Review

Epidemiology of Covid-19

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Epidemiology of COVID-19

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Abstract: We provide a summary of various epidemiological parameters related to COVID-19 such as incubation period, serial interval and other parameters. Understanding these parameters is important for developing prevention strategies. SARS-CoV-2 can be transmitted by droplets and close contact, but there is evidence of airborne transmission. Aerosol-generating procedures have been identified as one of the specific risk factors for healthcare workers. Super-spreading events refer to situations where a small number of individuals cause the majority of infections. The basic reproductive number (R0) and the spread parameter (k) are used to characterise the transmissibility of the disease. Estimated values for R0 range from 2 to 3 and the estimated value for k is 0.1.The duration of infectiousness depends on viral load and shedding. Viral load varies according to factors such as clinical spectrum, type of variant and vaccination status. The relationship between viral load and infectivity is not fully understood.With regard to the frequency of symptoms and signs of COVID-19, fever, cough, fatigue and dyspnoea are common. The prevalence of olfactory and gustatory dysfunction (OGD) varies between studies and countries. Age and comorbidities are factors associated with olfactory dysfunction.Estimates of the proportion of asymptomatic patients range from 6% to 96%. Asymptomatic transmission is considered likely and is important for control measures.We reviewed the quantitative semiology of COVID-19 is reported on sensitivity, specificity and likelihood ratios of signs.Finally, we also review risk factors for COVID-19 (including health care workers), co-infections, and epidemiology of variants..

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1. Introduction

Coronavirus disease 2019 (COVID-19) has caused significant public health burden and global health threats.

Estimating the epidemiological parameters of a disease, in addition to theoretical knowledge, makes it possible to establish or justify a prevention policy. For example, a good estimate of the transmission routes makes it possible to favour the use of personal protective devices such as surgical masks, or to favour a social approach such as distancing, or to combine several approaches.

The aim of this work is to synthesise the data on the different epidemiological parameters of Covid 19, focusing on the main meta-analyses or literature reviews published in recent years.

2. Materials and Methods

We conducted a comprehensive search using electronic scientific resources such as PubMed, Science Direct, Google Scholar and MedRxiv between 2020 and June 2023. Our aim was to identify relevant English-language articles using epidemiological terms such as "prevalence", "period of incubation", "risk factors", etc. in relation to "COVID-19", "SARS-CoV-2" or "severe acute respiratory syndrome".

Our focus was primarily on literature reviews and meta-analyses. We also searched for relevant original articles on the topic.

To supplement our search, we manually included references to recent research and thoroughly checked the reference lists of selected literature.

To be included in this review, articles had to meet the following eligibility criteria: (1) published in English and (2) meta-analyses, narrative reviews or original research articles.

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3. Results

3.1. Transmission and Infectivity

- Transmission and dichotomy

As pointed out by Escandon et al. [1], several false dichotomies have been used to polarize debates while oversimplifying complex issues.

The following words are commonly used in airborne terminology: airborne, aerosol, droplet, droplet nuclei and particle. Differences in understanding of airborne terminology between clinicians, aerosol scientists and the general public can be found in Romano-Bertrand [2].

Like many respiratory viruses, SARS-Cov-2, whatever variant it is, is transmitted by droplets and close contact [3]. However, there is evidence of airborne transmission [4].

Airborne transmission occurs through the diffusion of a continuum of infected particles of different sizes: large respiratory droplets (6-100 μm) to microparticulate aerosol (≤ 2-5 μm).

- Aerosol-generating procedures (AGP)

See "Specific risk factors for Health Care Workers (HCW)".

3.2. Superspreading Events and Infectious Doses

The transmissibility of infectious diseases can be characterised by at least two parameters: the basic reproductive number (R0) and the dispersion parameter, kappa (k). R0 describes, on average, how many individuals in a susceptible population will be infected by someone with that disease, and k describes the variation in individual infectiousness [5]. The smaller the value of k is, the greater the variation will be. This means that fewer cases causes the majority of infections, and a larger proportion of infections tend to be linked to large clusters via superspreading events (cf. SARS and MERS). This phenomenon is called overdispersion in transmission [5].

The consensus estimate for R0 is between 2 and 3 [6]. See Table 1.

Table 1. Some estimates of epidemiological parameters of SARS-CoV-2.

Authors, years	Incubation period (days)	Serial interval (days)	Mean generation time	R0	k
Xin et al. [94]. Meta-analysis	pooled median of the point estimates of: Mean: 6.3 (range: 1.8-11.9) Median: 5.4 (range: 2.0-17.9) 95th percentile: 13.1 (range: 3.2-17.8) Mean incubation: 6.5 (95%CI: 5.9-7.1)	weighted pooled mean: 5.2 (95%CI: 4.9–5.5)			
Lau et al. [95] Jointly estimation of generation time	Mean : 4.8 (95% CI: 4.1-5.6)		Mean: 5.7 days (95% CI: 4.8-6.5)	2.2 (95% CI: 1.9-2.4). (based on the estimated generation time)	

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and incubation period, accounting for sampling biases.				
Salzberger et al. [6],	Median: 5.7 (99% CI: 2-14)	4	2-3 (Range: 1.7-14.8)	0.1 (0.05-0.2)
Du et al [9] Meta-analysis				Mean estimates of dispersion parameters Range: 0.06-2.97 Pooled estimate: 0.55 (95% CI: 0.30, 0.79),
Wang et al. [8]				Range: 0.1-5.0.
Park et al. [7] Systematic review of 21 estimates of parameters	4 to 6.	4-8	Between 2.0 and 3.0 (range: 1.9-6.5).	
Khalili et al. [96] Meta-analysis	Pooled mean: 5.68 (99% CI: 4.78- 6.59).			

