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Reproductive number of coronavirus: A systematic review and meta-analysis based on global level evidence

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Abstract

Background

The coronavirus (SARS-COV-2) is now a global concern because of its higher transmission capacity and associated adverse consequences including death. The reproductive number of coronavirus provides an estimate of the possible extent of the transmission. This study aims to provide a summary reproductive number of coronavirus based on available global level evidence.

Methods

A total of three databases were searched on September 15, 2020: PubMed, Web of Science, and Science Direct. The searches were conducted using a pre-specified search strategy to record studies reported the reproductive number of coronavirus from its inception in December 2019. It includes keywords of coronavirus and its reproductive number, which were combined using the Boolean operators (AND, OR). Based on the included studies, we estimated a summary reproductive number by using the meta-analysis. We used narrative synthesis to explain the results of the studies where the reproductive number was reported, however, were not possible to include in the meta-analysis because of the lack of data (mostly due to confidence interval was not reported).

Results

Total of 42 studies included in this review whereas 29 of them were included in the meta-analysis. The estimated summary reproductive number was 2.87 (95% CI, 2.39–3.44). We found evidence of very high heterogeneity (99.5%) of the reproductive number reported in the included studies. Our sub-group analysis was found the significant variations of reproductive number across the country for which it was estimated, method and model that were used to estimate the reproductive number, number of case that was considered to estimate the reproductive number, and the type of reproductive number that was estimated. The highest reproductive number was reported for the Diamond Princess Cruise Ship in Japan

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Abbreviations: CCDC, Chinese Center for Disease Control and Prevention; COVID-19, Novel Coronavirus Disease 2019; CI, Confidence Interval; EGR, Exponential Growth Rate; GT, Generation Time; MCO, Movement Control Order; MCMC, Markov Chain Monte Carlo; MERS, Middle East Respiratory Syndrome; MLE, Maximum Likelihood Estimation; nCoV-19, Novel Coronavirus 2019; NGMA, Next Generation Matrix Approach; NIH, National Institute of Health; NP, Non-Pharmaceutical; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SARS, Severe Acute Respiratory Syndrome; SARS-COV-2, Severe Acute Respiratory Syndrome due to Coronavirus-2; SEIQ, Susceptible, Exposed, Infected, Quarantined; SEIHR, Susceptible, Exposed, Infected, Hospitalized, Removed/Recovered; SEIR, Susceptible, Exposed, Infected and Removed/Recovered; SI, Serial Interval; SIR, Susceptible, Infected and Removed/Recovered; USA, United States of America; WHO, World Health Organization.

(14.8). In the country-level, the higher reproductive number was reported for France (R, 6.32, 95% CI, 5.72–6.99) following Germany (R, 6.07, 95% CI, 5.51–6.69) and Spain (R, 3.56, 95% CI, 1.62–7.82). The higher reproductive number was reported if it was estimated by using the Markov Chain Monte Carlo method (MCMC) method and the Epidemic curve model. We also reported significant heterogeneity of the type of reproductive number- a high-value reported if it was the time-dependent reproductive number.

Conclusion

The estimated summary reproductive number indicates an exponential increase of coronavirus infection in the coming days. Comprehensive policies and programs are important to reduce new infections as well as the associated adverse consequences including death.

Background

Coronavirus (SARS-COV-2) is now a global concern that speared out to 213 countries or territories as of September 15, 2020. More than 29.5 million population have been infected so far worldwide, of which more than 933,720 are died [1]. Consequently, the World Health Organization (WHO) has declared it as pandemic and suggested countries to take aggressive measures to reduce new infections [2]. Given no treatments or vaccines available for this virus, countries are now imposing numerous non-medical measures to reduce further infections, which include restricting people's movements, banned international and local travels, quarantine, and isolation [3]. However, the new infections are rising exponentially, in all ages and sexes, irrespective of the countries [4, 5]. Reducing new infections, therefore, needs further comprehensive preventive measures.

Knowing the accurate reproductive number of coronavirus, defined as the capability of transmission per primary infected person to the secondarily infected persons, is significant for various reasons, including to assess epidemic transmissibility and to predict the future trend of spreading [6]. These are important to reduce new infections through designing effective control measures such as social distancing [7] and to know the expected duration of keeping control measures [5]. Moreover, it also helps to develop an effective epidemiological mathematical model considering possible transmission ways, such as, droplets and direct contacts with coronavirus infected patients (COVID-19), which are important to know the risk population and the appropriate epidemiologic parameters [8, 9].

There are various researches in the country level that have been reported the reproductive number of coronavirus. However, they were not consistent in terms of their measurement procedures and methods used, therefore, the estimated reproductive number was quite different [8, 10]. Other reported sources of variations of the reported reproductive number were the country for which the reproductive number was estimated and its stages of infection and preventive measures applied [11]. Another important source of variation of the estimated reproductive number was the type of reproductive numbers considered [8]. Of the three reproductive numbers estimated, namely the basic reproductive number (R_0), net reproductive number (R_e), and time dependent reproductive number (R_t), are applicable for different purposes. For instance, the basic reproductive number is used when an infected person can mix randomly to non-infected persons (i.e., no control intervention was applied), whereas, the net and time-dependent reproductive number are used when control interventions were applied.

To settle these disagreements on the reported reproductive number and know the current situation of infection, a summary estimate of the reproductive number is important. However, of the three studies that have been provided summary reproductive number so far were limited in several areas and did little to settle these disagreements [12–14]. For instance, they reported a summary estimate of the basic reproductive number without considering the net reproductive number and the time-dependent reproductive number. However, it is around 10 months that have already been gone since the first infection of the coronavirus in December 2019 and all countries have been imposed several prevention measures. Therefore, the estimation of the basic reproductive number was available only in a few studies of which these summary estimates were based. Moreover, these studies were also failed to address the heterogeneity of their estimated reproductive number though it was found higher [12–14].

