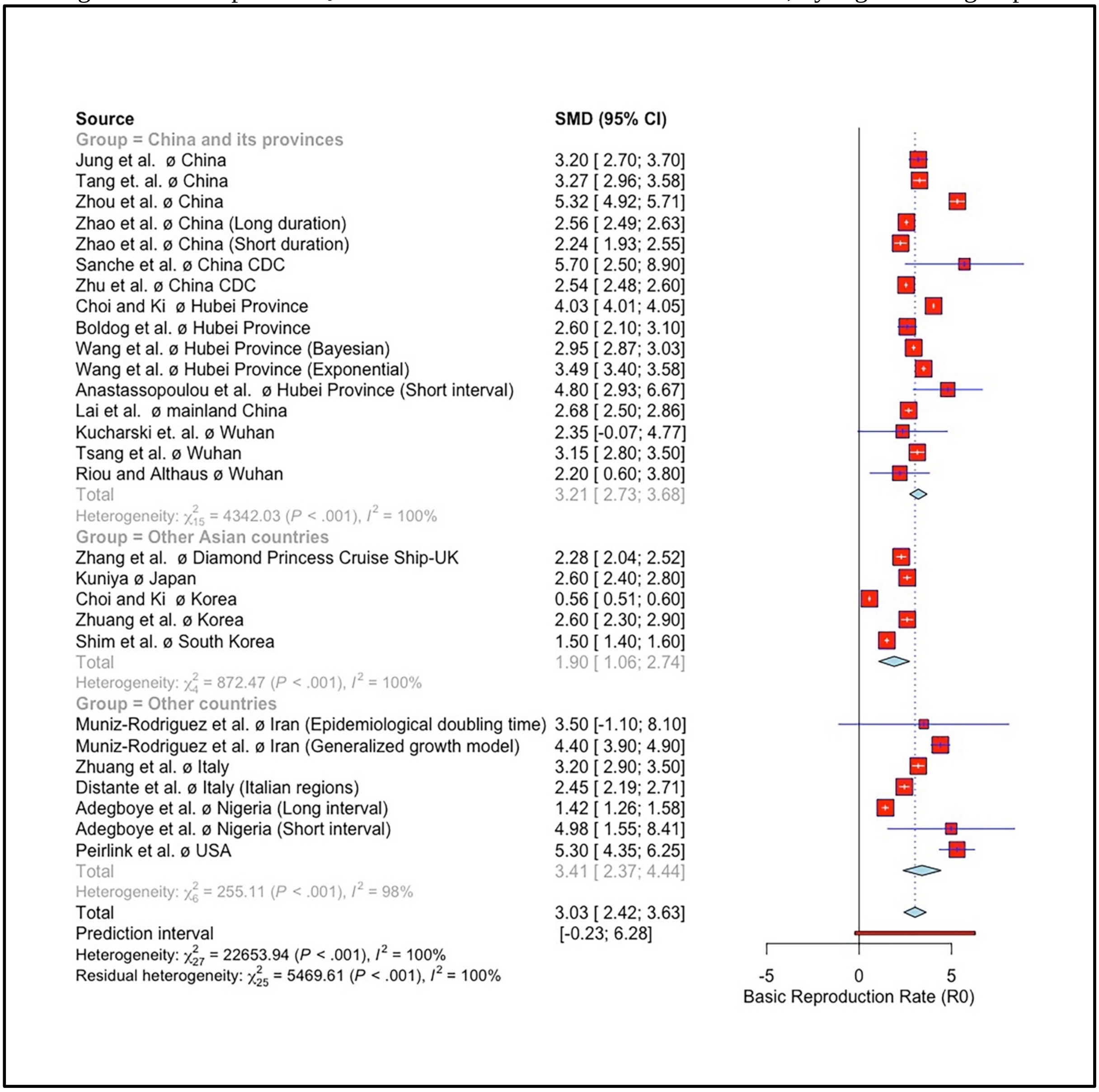
Statistics	Region			Test for Subgroup differences	Overall
	China and its provinces	Other Asian countries	Other countries		
Effect Size (random-effects model)	2.53 (1.91-3.14)	2.55 (-0.37-5.46)	2.77 (2.07-3.47)		2.63 (2.18-3.08)
I^2statistic	99.9%	99.4%	95.9%	0.22 (*p-value* =0.868)	99.7%
Tau-squared	-	-	-		1.06 (0.61- 3.48)
Cochran's Q statistics	-	-	-		8060.72*
n (sample=24)	11	3	10		24

Source: Own calculations (n=24) excluding outliers.