More specifically, acccording to the systematic review (SR) by Park at al. [7], of 21 estimates for R0 ranging from 1.9 to 6.5, 13 were between 2.0 and 3.0.

Superspreading events have been reported, with k estimated to be 0.1 [6].

Wang et al.'s meta-analysis (MA) [8] included 60 estimates of transmission heterogeneity from 26 outbreaks studies. The majority (90%) of k estimates for coronavirus were small, with values less than 1 (indicating an over-dispersed transmission). The point estimates of k for COVID-19 ranged between 0.1 and 5.0.

More specifically for SARS-CoV-2 and according to Du et al.'s MA [9], the mean estimates of k ranged from 0.06 to 2.97 accross eight countries (China, USA, India, Indonesia, Israel, Japan, New Zealand, and Singapore). Similar estimates were reported by Wegehaupt et al. (the mean k estimates ranged from 0.04 to 2.97) [10].

The pooled estimate was 0.55 (95% CI: 0.30-0.79), with changing means across countries and slightly decreasing with increasing R0. The expected proportion of cases accounting for 80% of all transmissions is 19% (95% CrI: 7-34) [9].

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An accurate quantitative estimate of the infective dose of SARS-CoV-2 in humans is not currently available. Karimzadeh et al. [11] suggest that it is small, perhaps around 100 particles.

Prentiss et al. [12], applied an aerosol transmission model to some well-known cases. Despite the uncertainties in the values of some parameters of the superspreading events in their model, they estimated an infectious dose of around 300 to 2,000 virions, which is similar to published values for influenza.

3.3. Period of Infectiousness (Contagiousness)

Period of infectiousness (PI) depends on viral load and viral shedding which are related.

Viral load varies according to many parameters:

(i) clinical spectrum: patients with severe disease have samples whose culture remains positive for a longer period [13], a period that is even longer in immunocompromised patients [13,14].

(ii) type of variant: the Delta variant has a higher viral load and lasts longer than the previous variants [15]. Data on the Omicron variant are sparse.

There may be a difference between delta and omega variants, as reported by Yuasa et al.[16]. The median copy number for Delta variant was 1.5 × 10(5) copies/µl (n = 174) vs 1.2 × 10(5) copies/µl (n = 328) for Omicron (p=0.052). There was, on the other hand, no statistically significant difference between Omicron BA.1 and BA.2.

(iii) vaccination: an infected person has an initial level of viral load that is identical to that of an unvaccinated person but which declines more rapidly [17,18].

There is a large variability in the methods used to estimate the PI, with a correspondingly large variability in the results.

For example, in Byrne's review and MA [19], the median presymptomatic PI varied between studies from <1-4 days.

The estimated mean time from symptom onset to two negative RT-PCR tests was 13.4 days (95%CI: 10.9-15.8), but was shorter when studies included children or less severe cases.

The estimated mean time from symptom onset to hospital discharge or death (maximum possible PI) was 18.1 days (95%CI: 15.1-21.0).

The relationship between the level of viral load level and contagiousness is not fully understood.

Okita et al. [20] in their MA (100 articles and 13,431 patients) estimated the duration of SARS-CoV-2 RNA positivity. It was 18.29 days in the upper respiratory tract samples (95% CI: 17.00-19.89). The duration in the sputum and the stool was longer, while that in the blood was shorter (23.79, 22.38 and 14.60 days, respectively). The duration in the upper respiratory tract samples was longer in patients who were older, had comorbidities, were more severely ill and were treated with glucocorticoids.

In a multivariate analysis, Li et al. [21] confirmed the association between older age and duration of shedding. Older age was the only independent risk factor associated with slow viral decline during the Omicron-dominant 2022 COVID-19 wave.

The patient's Ct should not be considered as an indicator of infectiousness, since it could not be correlated with the disseminated viral load [22]. However this result is based on a small sample size (n=22; no viral load was found, in coughs or air after the third day of symptoms) and is consistent with the proposed hypotheses of superspreaders.

3.4. Incubation; Inter Serial Interval and Other Parameters

Briefly and according to Siordia et al. [3], 2020, incubation is defined between J0 and J5; symptoms occur between J5 and J15; resolution of symptoms occur between J15 and J17. For transmission periods, latent period occurs between J0 and J3; infectious period occurs between J3 and J17.

The serial interval is commonly interpreted as the time between the onset of symptoms in sequentially infected individuals, within a chain of transmission. It is a key epidemiological quantity involved in estimating the reproduction number. The serial interval is closely related to other key

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quantities, including the incubation period and the generation interval (the time between sequential infections) [23].

Challen et al. [23] reported the following estimates in their MA : distributions for the serial interval: mean 5.9 (95% CI: 5.2-6.7) and SD 4.1 (95% CI: 3.8-4.7) days (empirical distribution); generation interval: mean 4.9 (95% CI: 4.2-5.5) and SD 2.0 (95% CI: 0.5-3.2) days (fitted gamma distribution); incubation period: mean 5.2 (95% CI: 4.9-5.5) and SD 5.5 (95% CI: 5.1-5.9) days (fitted lognormaldistribution).

Madewell et al. [24] have focused on the Delta and Omicron variants in their review. Mean serial interval for included studies ranged from 2.3 to 5.8 days for Delta and 2.1 to 4.8 days for Omicron. The pooled mean serial interval for Delta was 3.9 days (95% CI: 3.4–4.3) and Omicron was 3.2 days (95% CI: 2.9–3.5). Mean estimated serial interval for BA.1 was 3.3 days (95% CI: 2.8–3.7), BA.2 was 2.9 days (95% CI: 2.7–3.1), and BA.5 was 2.3 days (95% CI: 1.6–3.1).