Considering the higher variability of the reported reproductive number and lack of relevant research, in this study, an attempt has been made to provide a summary reproductive number of coronavirus. The sources of variation of the reported reproductive number were also addressed. Findings will help policymakers to know about the possible increase of coronavirus infected patients and take policies and programs accordingly.

Methods

Literature searches were conducted in three databases on September 15, 2020: PubMed, Web of Science, and Science Direct. The pre-specified search strategies were used to search databases (S1-S3 Tables in S1 File). We developed search strategies consisting of virus-specific (corona virus, coronavirus, SARS-CoV-2, COVID-19, nCoV-2019) and reproductive number related (reproduction number, transmissibility) keywords that were combined using the Boolean operators (AND, OR). Additional searches were conducted in the reference list of the selected articles, and the relevant journal's websites.

Inclusion and exclusion criteria

Studies meet the following inclusion criteria were included: wrote in the English language, presented a reproductive number of the coronavirus instead of considering its type (basic reproductive number, net reproductive number, and time-dependent reproductive number. We did not apply any time restriction, i.e. all studies from the onset of coronavirus to the date of conducting formal search were included. Studies that did not meet these criteria were excluded.

Data extraction

Two authors (MAB, MMM) extracted information by using a pre-designed, trailed, and modified data extraction sheet. The extracted information includes: year of publication, study's location, model used to estimate the reproductive number, time for when the reproductive number was estimated, number of cases considered to estimate the reproductive number, assumption(s) that was/were set to a calculate the reproductive number, intervention strategy, and the estimated reproductive number with its 95% confidence interval (CI). The corresponding author (MNK) solved any disagreement on information extraction.

Statistical analysis

The information recorded were mostly dichotomous where the numerical reproductive number was reported in all selected studies. We, therefore, used both narrative synthesis and meta-analysis to summaries findings from retrieved studies. Narrative synthesis was used to explain the findings of the studies where the reproductive number was reported, however, its 95%

confidence interval was missing that did not enable them to be included in the meta-analysis. Meta-analysis was used for the studies that consistently reported the reproductive number and its 95% confidence interval. We first use the fixed-effect meta-analysis to get a pool reproductive number for the studies which reported more than one reproductive number for a country calculated based on different assumptions. Later this pooled estimate was used to give a summary estimate of the reproductive number. We used the random-effect meta-analysis to estimate the summary reproductive number. The model was chosen based on the heterogeneity assessment (I^2) which reported a very high heterogeneity of the reported reproductive number across different included studies. Later we explored the sources of heterogeneity through subgroups analysis across the selected studies' characteristics. These include the country for which the reported reproductive number was estimated, the method and model that were used to estimate the reproductive number, total number of case that was considered to estimate the reproductive number and type of reproductive number that was reported. We also assessed the publication bias through visual inspection of the funnel plot and Egger's regression asymmetry test. The trim-and-fill procedure was used when evidence of publication bias was found. The National Institutes of Health (NIH) study quality assessment tool was used to assess study quality. The Stata software version 15.1 (Stata Corp, College Station, Texas, USA) was used to perform all analyses.

Results

Literature search results

Total of 541 studies included, 528 of them were extracted from three databases searched (Fig 1 and S1-S3 Tables in S1 File). Of these, 494 studies were excluded through title and abstract screening leaving 47 studies for full-text review. A total of 42 of them were finally included in this study and 29 of them were included in the meta-analysis. All included studies were moderate to high in quality (Table 1 and S4 Table in S1 File).

Majority of the studies selected were conducted in China (8) [6, 15–21] and its province (6) [22–27]. The remaining studies were conducted in Japan (3) [28–31] followed by South Korea (3) [32–34], Italy (2) [35, 36], Spain (2) [36, 37], and France and Germany (1) [36]. Four studies included were conducted based on multiple countries' data [7, 38–40].

Estimated reproduction number

The estimated summary reproductive number based on the 29 studies included in the meta-analysis was 2.87 (95% CI, 2.39–3.34) (Fig 2). We found a very high heterogeneity (99.5%) of the reported reproductive number of these included studies. However, we did not find any evidence of publication bias (Fig 3). We used the subgroup analysis to address the heterogeneity of the reported reproductive number across selected studies characteristics. Their results are reported in Table 2 and the details results are presented in the S1-S5 Figs in S1 File. We found heterogeneity of the reported reproductive number across the countries for which the reproductive number were estimated, models and methods that were used to estimate the reproductive number, and the total number of cases that was used to estimate the reproductive number, and the type of the reproductive numbers that were estimated. For instance, the estimated reproductive number was higher in outside of China (R, 4.56, 95% CI, 2.28–9.12) than the mainland of China (R, 3.14, 95% CI, 2.40–4.09). However, in the country level, the highest reproductive number was reported for France (R, 6.32, 95% CI, 5.72–6.98) following Germany (R, 6.07, 95% CI, 5.51–6.69) and Spain (R, 5.08, 95% CI, 4.50–5.73). South Korea was the only country reported <1 reproductive number (R, 0.76, 95% CI, 0.34–1.70). The higher reproductive number reported if it was estimated by the Markov Chain Monte Carlo method (MCMC)