Note: The estimates are based on the random-effects model. The estimates are significant at 1 % level of significance. *: significant at 95% confidence interval; Unit of CFR is expressed in percent. Other Asian countries include studies based on data from Japan, South Korea, and Philippines. Other countries include studies based on data from Europe, France, Latin America, Turkey, the UK, and the USA

Furthermore, for examining a regional variation, the meta-analysis was performed by subgroups of countries. A minimum sample of three studies is required for performing a subgroup analysis in a meta-analysis. The regional subgroups identified for meta-analysis of$R_0$are ‘China and its provinces,’ ‘other Asian countries’ that includes studies based on data from Japan and Korea, and ‘other countries’ that includes studies based on data from Nigeria, Iran, Italy, and the United States of America (USA). Figure 1 for R_0 and Figure 2 for CFR show Forest plot showing mean effect sizes by regional subgroups, along with the overall effect size, based on the random-effects model. The mean R_0 values for the regional subgroup ‘China and its provinces’ was 3.21 (2.73-3.68) persons, and for ‘other Asian countries’ was 1.90 (1.06-2.74) persons and for ‘other countries’ was 3.40 (2.36-4.44) persons (Table 6). The test of regional subgroup differences using the random-effects model is significant, with a p-value of 0.019. This confirms that the estimated mean R_0 values are significantly different across these regions of the world. The results revealed that, among these regions, it is the highest for the subgroup ‘other countries’, wherein it is the highest for the USA. The regional subgroups identified for a meta-analysis of CFR are ‘China and its provinces,’ ‘other Asian countries’ that includes study based on data from Japan, South Korea, and the Philippines, and 'other countries' that includes studies based on data from Europe, France, Latin America, Turkey, the United Kingdom (UK), and the USA. The mean CFR values for 'China and its provinces' was 2.53 (1.91-3.14) percent, for 'other Asian countries' was 2.56 (-0.26-5.38) percent, and for 'other countries' was 2.78 (2.08-3.47) percent (Table 7). The test for regional subgroup differences using the random-effects model was not significant (p=0.865).Hence, it implies that the CFR did not vary significantly across these regions even though the CFR was the highest in the USA and the lowest in South Korea.

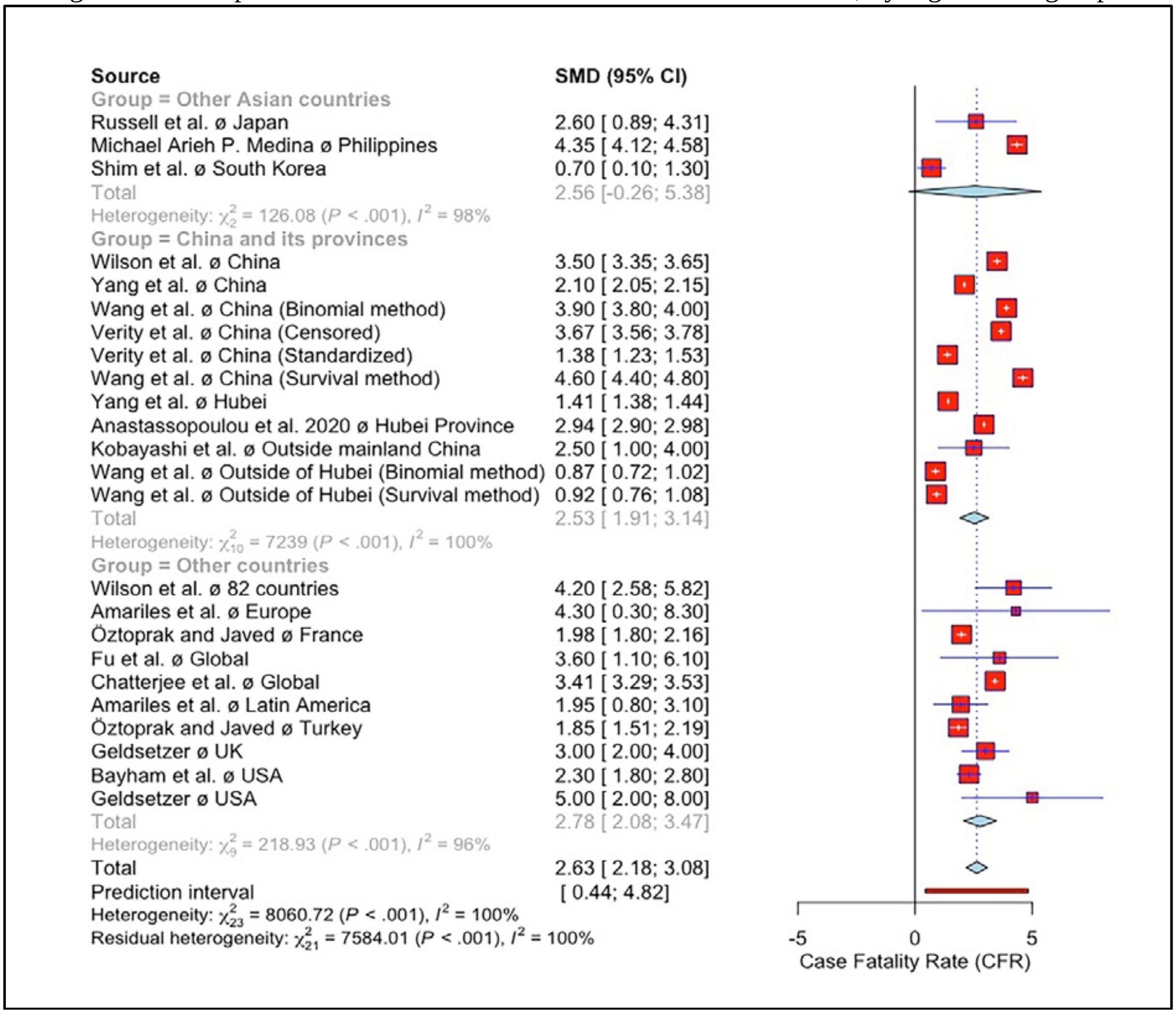
Figure 1: Forest plot of R_0 values based on the random-effects model, by regional subgroups