Various estimates of incubation period, serial interval and R0 are available from numerous studies.

See Table 1: some estimates of epidemiological parameters of SARS-CoV-2

3.5. Clinical Epidemiology

3.5.1. Frequency of Signs

The most common symptoms of Covid-19 in the first wave were fever (82.2 %), cough (61.7 %), fatigue (44.0 %), dyspnea (41 %) and anorexia (40.0 %). These symptoms are similar to those seen in other viral respiratory diseases. Other symptoms include myalgia (22.7 %), sore throat (15.1 %), nausea (9.4 %), dizziness (9.4 %), diarrhea (8.4 %), headache (6.7 %), vomiting (3.6 %) and abdominal pain (2.2 %) [3].

Older patients with COVID-19 were more likely to present without the most common symptoms, as reported by Goldberg et al. [25] (4536 in emergency department (ED) patients). Cough was the most common presenting complaint in all age groups (18-64, 65-74, and 75+): 71%, 67%, and 59%, respectively ($p < 0.001$). Neurological symptoms, especially altered mental status, were more common in older adults (2%, 11%, 26%; $p < 0.001$). Patients over 75 years of age had the highest odds of admission to the ED at the index visit of all age groups (adjusted odds ratio [aOR] 6.66; 95% CI 5.23-8.56), 30-day hospitalisation (aOR 7.44; 95% CI 5.63-9.99), and severe COVID-19 (aOR 4.26; 95% CI 3.45-5.27). However, alternative presentations of COVID-19 in older ED patients were not associated with increased odds of mechanical ventilation or death.

Olfactory and gustatory dysfunctions (OGD) is an important early symptom of COVID-19 infection [26,27]

Hannum et al [28] investigated how methodological differences (direct vs. self-report measures) may affect these estimates. Prevalence estimates were slightly but not significantly higher in studies using direct versus self-report methods.

According to Wu et al.'s MA [29], the pooled prevalence of olfactory dysfunction in COVID-19 was 53.56% (range 5.6-100%; 95% CI: 40.25-66.61%).

The prevalence of gustatory dysfunction was 43.93% (range 1.5-85.18%, 95% CI 28.72-59.74%), just behind fever (62.22%), cough (64.74%) and fatigue (56.74%). The prevalence of gustatory dysfunction was lower in the subgroup with objective evaluation than in those without (9.91% vs. 49.21%, $p<0.001$).

OGD vary between countries [30] (MA of 83 studies, 27 492 patients). The pooled prevalence of olfactory dysfunction was 47.85% (95% CI: 41.2-54.5). Olfactory dysfunction was 54.40% in European, 51.11% in North American, 31.39% in Asian, and 10.71% Australian COVID-19 patients. Anosmia, hyposmia, and dysosmia were observed in 35.39%, 36.15%, and 2.53% of patients, respectively. There were discrepancies in the results of studies with objective (higher prevalence) versus subjective (lower prevalence) evaluations.

For Galluzzi et al. [31], current smoking and history of allergy (especially respiratory) significantly increase risk of smell loss in COVID-19 patients. However, Liu et al. [32] (MA of 26

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studies; 13813 patients) showed that sex, age, smoking and comorbidity of patients with COVID-19 had no effect on gustatory dysfunction. Older patients with COVID-19 are more likely to experience olfactory dysfunction.

Several other clinical manifestations associated with SARS-CoV-2 have been reported.

Ousseiran et al. [33] showed in their MA that COVID-19 can be manifested by a wide range of neurological symptoms reported either in the early phase or during the course of the disease. However, a detailed understanding of these manifestations is required.

Li et al. [34] in their MA estimated a pooled prevalence of cutaneous manifestations of 5.6% (95% CI: 0.040-0.076), with the prevalence of detailed types as follows: maculopapular rash 2%, livedoid lesions 1.4%, petechial lesions 1.1%, urticaria 0.8%, pernio-like lesions 0.5%, vesicular lesions 0.3%.

Psychological manifestations associated with SARS-CoV-2 have also been reported. For example, in their umbrella review, Mazza et al. [35] estimated the prevalence of depression to range from 12% to 55%, with a pooled prevalence of depression of 31% (95% CI:25-38%) (with high and significant heterogeneity and publication bias).

Concerning long Covid, prevalence of the numerous signs and symptoms have been reported in detail by Natarajan et al. [36] in their MA.

See also Chen et al's MA [37] for a report on the worldwide prevalence of post COVID-19 condition.

3.5.2. Proportion of Asymptomatic Patients

Asymptomatic infections are silent transmitters of the SARS-CoV-2 virus.

After reviewing the evidence, the COVID-19 Rapid Guidance Working Party concluded that: "(i) presymptomatic transmission (meaning that an index case has no symptoms during the period of exposure of its close contacts, but later develops symptoms) is confirmed. (ii) Asymptomatic transmission (i.e. an index case never develops symptoms or signs of infection) is probable" [38].

Estimating the proportions of asymptomatic and presymptomatic infections is difficult but critical, as it can affect control measures.

If the predominant mode of transmission is from symptomatic individuals, then strategies should focus on testing, followed by isolation of infected individuals and quarantine of their contacts. However, if most transmission is from asymptomatic individuals, social distancing measures that reduce contact with potentially infectious individuals should be prioritised, supported by active case finding through testing of asymptomatic individuals [39].