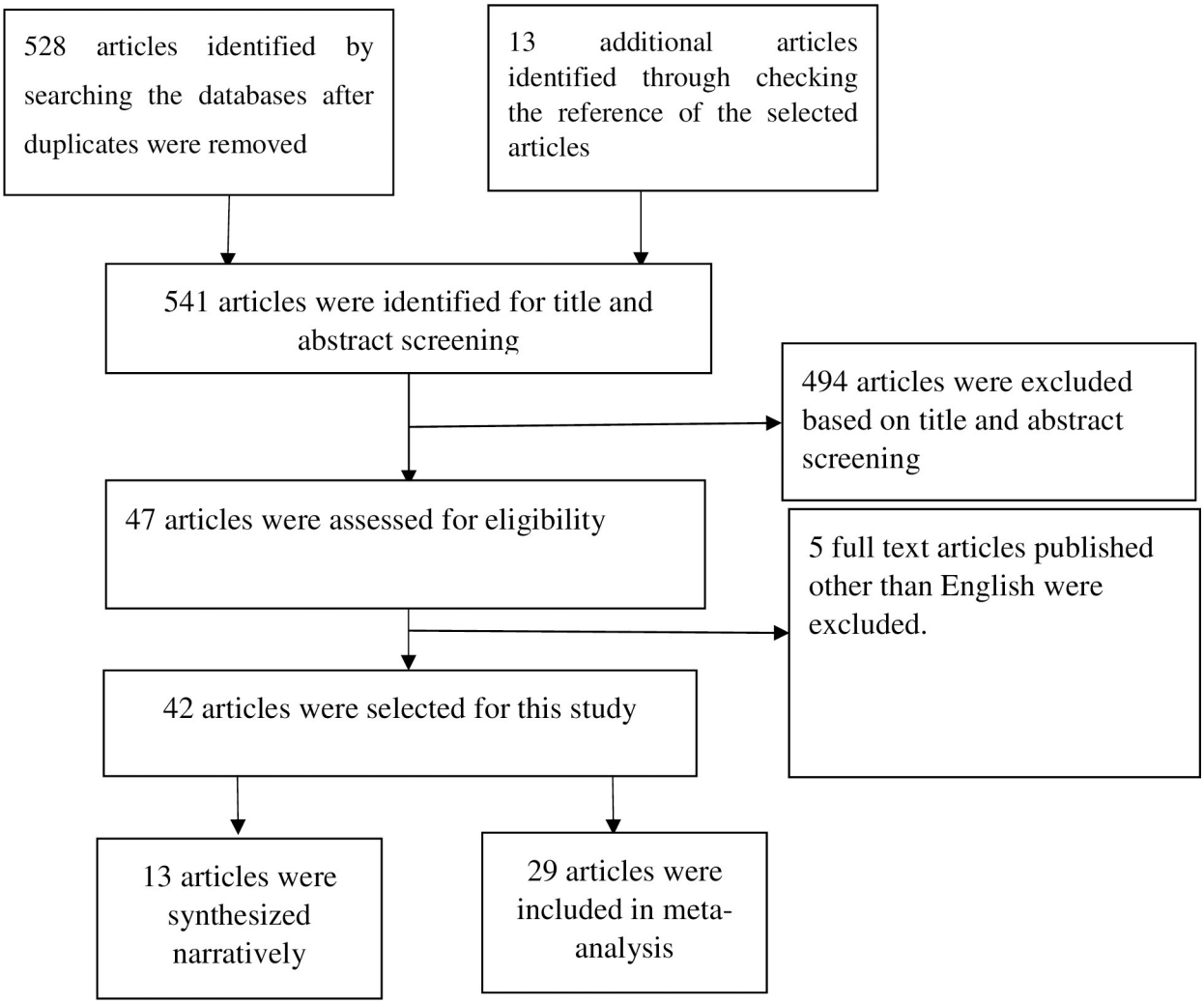

Fig 1. Schematic representation of the included studies reporting the reproductive number of coronavirus published between December 2019 and September 2020.

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method (R, 4.57, 95% CI, 2.68–7.78) and by the Epidemic curve model (R, 3.04, 95% CI, 2.60–3.55). The summary reproductive number was found higher if it was estimated for >3162 cases (R, 3.27, 95% CI, 2.47–4.31) than ≤3162 cases (R, 2.51, 95% CI, 1.91–3.28). Variations were also found across the type of reported reproductive numbers- the time-dependent reproductive number was found around double (R,4.42; 95% CI, 3.05–6.40) than the net reproductive number (R,1.95; 95% CI, 1.63–2.34). However, we found, through using the meta-regression, these differences were only significant across the countries of the reported reproductive number and the methods used to estimate the reproductive number.

The results of the 13 studies that are narrative synthesized are presented in Table 3. Their findings were in line with our estimated summary reproductive number. Only a study conducted for Diamond Princes Cruise Ship, Japan reported a very high reproductive number, 14.8 for the period of 21 January to 19 February 2020 [30]. However, this estimated reproductive number was conditioned for not to be applied any preventive intervention and the infected person can mix randomly to the non-infected persons. When preventive interventions applied this number was reduced to 1.78.

Table 1. Background characteristics of the 29 studies included in the meta-analysis.