Source: Own calculation; n=28 excluding outliers;

Note: Unit of R_0 is expressed in persons. Other Asian countries include studies based on data from Japan and Korea. Other countries include studies based on data from Nigeria, Iran, the United States of America, and Italy.

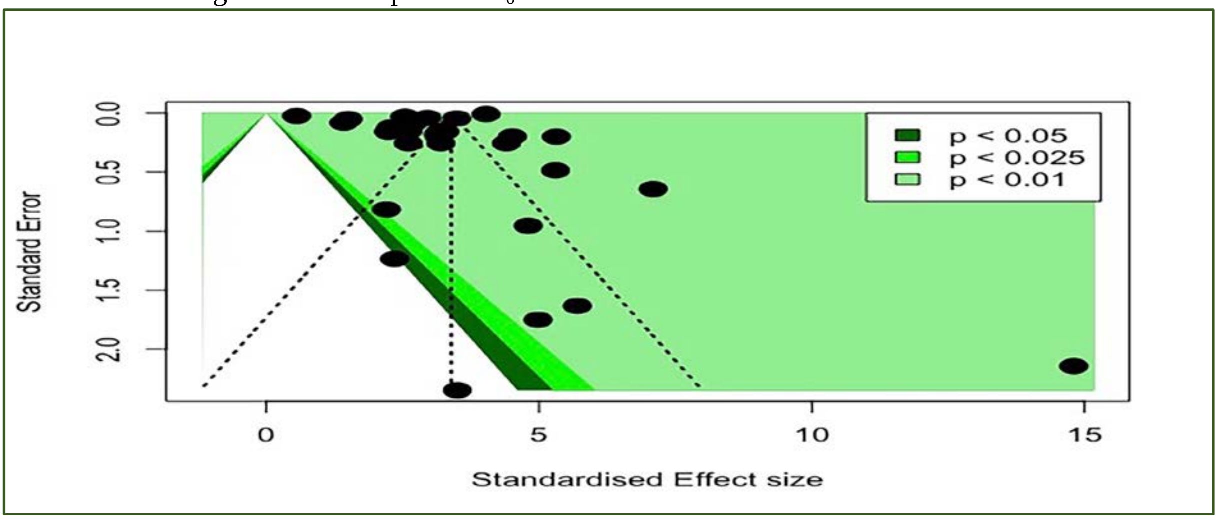
Figure 2: Forest plot of CFR values based on the random-effects model, by regional subgroups



Source: Own calculations (n=24) excluding outliers;