Estimates of the asymptomatic proportion of Covid-19 infections found in the literature vary widely, ranging from 6% to 96% [40].

Wang et al. [41] found that based on high quality studies, asymptomatic infections account for at least one third of all cases, whereas based on systematic reviews and meta-analyses, the proportion is around one fifth.

Ravindra et al. [42] in and MA of clusters showed asymptomatic transmission rates in family clusters, adults, children and healthcare workers of 15.72%, 29.48%, 24.09% and 0%, respectively. Overall, asymptomatic transmission was 24.51% (95% CI: 14.38-36.02).

Based on Buitago-Garcia's MA [39], most SARS-CoV-2 infections were not persistently asymptomatic, and asymptomatic infections were less infectious than symptomatic infections.

Finally, using Bayesian inference to account for methodological difficulties, Cahoy et al. [43] provided several re-analysed estimates of asymptomatic COVID-19 infection rates.

Asymptomatic transmission is likely related to age, with the proportion of asymptomatic and severe patients increasing across 10-year age groups [44].

Based on Buitago Garcia's MA [39], most SARS-CoV-2 infections were not persistently asymptomatic, and asymptomatic infections were less infectious than symptomatic infections.

The risk of asymptomatic infection between fully vaccinated and unvaccinated individuals was estimated by Lee et al. [45] (MA of 18 studies). It was not statistically significant with an RR of 0.56 (95% CI: 0.27-1.19).

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3.5.3. Quantitative Semiology: Sensibility, Specificity, Likelihood Ratio

Sensitivity, specificity and likelihood ratio of signs have been reviewed by Struyf et al. [46]. The prospective studies included (42 studies; 52 608 patients) did not clearly distinguish between mild COVID-19 disease and COVID-19 pneumonia. The results are therefore presented for both conditions together. In addition, several of the trials had a high risk of patient selection bias.

Twenty-four studies assessed combinations of different signs and symptoms, mostly combining olfactory symptoms; 96 symptoms or combinations of signs and symptoms were found. See Table 2: quantitative semiology (Struyf et al. 2022) for details.

Table 2. Quantitative semiology [46].

Signs	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)
Cough (11 studies)	62.4% (50.6%-72.9%)	45.4% (33.5%-57.9%)	1.14 (1.04-1.25)
Fever (7 studies)	37.6% (23.4%-54.3%)	75.2% (56.3%-87.8%).	1.52 (1.10-2.10).
Sore throat (20 studies)	21.2% (13.5%-31.6%);	69.5% (58.1%-78.9%);	0.694 (0.565-0.853)
Dyspnoea (12 studies)	23.3% (16.4%-31.9%)	75.7% (65.2%-83.9%)	0.96 (0.83-1.11)
Fatigue (8 studies)	40.2% (19.4%-65.1%)	73.6% (48.4%-89.3%).	1.52 (1.21 to 1.91)
Anosmia alone (7 studies)	26.4% (13.8%-44.6%)	94.2% (90.6%-96.5	4.55 (3.46-5.97)
Ageusia alone (5 studies)	23.2% (10.6%-43.3%)	92.6% (83.1%-97.0%).	3.14 (1.79-5.51).
Anosmia or ageusia (6 studies)	39.2% (26.5% to 53.6%)	92.1% (84.5%-96.2%).	4.99 (3.22-7.75)

3.6. Special Cases

3.6.1. Nosocomial Contaminations

The sources of infection highlighted in the study of cases of infection among healthcare workers are either community (family) or intra-hospital. In the latter case, it is either contamination between professionals, especially during shared meals, or situations where the individual and collective barrier measures mentioned above are not optimally respected [47–50].

These findings corroborate those of the French ComCor study, which included more than 160 000 participants with acute SARS-CoV-2 infection at the beginning of 2021. This study made it possible to describe the places and circumstances of contamination by this virus [51].

Hospital-acquired COVID-19 infections in patients before the introduction of COVID-19 vaccinations were studied by Ngandu et al. [52]. 45 articles were included in their review. The proportion of COVID-19 HAIs ranged from 0% when strict NPPIs were applied to 65% otherwise. Estimates of COVID-19 HAIs did not differ by country, but were lower in studies conducted after the introduction of NPPIs and in specialised surgical hospitals. Studies conducted before the introduction of NPPIs or in long-term care and psychiatric wards often reported high estimates of HAIs. Although there was no clear trend in general wards, wards in academic hospitals managed to

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reduce HAI rates under strict NPPI protocols. Surgical wards, in contrast to psychiatric wards, were effective in preventing COVID 19 HAIs with tailored NPPIs.

Braun et al. [48] (Braun et al. 2021) investigated SARS-CoV-2 infection clusters involving 95 HCP and 137 possible patient contact sequences. The majority of HCP infections could not be linked to a patient or healthcare worker (55 of 95 [57.9%]) and were genetically similar to viruses circulating concurrently in the community. They found that 10.5% of HCP infections (10 out of 95) could be traced to a healthcare worker. Strikingly, only 4.2% (4 out of 95) could be traced to a patient source. They concluded that healthcare-associated infections place an additional burden on the healthcare system and put patients, healthcare workers and communities at risk. They found no evidence of healthcare-associated transmission in the majority of HCP infections studied. Although they cannot rule out the possibility of cryptic healthcare-associated transmission, it appears that HCP are most commonly infected with SARS-CoV-2 through community exposure.