Serial number	Author, Study's location	Model used to estimate the reproductive number	Time/period for which the reproductive number was estimated	Assumption(s) that was/ were considered to estimate the reproductive number	Method used to estimate the reproductive number	Reproductive number (95% CI)	Study-quality assessment (earned score in the scale of 9)[++]
1	Read et al, 2020 [40], China and overseas	Susceptible-Exposed-Infected-Removed (SEIR) model	1st Jan 2020 to 22nd Jan 2020	Cases daily time increase follows a Poisson distribution	MLE[1]	3.11 (2.39–4.13)	7
2	Zhang et al., 2020 [31], Diamond Princess Cruise ship, Japan	Epidemic model incorporated by the data	16th Feb 2020	The mean serial interval (SI)[2] 7.5 days, standard deviation (SD) 3.4 days	MLE	2.28 (2.06–2.52)	7
3	Liu et al., 2020 [39], China and overseas	No model mentioned	before 23rd Jan 2020	With generation time (GT)[3] of 8.4 days	EGR	2.90 (2.32–2.52)	8
					MLE	2.92 (2.28–3.67)	
4	Majumder & Mandl, 2020 [24], Wuhan, China	Susceptible-Infected-Recovered/ Removed (SIR) model	Dec 8, 2019, to Jan 26, 2020	Mean SI 8 (range 6–10) days	SEIR method	2.55 (2.00–3.10)	6
5	Riou & Althaus, 2020 [7], China and overseas	No model mentioned	before 18th Jan 2020	The mean GT varied 7–14 days	Stochastic simulation	2.2 (1.4–3.8)	8
6	Tang et al., 2020 [18], China	SEIR model (with isolation, quarantined)	31 Dec 2019 to 15th Jan 2020	The incubation period is 7 days	NGMA[1]	6.47 (5.71–7.23)	9
7	Zhao, Lin et al., 2020 [19], China	Epidemic curve by time-series data	10th Jan to 24th Jan 2020	8-fold reporting rate	EGR	2.24 (1.96–2.55)	7
				2-fold reporting rate		3.58 (2.89–4.39)	
				0-fold reporting rate		5.71 (4.24–7.54)	
8	Zhao, Musa, et al., 2020 [20], China	Epidemic curve using time series information	1st Jan to 15th Jan 2020	Constant screening effort applied in the Wuhan at the same point in time.	EGR	2.56 (2.49–2.63)	8
9	Shen et al., 2020 [25], Hubei province, China	SEIR model	12th Dec 2019 to 22nd Jan 2020	5–6 days of incubation	SEIR method[1]	4.71 (4.50–4.92)	8
				With intervention and 5–6 days of the incubation period	SEIR method	2.08 (1.99–2.18)	
10	Q. Li et al., 2020 [23], Wuhan, China	Epidemiologic time delay distribution	Before 22nd Jan 2020	Mean SI 8.4 days and SD 3.8 days	Fitted transmission model with zoonotic infection	2.20 (1.40–3.90)	8
11	J. T. Wu et al., 2020 [27], Wuhan, China	SEIR model	31 Dec 2019 to 28th Jan 2020	Mean SI of 8.4 days	MCMC[1]	2.68 (2.47–2.86)	9
12	Imai et al., 2020 [15], China	No model mentioned	before 18th Jan 2020	High level of variability & generation time is 8.4 days	Computational modelling epidemiologic trajectories	2.60 (1.50–3.50)	7
13	Kucharski et al., 2020 [38], Wuhan and international travellers	SEIR model	29th Dec 2019 to 23rd Feb 2020	Mean incubation period is assumed to be 5.2 days & SD 3.7 days	MLE	2.35 (1.15–4.77)	9
				Intervention with mean incubation period 5.2 days & SD 3.7 days	MLE	1.05 (0.41–2.39)	
14	Ki, 2020 [33], South Korea	Epidemic curve fitting	20 Jan to 10 Feb 2020	Not Available (NA)	EGR	0.48 (0.25–0.84)	9
15	Choi & Ki, 2020 [32], South Korea	SEIR model	20 Jan to 17 Feb, 2020	Overseas infections are separated	SEIR method	0.56 (0.51–0.60)	9

(*Continued*)

Table 1. (Continued)