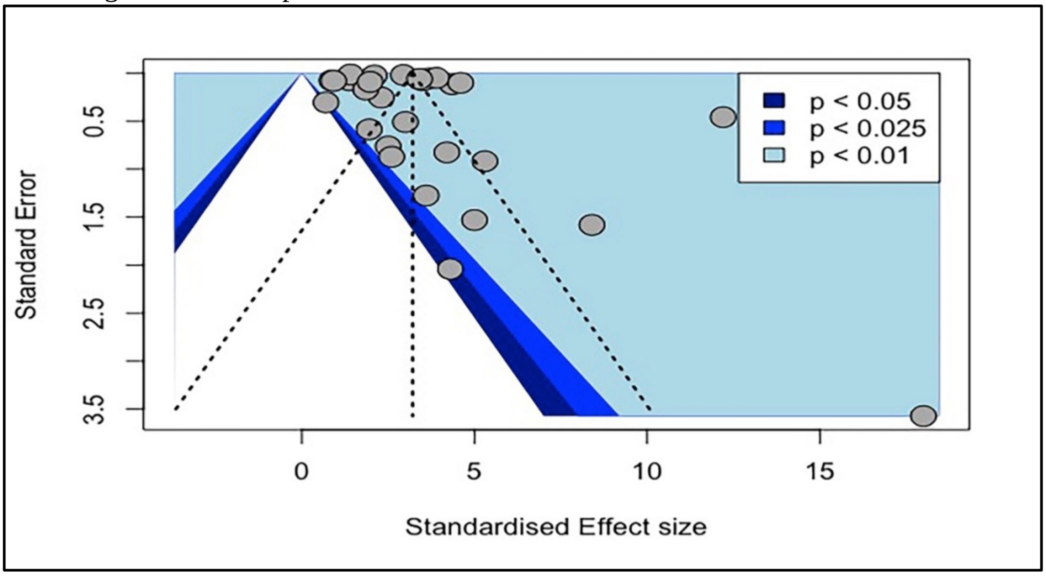
Note: Unit of CFR is expressed in percent. Other Asian countries include studies based on data from Japan, South Korea, and Philippines. Other countries include studies based on data from Europe, France, Latin America, Turkey, the United Kingdom, and the United States of America.

Figure 3: Funnel plot for R_0 values based on the random-effects model



Source: Own calculation; n=30 (all studies); The circles are the selected peer-reviewed articles

Figure 4: Funnel plot for CFR values based on the random-effects model



Source: Own calculation; n=28 (all studies); The circles are the selected peer-reviewed articles

We have also looked at publication bias to test the significance of these studies for a meta-analysis. The Funnel plot for R_0 values computed from the random-effects model is shown in Figure 3. This Funnel plot clearly shows that the selected studies of $R_0$for this meta-analysis are significant at a one percent level of significance, except for two studies, which are Muniz-Rodriguez et al. 2020 with the method of doubling time and Kucharski et al. 2020. Similarly, the Funnel plot of CFR is shown in Figure 4, based on the random-effects model. It clearly shows that all studies are significant at one percent level of significance. The results from the Funnel confirm that even the small sample size studies have also been published in addition to moderate sample size studies and large sample sized studies which are generally project-based.

Discussion

This study aims to provide a summary statistic of the basic reproduction rate (R_0) and the case fatality rate (CFR) for a generalised population based on peer-reviewed published estimates of $R_0$and CFR from epidemiological models applied on a susceptible population. After an electronic search for such conditions between the dates 15 December 2019 and 3 May 2020 and using various inclusion and exclusion criteria, this study came across 24 and 17 works of literature for R_0 and CFR, respectively, that qualified for a meta-analysis. These studies provided 30 counts of $R_0$and 29 counts of CFR for a meta-analysis. The study examined the characteristics of studies and computed the overall effect size or mean $R_0$and CFR value. We applied the test of heterogeneity, which are Higgin's & Thompson'sI^2statistic, tau-squared (τ^2) statistic, and Cochran's Q-statistic. This test of heterogeneity reveals a high heterogeneity across the studies. The studies included in the meta-analysis had the sources of errors not only from sampling errors but also from the distributions of individual mean effect size. The R_0 and CFR values extracted from different studies had their distributions that were different from an overarching distribution. Therefore, the random-effects model was most appropriate for computing mean R_0 value and mean CFR value based on a meta-analysis. After excluding outliers, the estimates of $R_0$and CFR from these studies were calculated at 3.02 (2.42-3.68) persons (Table 4: column (f)) and 2.63 (2.18-3.08) percent (Table 5: column (f)), respectively, based on the random-effects model. For R_0, the variation by subgroups of regions was significant. It reveals that the R_0 values were significantly different across these regional subgroups.However, the regional subgroups differences for CFR was not a significant one. Hence, we conclude that the CFR did not vary across the regions.