3.6.2. Children

Vosoughi et al. [53] focused on Covid-19 in children in their MA. They estimated an overall rate of involvement at 12% (95% CI: 9-15) in children. The proportion of household exposure was calculated to be 50.99% (95% CI: 20.80-80.80) and the proportion of admitted cases was calculated to be 45% (95% CI: 24–67). In addition, the prevalence of cough, fatigue, fever and dyspnea was calculated to be 25% (95% CI: 0.16–0.36), 9% (95% CI: 0.03-0.18), 33% (95% CI: 0.21-0.47) and 9% (95% CI: 0.04-0.15), respectively. An estimated that 4% (95% CI: 1-8) of cases required admission to an intensive care unit.

3.7. Risk Factors

Li et al. [54] summarised the main risk factors for the early phase of Covid-19 in their MA (212 studies from 11 countries/regions; 281 461 patients).

Underlying immunosuppression, diabetes and malignancy were most strongly associated with severe COVID-19, while older age, male sex, diabetes and hypertension were also associated with higher mortality. Gastrointestinal (nausea, vomiting, abdominal pain) and respiratory symptoms (shortness of breath, chest pain) were associated with severe COVID-19, while pneumonia and end-organ failure were associated with mortality.

We will describe the risks associated with: infection and clinical symptoms; severity of illness (hospitalisation, readmission and ICU admission); long-term complications (long COVID); death. Specific risk factors for HCWs are also described. See Table 3: risk factors

Table 3. Risk factors.

Risk factors	Adverse events Susceptibilityin patients with Covid-19	Hospitalisation (ICU)	Readmission	Long Covid	Death
Age			[97] Others: diabetes, high length of stay, COPD, CKD, liver disease, metastatic disease, and CAD.		[76] pooled OR (pOR): 2.61 (95% CI: 1.75-3.47) pooled Hazard Ratio (pHR) : 1.31 (95% CI: 1.11-1.51) [77].

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				OR: 1.05 (95% CI: 1.04-1.07) per one year of age increase; 10 studies)
Gender (Male)				[76] pOR : 1.45 (95% CI : 1.41-1.51) pHR : 1.24 (95% CI : 1.07-1.41) [77]. OR: 1.32 (95% CI: 1.18-1.48; 20 studies)
Immunity and endocrine system	[55]			
Hypertension		[98] Increased risk of COVID-19-related hospitalisations	[61] Compared with nonsevere (non-ICU) patients, severe (ICU) disease OR: 2.40 (P < .001)	[76]
Obesity		[98] Risk of COVID-19-related hospitalisations Overweight : Risk of COVID-19-related hospitalisations OR 1.19 (95% CI: 1.12 to 1.28; 21 studies) Obesity:		[98] Death: OR: 1.25 (95% CI: 1.19-1.32; 77 studies) [76] [77]. OR: 1.59 (95% CI: 1.02-2.48; 4 studies)

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	Risk of COVID-19-related hospitalisations OR: 1.72 (95% CI: 1.62 to 1.84; 58 studies) [99] Obesity (body mass index ≥ 30 kg/m2), as compared to individuals without obesity *Increased risk for hospitalization OR: 1.40-2.4	[99] *Admission to the intensive care unit OR: 1.30-2.32 *invasive mechanical ventilation OR: 1.47-2.63
Overweight	[98] Increased risk of COVID-19-related hospitalisations.	[98] Death: OR 1.02 (95% CI: 0.92-1.13; 21 studies)
Extreme obesity	[98] risk of COVID-19-related hospitalisations OR 2.53 (95% CI: 1.67-3.84; 12 studies) Linear dose-response relationship between these obesity categories and COVID-19 outcomes [98] . But the strength of the association has	[98] Death: OR: 2.06 (95% CI 1.76 to 3.00; 19 studies)

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	decreased over time [100].			
Cerebrovascular diseases		[61] OR: 2.68 (P = .008)		
Coronary heart disease		[61] OR: 2.66 (P < .001)		
CVD(Cardio-Vascular Disease)				[76]
Diabetes	[98] Increased risk of COVID-19-related hospitalisations	[61] OR: 3.17 (P < .001)	[97]	[76] [77]. OR: 1.25 (95% CI: 1.11-1.40; 11 studies)
Smoking		[61] Compared with nonsevere (non-ICU) patients (p=003)		[76] Current smoker pOR: 1.42 (95% CI 1.01-1.83) [77]. Current smoker Statistically non-significant (5 studies)
COPD (chronic obstructive pulmonary disease)		[61] OR: 5.08 (P < .001)	[97]	[76] [77] Statistically non-significant (5 studies)
CKD			[97]	
Liver disease			[97]	

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			[76]
Malignancy		[61] OR: 2.21 (P = .040).	[77]. Statistically non-significant (4 studies)
Metastatic disease		[97]	
Acute kidney injury			[76]
Chronic kidney diseases			[77]. OR: 1.57 (95% CI: 1.27-1.93; 6 studies)
Increase D-dimer			[76]
Genetic factors (Higher expression, polymorphisms, mutations, and deletions of several genes…)	[101].	[101].	

3.7.1. Susceptibility to Covid-19

Regarding susceptibility to Covid-19, age and related immunosenescence, imunity and endocrine system [55] are important risk factors.

- ABO blood group

Since the beginning of the COVID-19 pandemic, ABO blood group has been described as a possible biological marker of susceptibility to the disease.

Banchelli et al's MA [56] showed associations between blood groups and SARS-CoV-2 infection. Group O was slightly less associated with infection, as compared to the other three blood groups (OR: 0.91; 95% CI: 0.85-0.99; p = 0.02). Conversely, group A was slightly more associated with infection, as compared to the other three groups (OR: 1.06; 95% CI: 1.00-1.13, p = 0.04). But these results seem fragile [57].