Serial number	Author, Study's location	Model used to estimate the reproductive number	Time/period for which the reproductive number was estimated	Assumption(s) that was/were considered to estimate the reproductive number	Method used to estimate the reproductive number	Reproductive number (95% CI)	Study-quality assessment (earned score in the scale of 9)[++]
16	Shim et al., 2020 [34], South Korea	Epidemic curve fitting with the growth model	20th Jan to 26th Feb 2020	With mean GT 4.41 days and SD 3.17 days	Simulation	1.50 (1.40–1.60)	8
17	Lai et al., 2020 [41], Genetic data from GISAID	Phylogenetic estimation	4th Feb 2020	Based on the exponential growth rate of 0.218 per days	EGR	2.60 (2.10–5.10)	9
				The evolutionary rate set to the value of 8.0 × 10–4 subs/site/year	Birth-death skyline estimate	1.85 (1.37–2.40)	
18	Jung et al., 2020 [42], Outside of China	No model mentioned	before 24 Jan 2020	Mean SI 7.5 days and SD 3.4 days	EGR	3.19 (2.66–3.69)	8
19	Song et al., 2020 [17], China	SEIR model	15 to 31 Jan 2020	Using generation intervals	EGR	3.74 (3.63–3.87)	6
				Using generation intervals	MLE	3.16 (2.90–3.43)	
				The model fitted best 27th Jan	SEIR method	3.91 (3.71–4.11)	
20	Sanche et al., 2020 [16], China	SEIR model	15 to 30 Jan 2020	with 7–8 days of the SI	EGR	5.80 (4.40–7.70)	7
				with 6–9 days of the SI		5.7 (3.80–8.90)	
21	Mizumoto & Chowell, 2020 [29], Diamond Princes Cruise ship, Japan	No model mentioned	20 Jan to 18 Feb, 2020	Mean SI 7.5 days and SD 3.4	NGMA	5.8 (0.6–11.0)	9
22	Kuniya, 2020 [28], Japan	SEIR model	15 Jan to 29 Feb 2020	Infected increases at a rate of daily time increment	NGMA	2.60 (2.40–2.80)	6
23	Iwata & Miyakoshi, 2020 [43], Outside of China	SEIR model	Not Available (NA)	One infected entered a community of 1000 population.	MCMC	6.5 (5.6–7.2)	7
24	Wan et al., 2020 [26], Wuhan, China	SEIR model	22 Jan to 07 Feb 2020	7 days incubation period and 14 days of the infectious period	SEIR method	1.44 (1.40–1.47)	8
25	Yuan et al., 2020 [36], Italy	No model mentioned	23 Feb to 9 Mar 2020	Mean GT 5.6 days and SD 2.6 days	EGR	3.27 (3.17–3.38)	9
	Yuan et al.,2020 [36], France					6.32 (5.72–6.99)	
	Yuan et al.,2020 [36], Germany					6.07 (5.51–6.69)	
	Yuan et al.,2020 [36], Spain					5.08 (4.51–5.74)	
26	Chintalapudi et al., 2020 [44], Italy	No model	26 Feb to 20 Apr 2020	Using estimated SI with non-pharmaceutical (NP) interventions	MLE	1.85 (0.60–2.30)	8
27	Hyafil and Morina, 2020 [37], Spain	SIR model	Upto 13 Mar 2020	Based on the hospitalized data with 7.65 days incubation period	SEIR method	5.89 (5.86–7.09)	8
	Hyafil and Morina, 2020 [37], Spain	SIR model	Upto 13 Mar 2020	Based on the detected cases with 10.2 days incubation period	SEIR method	6.91 (6.95–7.39)	
	Hyafil and Morina, 2020 [37], Spain	SIR model	16 Mar to 15 Apr 2020	Based on the hospitalized data with 7.65 days incubation period with initial interventions	SEIR method	1.86 (1.10–2.63)	

(*Continued*)

Table 1. (Continued)

Serial number	Author, Study's location	Model used to estimate the reproductive number	Time/period for which the reproductive number was estimated	Assumption(s) that was/were considered to estimate the reproductive number	Method used to estimate the reproductive number	Reproductive number (95% CI)	Study-quality assessment (earned score in the scale of 9)[++]
	Hyafil and Morina, 2020 [37], Spain	SIR model	16 Mar to 15 Apr 2020	Based on the detected cases with 10.2 days incubation period with initial interventions	SEIR method	2.22 (1.92–2.74)	
	Hyafil and Morina, 2020 [37], Spain	SIR model	31 Mar to 12 Apr 2020	Based on the hospitalized data with 7.65 days incubation period with interventions for full restrictions	SEIR method	0.48 (0.15–1.17)	
	Hyafil and Morina, 2020 [37], Spain	SIR model	31 Mar to 12 Apr 2020	Based on the detected cases with 10.2 days incubation period with interventions for full restrictions	SEIR method	0.85 (0.50–1.05)	
28	Zhang et al., 2020 [45], Wuhan, China	SEIQ model	21 Jan to 20 Feb 2020	Mean SI 5.2 days and hospital quarantine 12.5 days	MCMC	5.50 (5.20–5.80)	7
29	Shao et al., 2020 [46], China	Fiduan-CCDC model	Not specified	Mean SI 7.5 days with SD 3.4 days	SEIR method	3.32 (3.25–3.40)	7

Note: All studies included in the meta-analysis were summarized in this table. Studies included in the narrative synthesis were summarized in Table 3. [1]EGR: Exponential growth rate method; MLE: Maximum Likelihood Method; MCMC: Markov Chain Monte Carlo Method; NGMA: Next-Generation Matrix Approach and SEIR method = β/γ method. R: Reproductive number, 95% CI, 95% Confidence Interval.

[2]Serial interval refers to the duration of time between the onset of symptoms in an index case and a secondary case.

[3]Generation time refers to the time interval between successive infections in the chain of transmission.

[++]Study quality was assessed through the National Institutes of Health (NIH) study quality assessment. Details results are presented in S4 Table in S1 File.

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Discussion

This review aimed to provide the summary reproductive number of the coronavirus based on the global level evidence. A total of 42 studies selected for this study of which 29 studies were included in the meta-analysis. Majority of the included studies were conducted in China. The estimated summary reproductive number was 2.87. We found evidence of higher heterogeneity of the reported reproductive number across different studies. The sources of heterogeneity were the country for which the reproductive number was estimated, models and methods that were used to estimate the reproductive number, and the total number of case that was used to estimate the reproductive number.

The average estimated reproductive number was 2.87; which is higher than the WHO's estimate of 1.4 to 2.5. However, this estimate is lower than the previous summarized reproductive number of coronavirus, 3.38 estimated by Alimohamadi and Colleagues based on the 23 studies [12], 3.15 reported estimated by He and colleagues [14] based on the 7 studies, and 3.28 estimated by Liu and colleagues based on the included 12 studies [13]. Numerous measures to reduce new infections of coronavirus such as social distancing, and controlling international travels are associated with such reduction [54, 55]. However, our estimated reproductive number is still very high that could have the potential to an exponential increase in new infections. Moreover, the estimated number is still very higher than previous rounds of coronavirus like infectious diseases, such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) if we considered the period between the when was estimation