Acknowledging the severity of this disease, the estimated R_0 value of 3.02persons in a narrow confidence interval is a higher and riskier statistic applicable for any generalized population. This R_0 statistic implies that one infectious person is transmitting to two to three other susceptible persons in the absence of any control measures. The R_0 value is the overall effect size based on various heterogeneous studies. Therefore, this R_0 value is most reasonable and sensible for a country or a region encountering the emergence of COVID-19 during the first phase or in the very initial stage of this infectious disease. The meta-analysis by regional subgroups reveals the variation in R_0across the regions (Table 6).Therefore, this study suggests thatR_0values based on a meta-analysis from the pieces of evidence across the regions would range between 1.90 (1.06-2.73) persons and 3.40 (2.36-4.44) persons. The CFR statisticis based on the period of approximately one-and-a-half months, but it translates to toll deaths in a short span of time. The results of regional subgroup analysis in meta-analysis confirm that the CFR did not vary across the regions. The estimated CFR value of 2.63 per cent (Table 7) without much variation is applicable to any generalised population. For a developing country like India, the second most populated country in the world, the CFR value of 2.63 is a concern. Necessary precautions and strategies are of utmost importance as early as possible to prevent the outbreak of this disease.

India is a country with a vast population spread over wide geographical areas. The districts and states' boundaries have their local administrative bodies governed by state and central legislative assemblies. The transmission of COVID-19 disease from one infectious area to other susceptible areas is quite easy in various forms of travelling and commuting. Also, given the shortfall of medical infrastructure in this country as compared to developed nations, in general, it indicates practical complications for applying control measures. Even the lowest limit of R_0value of 1.06 persons estimated in this paper has the potential to multiply rapidly in a populated country like India, in the absence of control measures. In particular, urban areas are at higher risk of this disease because of the high-density population and urban poverty. The city of each district is at much higher risk because of the densely population and well connectivity with other districts and metro cities. This disease has a chance of spreading at a high rate in the city and urban parts of these capital districts. It is not necessary that the spreading of this disease would be apparent very soon. For these capital districts, the incubation period is not important, but the influx of persons from time to time is more important. The onset of this disease for any capital district of India is indeterminate. This adds to the complexity, and perhaps, a higher R_0value of more than two persons is more appropriate.

Conclusion

This paper suggests a robust estimate of $R_{0,}$ which is3.02 (2.42-3.68) persons in the absence of any control measures and a robust estimate of CFR equals to 2.63 (2.18-3.08) percent for a generalized population in one-and-a-half months from the onset of disease COVID-19. The analysis by subgroups of regions showed in the Forest plot confirms a significant variation for R_0, but the same is not found significant for CFR. The R_0values would most probably be in the range of 1.90 (1.06-2.73) persons and 3.40 (2.36-4.44) persons for a region. The Funnel plot confirms that the included studies were significant, and therefore, it establishes the robustness of R_0 and CFR based on the data of these studies in a meta-analysis.We proclaim that one person is likely to infect two to three persons in the absence of any control measures, and around three percent of the population are at the risk of death in one-and-a-half months from the onset of disease COVID-19 in a generalized population.

The estimates of R_0 and CFR are unequivocally applicable to any generalized population at the point of emergence of the disease COVID-19. Hence these estimates are worthwhile for a region/country and its lower geography. These robust estimates are applicable for developing country India and its states or districts.

Limitations of the study

This study is based on a meta-analysis of recently published articles that estimated for parameters of epidemiological models for COVID-19. The period for analysis for COVID-19 is more than three months from 15 December 2019 to 3 May 2020. We retrieved studies that are peer-reviewed research papers and are mostly from the regions which have encountered the epidemic in an area or pandemic in a country or nation at the very early emergence of SARS-CoV-2. Many of these peer-reviewed studies have used data mainly from China and its provinces. Some of these studies had analysed data from other Asian countries and a few from other parts of the world. Therefore, a wide and rich regional as well as by social and economic groups view of data was not available in the period of study. Most of these studies in itself have the disadvantage of small sample size and missing information on the time of onset of SARS-CoV-2. Accordingly, the authors of these selected published papers have used generalized epidemiological models to get robust estimates. Most of these have used time-varying models using simulation methods and the moments of statistical distributions for estimating parameters of the epidemiological models. We also, to overcome such limitations of small sample size, have estimated the mean R_0 and CFR values using the random-effects model, which make the estimation of parameter based on the assumption that these studies stem from a universe of population and hence the analysis accounts for the heterogeneity of the studies. Therefore, the estimates of R_0 and CFR in this study are robust and applicable to a generalized population. In addition to that, nonetheless, the Funnel plot for both R_0 and CFR showed that these publications are important to consider for a meta-analysis, as these studies are found statistically significant for examining COVID-19.

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