This association between group O and Covid-19 infection have also been reported in Gutiérrez-Valencia et al.'s MA [58], with an OR of 0.88 (95% CI: 0.82-0.94) and no effect on disease prognosis of the. Group A may be a risk factor for COVID-19 infection (OR: 1.08; 95% CI: 1.02-1.15) and mortality (OR 1.13; 95% CI: 1.03-1.23). Group B may not modify the risk of COVID-19 infection but may have a lower risk of mortality (OR 0.88; 95% CI: 0.80-0.96).

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Jerico et al. [59] reported an association between patients with blood group O and their lower susceptibility to SARS-CoV-2 infection, both for those admitted to the hospital ward and for those who requiring admission to the ICU.

Enguita-Germán et al. [60] also observed a protective role of group O and a higher risk of Covid-19 infection in group A. However, no association was observed between blood groups and hospitalisation, ICU admission, or death in SARS-CoV-2 infected individuals.

However, these findings on ABO blood group should be interpreted with caution, considering the high heterogeneity found between the studies.

- Risk of COVID-19-related ICU admissions

In their MA (12 cohort studies; 2 445 patients), Li et al. [61] examined the clinical characteristics and outcomes of confirmed COVID-19 cases and compared severe (ICU) and non-severe (non-ICU) groups. Compared with non-severe (non-ICU) patients, severe (ICU) disease was associated with a smoking history and comorbidities. See Table 3: risk factors.

Significant differences were found between the two groups for fever, dyspnea, decreased lymphocyte and platelet counts, and increased leukocyte count, C-reactive protein, procalcitonin, lactose dehydrogenase, aspartate aminotransferase, alanine aminotransferase, creatinine kinase, and creatinine levels.

In Lin et al. 2021 [62], detectable viral RNA in anal swabs (hazard ratio [HR]: 2.50; 95% CI: 1.20-5.24), elevated C-reactive protein (HR: 3.14; 95% CI: 1.35-7.32) and lymphocytopenia (HR, 3.12; 95% CI: 1.46-6.67) were independently associated with ICU admission. The cumulative incidence of ICU admission was higher in patients with detectable viral RNA in anal swabs (26.3% vs 10.7%, p = .006).

3.7.2. Specific Risk Factors for Health Care Workers (HCW)

- Frontline HCWs

Compared to non-frontline HCWs, frontline HCWs were not at increased risk of infection (OR: 1.34; 95% CI: 0.75-2.40))[63].

The nationwide matched case-control study by Belan et al. [64] showed that HCWs were more likely to acquire COVID-19 in their personal environment than in their professional activities. Independent risk factors for COVID-19 in HCWs were exposure to an infected person outside work (adjusted OR: 19.9; 95% CI: 12.4-31.9), an infected colleague (2.26 [1.53-3.33]) or COVID-19 patients (2.37 [1.66-3.40]). Compared to medical professions, being a nurse (3.79 [2.50-5.76]) or a nurse's aide (9.08 [5.30-15.5]) was associated with COVID-19.

See Leal et al. [65] for further comments on this topic.

- Personal protective equipment (PPE):

Schoberer et al. [66], analysed 461 reviews (and 208 primary studies, of which 16 were systematic reviews) and found that wearing PPE conferred significant protection against infection with COVID-19 compared with not wearing adequate PPE. They also found that wearing face masks can significantly protect HCWs from infection (OR: 0.16; 95% CI: 0.04-0.58; moderate quality of evidence). No effect was found for wearing gloves and gowns (very low quality of evidence)

Thorough hand hygiene and the use of appropriate PPE showed a protective but not statistically significant effect compared to the absence of appropriate PPE (OR: 0.43; 95% CI: 0.11 to 1.64; very low quality of evidence).

In Dzinamarira et al. 2022[67], HCWs who reported use PPE were 29% (95% CI: 16%-41%) less likely to test positive for COVID-19.

- Aerosol generating procedure (AGP)

It is important to consider AGP. Examples are intubation, extubation and aerosol therapy.

There are as many lists of these AGP as there are learned societies concerned, not forgetting that the composition of these lists varies from country to country.

The questions that arise are: are certain procedures well known as aerosol generators really so? If so, what is the level of evidence?

Already in 2012, Tran et al. [68] published a MA on the association between acute respiratory infections and AGPs. They suggested that certain procedures that could potentially generate aerosols

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were a risk factor for transmission of infection. The most commonly identified association was tracheal intubation. However, the level of scientific evidence was low.

The findings of Tran et al. [68] were confirmed by a review of the literature by Harding et al. [69]. They concluded: (i) that there is no evidence of an increased risk of infection associated with AGPs for SARS-CoV-2; (ii) that there is, however, a risk specific to intubation for related viruses; and (iii) that it is possible that other AGPs pose such a risk.

Brown et al. [70] showed that intubation produced fewer aerosols than extubation, which in turn produced fewer aerosols than coughing.

Chan et al (MA) [71], found that endotracheal intubation (OR: 6.69, 95% CI: 3.81-11.72), non-invasive ventilation (OR: 3.65; 95% CI: 1.86-7.19) and administration of nebulised medication (OR: 10.03; 95% CI: 1.98-50.69) increased the odds of HCW contracting SARS-CoV-2.

Specifically for tracheal intubation, HCWs performing this procedure were 34% (95% CI: 14% to 57%) more likely to test positive for COVID-19 [67].

In Tian et al. [63], AGP (endotracheal intubation, chest compressions, and other airway manipulations) was not associated with infection (OR: 1.54; 95% CI: 0.64-3.70).

Guidelines suggest that airway and pleural procedures are relatively safe as long as appropriate precautions are taken [72].