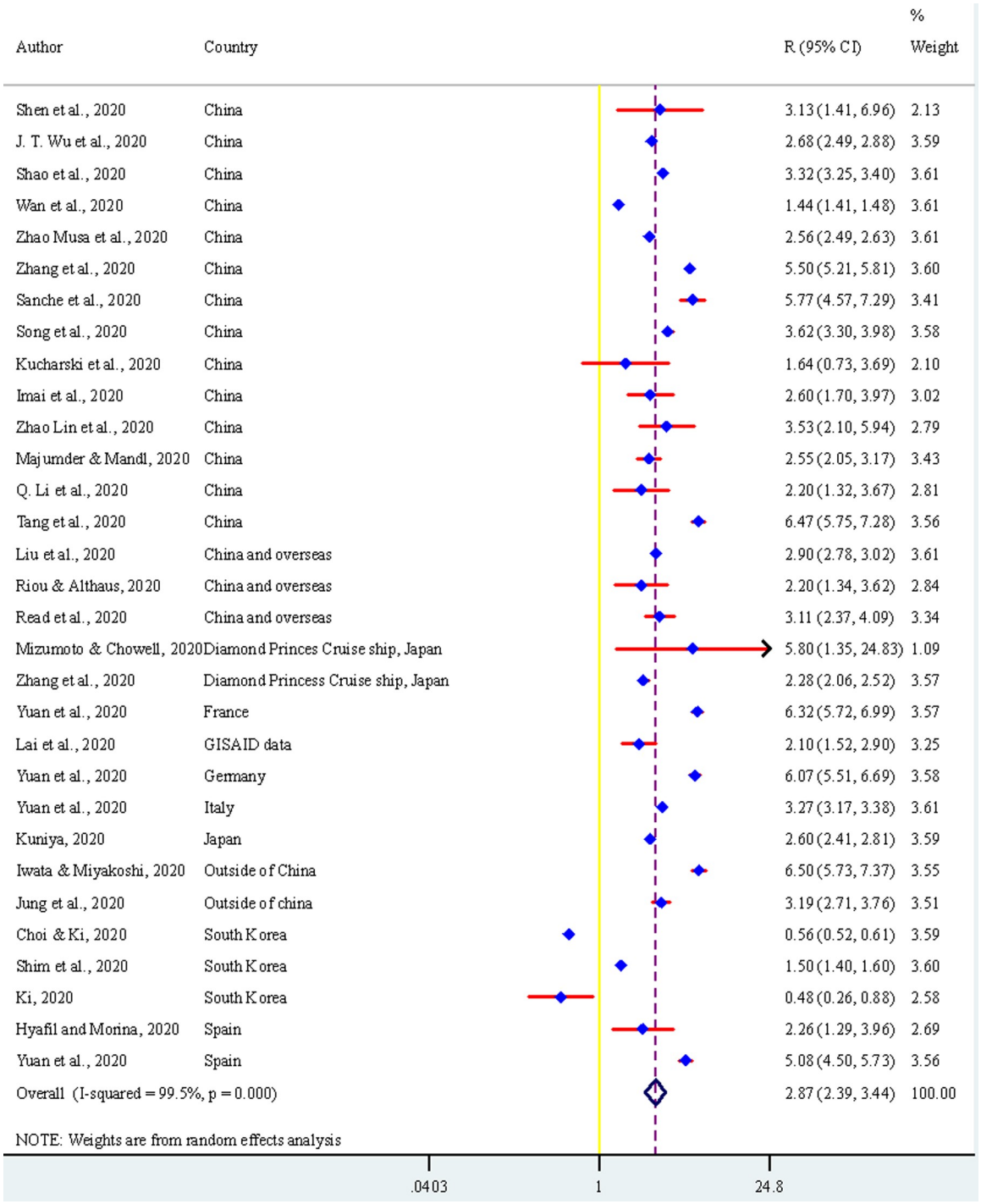

Fig 2. Estimated summary reproductive number of coronavirus based on 29 studies with 32 times report. Note: One study [36] reported estimates for four different countries: France, Germany, Italy, and Spain.

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done and infections were initially detected. For instance, the reproductive numbers of SARS and MERS were reduced to 0.95 (95% CI, 0.61–1,23) and 0.91 (95% CI, 0.36–1.44), respectively, after 3rd generation of the infection [56]. There are numerous reasons for such a higher reproductive number. First, biological facts of the infection rate and duration of contagion are