According to the French position, the use of an FFP2 mask is recommended for AGP [73].

- Others risk factors: gender

Female HCWs have an 11% higher risk (RR: 1.11; 95% CI: 1.01-1.21) of COVID-19 than their male counterparts [67]. (Note: the lower limit of the confidence interval is close to 1).

3.7.3. Risk of Long Covid-19

Most people with COVID-19 make a full recovery. But about 10-20% of them develop a variety of symptoms after recovering from their initial illness. Long COVID can develop in any patient; however, several studies suggest that the development of long COVID may be related to the severity of the acute illness[74].

Mechanism of long COVID not understood.

Associated risk factors may include female sex, more than five early symptoms, early dyspnoea, previous psychiatric disorders and certain biomarkers (e.g. D-dimer, CRP and lymphocyte count)[75]. Some other risk factors of long covid have been reported: hospitalisation (with mechanical ventilation), admission to intensive care, age (over 50 years) and comorbidities

3.7.4. Risk of COVID-19-Related Death

A pooled prevalence of mortality among hospitalised patients with COVID-19 was estimated by Dessie et al. [76] in their MA (42 studies and 423,117 patients). It was 17.62% (95% CI 14.26%-21.57%). Prognostic factors were age, gender, smoking, COPD, CVD, diabetes, hypertension, obesity, cancer, acute kidney injury and elevated D-dimer.

Li et al [77] found that the following factors were associated with an increased risk of mortality: sex, age, obesity diabetes and chronic kidney disease (40 studies reviewed ; 73% rated as "good quality »)

Kurzeder et al. [78] derived (and validated) a simple scoring system based on data available shortly after hospital admission that has a high predictive value for death related to COVID-19. This score includes age (> 70 years), oxygen saturation (≤ 90%) oxygen supply on admission, eGFR (≤ 60 ml/min) and Ct value (≤ 26).

3.8. Co-infections and Reinfections

3.8.1. Co-infections

Bacteria are more commonly associated with COVID-19 than other viruses.

- Bacterial co-infections

 doi:10.20944/preprints202307.0921.v1

The overall proportion of COVID-19 patients with bacterial infection estimated by Langford et al. [79] (MA) was 6.9% (95%CI: 4.3-9.5%). Bacterial infection was more common in critically ill patients (8.1%, 95%CI 2.3-13.8%).

Lansbury et al. [80] (MA) also provided a pooled proportion with a bacterial co-infection, which was 7% (95% CI: 3-12%). The most common bacteria were Mycoplasma pneumoniae, Pseudomonas aeruginosa and Haemophilus influenzae.

IgM against Mycoplasma pneumoniae was most common with a rate of 17.30 % [3].

Finally, Che Yusof et al. [81] reported in their MA several pooled prevalences of bacterial co-infections (published studies from 2020 to 2022).

The pooled prevalence of bacterial co-infection in hospitalised COVID-19 patients was 26.84% (95% CI: 23.85-29.83). The pooled prevalence of bacterial isolates for Acinetobacter baumannii was 23.25% (95% CI: 19.27-27.24); Escherichia coli was 10.51% (95% CI: 8.90-12. 12); Klebsiella pneumoniae, 15.24% (95% CI : 7.84-22.64) ; Pseudomonas aeruginosa, 11.09% (95% CI :8.92-13.27) and Staphylococcus aureus, 11.59% (95% CI [9.71-13.46]).

However, the pooled prevalence of antibiotic-resistant bacteria for extended-spectrum beta-lactamase-producing Enterobacteriaceae was 15.24% (95% CI: 7.84-22.64), followed by carbapenem-resistant Acinetobacter baumannii (14.55%; 95% CI: 9.59-19. 52%), carbapenem-resistant Pseudomonas aeruginosa (6.95%; (95% CI: 2.61-11.29), methicillin-resistant Staphylococcus aureus (5.05%; 95% CI: 3.49-6.60), carbapenem-resistant Enterobacteriaceae (4.95%; 95% CI: 3.10-6.79) and vancomycin-resistant Enterococcus (1.26%; 95% CI: 0.46-2.05).

- Viral co-infections

The pooled rate of viral co-infection was 3% (95% CI: 1-6%), with Respiratory Syncytial Virus (RSV) and influenza A being the common [80] (MA). More specifically, RSV was present at a rate of 1.44%. Influenza A and B were present at rates of 6.47% and 5.76% respectively [3].

Varshney et al. [82] reported the clinical characteristics of influenza-COVID-19 co-infection, including proportions of various clinical signs, in their MA. Co-infected patients have similar symptoms to those infected with COVID-19 or influenza alone.

- Bacterial/fungal co-infections

In COVID-19, 8% of patients (62/806) were reported to have had a bacterial/fungal co-infection during hospitalisation [83].

- Mortality and co-infections

For influenza, co-infection with SARS-CoV-2 virus had no effect on all-cause mortality [82,84].

3.8.2. Reinfections

Deng et al. [85] estimated the risk of reinfection in their MA.The pooled SARS-CoV-2 reinfection incidence rate was 0.70 (standard deviation: 0.33) per 10,000 person-days. The incidence of reinfection was lower than the incidence of new infection (HR = 0.12, 95% CI: 0.09-0.17). However, this study was conducted before the emergence of the more transmissible omicron variant. Finally, information on vaccination status was not available in the included studies.

3.9. Epidemiology of Variants

The emergence of new viral variants has caused an increase in their infectivity and spread.

The Omicron variant has the same transmission mechanisms as the previous variants.