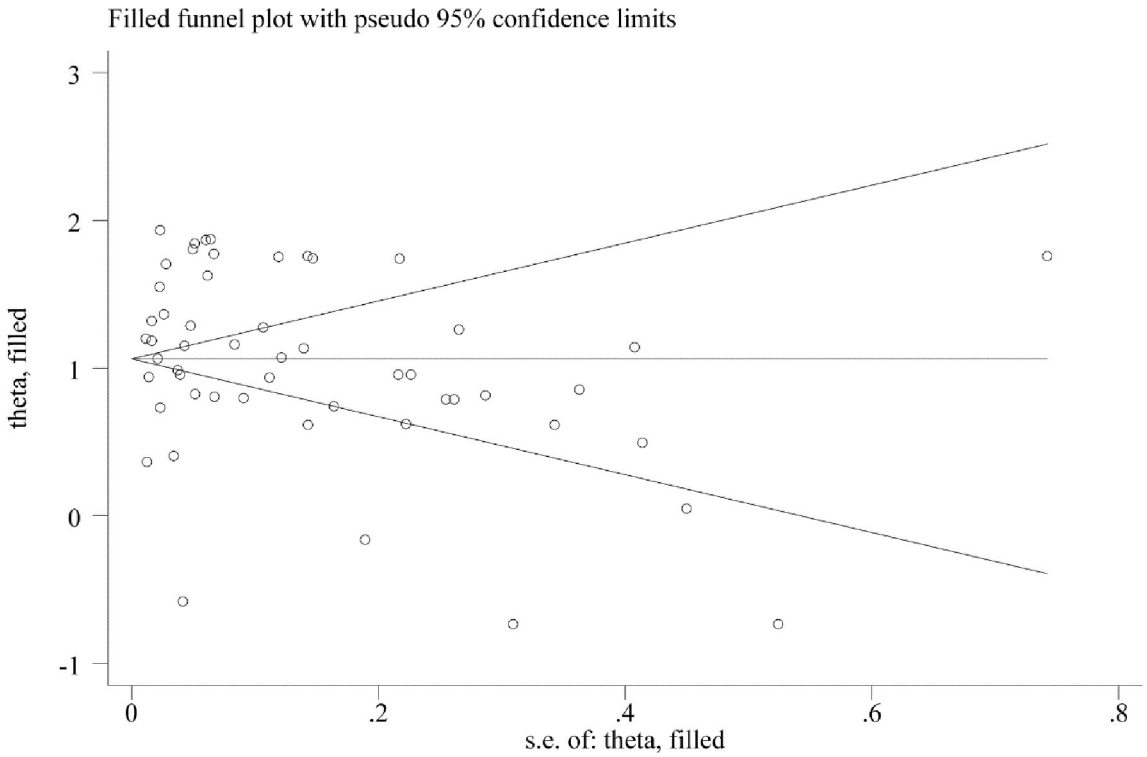

Fig 3. Funnel plot to identify publication bias including all studies used to estimate the summary reproductive number of coronavirus (Egger test p-value, 0.556).

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important to explain such higher reproductive number instead of strict control measures that placed to reduce new infections [57]. For instance, a person could be infected in numerous ways, such as gets physically contacted with the infected person or through environmental transmission by respiratory droplets [58]. Moreover, coronavirus infected patients may not show symptomatic characteristics upto two weeks of infection. This pre-symptomatic stage is another vital source to increase new infections exponentially as in this period an infected person is usually confounded in the community with other people. This risk is further increased significantly for the country where population density is high [59].

This study also found evidence of the very high (99.5%) heterogeneity of the estimated reproductive number. Along with the factors described above, the study's characteristics were found as the important sources for such higher heterogeneity. For instance, the reproductive number found higher for the countries where no restriction was applied, or restriction was applied in delayed. The forms of restrictions were to control people's movement, to monitor personal hygiene, and to impose to wearing a mask [60, 61]. These implications act to control virus transmission from an infected to the susceptible and reduce the new infections. These also affect the average transmissibility of coronavirus within the specific population and settings [62, 63].

Estimation models, assumptions applied, and estimation processes were empirical sources of variability of the estimated reproductive number of coronavirus [64]. For instance, studies included in this analysis were followed assumption of generation time (which is followed by the gamma distribution) or serial interval (which is followed by the poison distribution) which is an important source of heterogeneity [65–67]. The reason of such difference is the underlying concept: generation time refers to the average time between transmission the virus from an

Table 2. Sub-group analyses across study characteristics to explore the sources of heterogeneity of the estimated coronavirus's reproductive number.

Characteristics	Number of Reportings**	R (95% CI)	P	
			Heterogeneity	Meta-regression
Country				
China	14	3.14 (2.40–4.09)	<0.01	<0.01
China and overseas	3	2.90 (2.78–3.02)	0.490	
Outside of China	2	4.56 (2.27–9.17)	<0.01	
Japan	1	2.60 (2.41–2.81)	NA	
Diamond Princes Cruise ship, Japan	2	2.71 (1.33–5.52)	0.290	
South Korea	3	0.76 (0.34–1.70)	<0.01	
Italy	1	3.27 (3.16–3.38)	NA	
Germany	1	6.07 (5.51–6.69)	NA	
Spain	2	3.56 (1.62–7.82)	<0.01	
France	1	6.32 (5.72–6.99)	NA	
Global Initiative on Sharing Al Influenza Data	1	2.10 (1.52–2.90)	NA	
Method considered				
MLE	4	2.63 (2.18–3.18)	<0.01	<0.05
EGR	9	3.67 (2.91–4.64)	<0.01	
SEIR	6	1.97 (1.14–3.40)	<0.01	
MCMC	3	4.57 (2.68–7.78)	<0.01	
NGMA	3	4.36 (1.94–9.76)	0.280	
Others	6	2.11 (1.60–2.79)	<0.01	
Model considered				
SEIR model	11	2.81 (1.83–4.31)	<0.01	0.5216
SIR model	2	2.51 (2.05–3.08)	<0.01	
Epidemic curve	18	3.04 (2.60–3.55)	<0.01	
Number of cases				
≤3162	16	2.51 (1.91–3.28)	<0.01	0.7758
>3162	15	3.27 (2.47–4.31)	<0.01	
Type of reproductive number				
Basic reproductive number (R_o)	32[a]	3.17 (2.62–3.84)	<0.01	0.2047
Net reproductive number (R_e)	12[b]	1.95 (1.63–2.34)	<0.01	
Time-dependent reproductive number (R_t)	6[c]	4.42 (3.05–6.40)	<0.01	

Note: ** Number of studies 29 with reproductive number record 32 times (one study reported estimate for four different countries).

[a] Total 24 studies reported 32 different Ro,

[b] total 6 studies reported 12 different Re and

[c] total 3 studies reported 6 different Rt.

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infected person to the non-infected person whereas serial interval refers duration between onset of symptoms in an index case to the transmission in a secondary case [65, 66, 68]. Moreover, the estimated reproductive number generated by mathematical models is dependent on numerous decisions made by the researcher such as homogeneity or heterogeneity of the population considered; use a deterministic or stochastic approach and which distributions to be used to describe the probable values of parameters [57].

We found the type of reproductive number considered was another important source of heterogeneity of the estimated reproductive number. For instance, this study found the summary of the basic reproductive number was 1.95, around half of the summary of the estimated time-dependent reproductive number (4.42). Three previous meta-analyses found the

Table 3. Narrative synthesis of the studies included in the review.

Author, Study's Location	Model	Time/ period	Assumptions and method	Results
T. Zhou et al, 2020 [6], **China**[b]	SEIR model	before 26th Jan 2020	With generation time of 8.4 days and 10 days and using the exponential growth rate method	Estimated basic reproductive number was varied from 2.83 to 3.34 (for 8.4 days generation time) or 3.28 to 3.93 (for 10 days generation time).
Tang et al., 2020 [18], **China**[b]	SEIR model (with isolation, quarantined)	31 Dec 2019 to 15th Jan 2020	The incubation period was 7 days, ignoring the asymptomatic infection in the model and using the next generation matrix approach	The estimated reproductive number was 6.47 (5.71–7.23) during the control measures of isolation and quarantine are implementing.
T.-M. Chen et al., 2020 [22], **Wuhan, China**[b]	SEIR (Bat-Host-Reservoir-People network model)	10th Jan to 24th Jan 2020	Assuming the mean incubation 5.2 days, mean infectious period 5.8 days and using the next generation matrix approach	The basic reproduction number estimated was 2.30 from the reservoir to person. It was increased to 3.58 when reached person-to-person level transmission.
W. Zhou et al., 2020 [21], **China**[b]	SEIHR model extended by quarantined	before 10 Jan 2020	Parameterizing cumulative cases, deaths, the daily number of media reports and proportion of quarantined exposed by the virus and the estimation method was the next generation matrix approach	The basic reproductive number was 5.32.
Rocklov et al., 2020 [30], Diamond Princess Cruise ship, Japan[b]	SEIR model	21 Jan to 19 Feb 2020	The individual can mix randomly, the infectious period was 10 days and the contact rate were the same as early outbreak using the SEIR method.	The basic reproductive number was 14.80 without any intervention by using 79% infected persons in the ship. However, isolation and quarantine before 62.35% infected cases reduce this number to 1.78.
D'Arienzo & Coniglio, 2020 [35], **Italy**[b]	SIR model	25 Feb to 12 Mar 2020	Nearly everyone in Italy was considered as susceptible using the general SEIR method	The basic reproductive number was 3.10 while the number varies from 2.46 to 3.09 in different region across Italy.
Najafi et al., 2020 [47], Western Iran[b]	Infector-Infectee model	22 Feb to 9 Apr 2020	The Weibull distribution provides the best fit for GT and the mean 5.71 days and SD 3.89 days	The time-dependent reproductive number varied from 0.79 to1.88 for 7-day and from 0.92 to 1.64 for 14-day time-lapse. The decreasing trend inverses in April for both 7- and 14-day time-lapses.
Wahaibi et al., 2020 [48], Oman	Infector-Infectee model	24 Feb to 03 Jun 2020	Median SI is estimated 6 with inter-quartile range 3–14 that follow the gamma distribution.	The time-dependent reproductive number decreased from 3.70 (2.80–4.60) in mid-March to 1.30 (1.20–1.50) in late April 2020 due to non-pharmaceutical interventions.
Al-Raeei, 2020 [49], Different countries	SIR model	Upto 30 July 2020	Based on the estimated coefficient of infection, recovery and mortality.	The basic reproductive number varies from 1.00 to 2.79 in different countries.
Sarkar et al., 2020 [50], India	SEIR model	Upto 30 April 2020	Used next-generation matrix model	The average estimated basic reproductive number was 2.05.
Aldila et al., 2020 [51], Indonesia	SEIR model	03 Mar to 10 Apr 2020	Population is mixed homogeneously.	The basic reproductive number was reduced to 1.22 after implementation of movement control order (MCO) from 1.75.
Bagal et al., 2020 [52], India	SIR model	22 Jan to 31 May 2020	Lockdown protocol homogeneously implemented across the country	The net-reproductive number was estimated at 1.37.
Ullah and Khan, 2020 [53], Pakistan	SEIR model	01 Mar to 31 May 2020	Hospitalized people can transmit after interacting with the general susceptible people	The average estimated basic reproductive number was 1.87

Note: Studies included in the meta-analysis were summarized in Table 1.

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summary estimate of the basic reproductive number ranged from 3.15 and 3.38 [12–14]. The sources of such heterogeneity are the underlying assumptions and the period between the initial infection and date of estimation [65, 69].

This study was first of its kind that provides an estimation of reproductive numbers based on the global literature. Moreover, we have considered the heterogeneity of the reproductive numbers estimated worldwide and explored the sources of heterogeneity across the characteristics of the selected papers. However, many other factors may explain the sources of

heterogeneity of the reported reproductive number of coronavirus worldwide which was not explored in this study because of the lack of data.

Conclusion

The estimated summary reproductive number was 2.87. We found evidence of higher heterogeneity of the reproductive number reported worldwide. We found the country for which the reproductive number was estimated and the method that was used to estimate the reproductive number were significant for such heterogeneity. Our analyses indicate the possibility of a significant increase of coronavirus infections in near future. Strengthening existing preventive measures, as well as new policies and programs, are important to reduce new infections.

Supporting information

S1 File.
(DOCX)

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