3.9.1. Variants, Clinical Signs and Hospitalisation: Example of Omicron

The prevalence of symptoms characteristic of omicron infection differs from that of delta variant, with less lower respiratory tract involvement and a lower likelihood of hospitalisation. Loss of smell was less common in participants infected during the omicron period (16.7% vs. 52.7%; OR: 0.17; 95% CI: 0.16-0.19). Sore throat was more common during the omicron period (70.5% vs 60.8%, OR: 1.55; 95% CI: 1-43-1-69). There was a lower rate of hospital admission during the omicron period (1.9% vs 2.6%; OR: 0.75; 95% CI: 0-57-0-98) [86].

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Von Bartheld et al. [87] have specifically estimated the olfactory dysfunction associated with the omicron variant in their MA. The Omicron-induced prevalence of olfactory dysfunction in populations of European ancestry was 11.7%, whereas it was significantly lower in all other populations, ranging from 1.9% to 4.9%. Taking into account ethnic differences and population size, the global prevalence of olfactory dysfunction in adults was estimated to be 3.7%. The effect of omicron on olfaction is two to ten times less than that of alpha or alpha and delta variants.

3.9.2. Variants and Incubation Period

Tanaka et al. [88] compared the range of incubation periods in patients infected with the omicron variant with those infected with the alpha variant.

The observed incubation period was 3.03 ± 1.35 days (mean ± SDM). Under the hypothesis of a log-normal distribution, the 5th, 50th and 95th percentile values were 1.3 days (95% CI: 1.0-1.6), 2.8 days (2.5-3.1) and 5.8 days (4.8-7.5), significantly shorter than in patients with the alpha variant (4.94 days ± 2.19; 2.1 days (1.5-2.7); 4.5 days (4.0-5.1) and 9.6 days (7.4-13.0); $p < 0.001$).

Galmiche et al. [89], in their case series analysis (ComCor study, INCEPTION project) estimated the incubation period for each variant of concern, compared with the historical strain and identified individual factors and circumstances associated with its duration.

The mean incubation period varied between variants:

4.96 days (95% CI: 4.90-5.02) for alpha (B.1.1.7); 5.18 days (4.93-5.43) for beta (B.1.351) and gamma (P.1); 4.43 days (4.36-4.49) for delta (B.1.617.2), and 3.61 days (3.55-3.68) for omicron (B.1.1.529), compared with 4.61 days (4.56-4.66) for the historical strain.

Participants with omicron had a shorter incubation period than those with the historical strain (-0.9 days, 95% CI:-1.0 to-0.7). The incubation period increased with: age (participants aged ≥70 years had an incubation period 0.4 days [0.2 to 0.6] longer than participants aged 18–29 years); female participants (by 0.1 day, 0.0 to 0.2); those wearing mask during contact with the index case (by 0.2 days, 0.1 to 0.4).

The incubation period was shortened in those for whom the index case was symptomatic (-0.1 days, -0.2 to -0.1).

3.9.3. Variants and Duration of Shedding

The viral decay kinetics of the Omicron variant and the duration of shedding of culturable virus were characterized by Boucau et al. [90]. In their model (Cox proportional hazards model that adjusted for age, sex, and vaccination status), the number of days from an initial positive polymerase chain reaction (PCR) assay to a negative PCR assay (aHR: 0.61; 95% CI: 0.33-1.15) and the number of days from an initial positive PCR assay to culture conversion (aHR: 0.77; 95% CI, 0.44-1.37) were similar for the two variants. The median time from first positive PCR assay to culture conversion was 4 days (interquartile range or IQR: 3-5) in the Delta group and 5 days (interquartile range, 3 to 9) in the Omicron group; the median time from symptom onset or first positive PCR assay, whichever was earlier, to culture conversion was 6 days (IQR: 4 to 7) and 8 days (IQR: 5 to 10), respectively. There were no between-group differences in the time to PCR conversion or culture conversion, according to vaccination status

NB: the sample size was small; so estimates were imprecise.

3.9.4. Variants and Contagiousness

Omicron is significantly more contagious than previous variants [91].

A large number of infections are symptomatic or paucysymptomatic, while patients are infectious [92].

4. Discussion

- Established points

Several epidemiological parameters have been clarified or quantified during the course of the CoV-19 epidemic.

Regarding SARS-CoV-2 transmission, the simplistic dichotomisation between "air" and "droplet" transmission tends to be abandoned. Similarly, the role of superspreaders seems to be better appreciated.

Quantitative semiology has also been clarified throughout the pandemic, with estimates of not only sensitivities and specificities, but also predictive values (positive or negative).

Risk factors for the occurrence of covid-19 and prognostic factors for prolonged covid or death have been well characterised. For example, Hamilton et al. [93] proposed the following factors to be included in the risk matrix for respiratory transmission of SARS-CoV-2: patient risk (by far the largest risk factor; the probability of the patient having the infection and the time since acquisition. risk based on symptoms, PCR positivity and vaccination status); duration of exposure; healthcare worker risk from COVID-19; proximity risk (exposure to any healthcare intervention requiring close patient contact increases risk); environmental risk (ventilation, humidity, temperature).

- Unresolved issues

We can mention the infectious doses, which need to be better characterised; the role of ABO blood groups as a protective or detrimental factor (Covid 19 infection, clinical forms, death-related); the AGP most at risk from Covid-19, which needs to be defined.

- Limitations of the study

One of the limitations of this review is that it is not a systematic review of the literature. Our work is therefore essentially subjective. However, it is difficult to carry out such a systematic review of the entire epidemiology and prevention of Covid-19 because there are thousands of articles published on the subject.

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