Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
A clinician’s primer on epidemiology for COVID-19

Azman Rashid,1,2 Karla Therese L. Sy,3,4 Jacob M. Cabrejas,5 Brooke E. Nichols,4,6 Nahid Bhadelia,7 and Eleanor J. Murray1,*

SUMMARY
The coronavirus disease 2019 (COVID-19) pandemic has resulted in a concomitant deluge of medical, biological, and epidemiologic research. Clinicians are interested in incorporating the best new evidence-based practices when treating individuals with COVID-19 and instituting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission prevention protocols. However, without sufficient background knowledge, evaluating epidemiologic studies can be challenging, and failure to identify sources of bias could lead to poor treatment decisions. Here we provide a brief primer on key concepts and terms related to COVID-19 epidemiology to provide clinicians with a starting point for evaluating the emerging COVID-19 literature.

INTRODUCTION
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people globally; there were over 2 million reported deaths and almost 95 million confirmed cases of coronavirus disease 2019 (COVID-19) worldwide from January 2020 to January 2021.1 The pandemic has also spurred a huge scientific effort to understand the biology, epidemiology, and clinical treatment of the virus. Epidemiology is the study of the distribution and determinants of disease states in human populations, and many epidemiological studies of SARS-CoV-2 have emerged and contributed to a better understanding of the disease. Moreover, these epidemiological findings can inform clinical practice to improve outcomes. However, many clinicians may be unfamiliar with the basic epidemiology concepts needed to read, evaluate, and incorporate evidence-based medicine into their clinical practice, particularly as they apply to emerging infectious diseases.

In this review, we aim to elucidate common epidemiological concepts essential for understanding the COVID-19 literature, with a particular focus on clinicians. Essential epidemiological concepts are discussed, such as the terms to define morbidity and mortality, disease progression in infected individuals, and disease transmission between individuals. We also explore basic infectious disease modeling terms. Mathematical modeling has been beneficial in making predictions about the spread of disease and assessing intervention strategies to support population-based policy decisions. Finally, we examine different study designs in epidemiological studies and explore common biases, such as confounding and causality, to aid clinicians in critically evaluating the current and rapidly changing literature on clinical treatments for COVID-19.

KEY TERMS AND CONCEPTS
We begin by reviewing some basic concepts and key terms related to infectious disease epidemiology. The case fatality rate (CFR) and infection fatality rate (IFR)
highlight the mortality of the pathogen and are useful measures to compare outcomes across different groups and populations. The CFR is the proportion of fatal cases because of the disease among all individuals who were diagnosed with the disease in a given population. There are numerous factors that influence the CFR and can increase or decrease the calculated value. In particular, the CFR can be greatly affected by case definition and guidelines for testing access. Because these vary across jurisdictions, there is unlikely to be a single CFR value that applies universally. For SARS-CoV-2, access to testing for symptomatic and asymptomatic individuals and the listed cause of death—pneumonia versus SARS-CoV-2 versus pulmonary emboli—are particularly important determinants of the CFR. Expanding upon the CFR is the idea of an IFR, which is the proportion of fatal cases because of a given pathogen among the total number of infected individuals. Calculation of the IFR therefore expands the total number of individuals included in the numerator and denominator to also incorporate those who were not officially diagnosed with SARS-CoV-2. Depending on the jurisdiction, this could include individuals with mild symptoms or asymptomatic individuals or those with self-reported influenza-like illnesses who were unable to receive confirmatory testing. The larger denominator means that the value of the IFR is always equal to or lower than the CFR. Often, at the beginning of emerging infectious diseases outbreaks, the lack of widespread diagnostic testing can lead to overestimation of IFR and CFR because only the sickest individuals seek care and are diagnosed. Over time, as the full range of disease is understood, these values generally tend to decrease. In United States jurisdictions, a recent seroprevalence study reported a broad range of 1%–23% for detectable SARS-CoV-2 antibodies from July to September 2020; however, there was little evidence of infection in many geographic areas. Widespread access to diagnostic testing or methodic population-based surveillance testing is necessary to accurately estimate the CFR and IFR.

As mentioned above, the CFR depends heavily on the case definition for COVID-19. There is often a multitude of disease presentations of SARS-CoV-2 across a population. To explain the average progression of a disease in infected individuals, various terms are used to classify an individuals’ current display of disease, including asymptomatic, paucisymptomatic, pre-symptomatic, and symptomatic. A classification of being asymptomatic means that the person is infected by a pathogen but has an “infection with subclinical manifestation of disease” that can be detected and confirmed via laboratory tests. In a SARS-CoV-2 systematic review, approximately 20% of “people who become infected with SARS-CoV-2 remained asymptomatic throughout infection,” but other studies have reported a higher estimate of 40%–45%. Four separate studies found evidence of a small percentage of asymptomatic individuals infecting others, but it is difficult to assess the extent of this mode of transmission; one study reports 6% transmission from asymptomatic individuals. The classification of pre-symptomatic is similar to asymptomatic; a pre-symptomatic individual has an initial asymptomatic period in their disease course that later develops into a typical symptomatic state. One review reports a pre-symptomatic disease proportion between 0%–10% that increases in older populations and closed environments (i.e., cruise ships, nursing homes) cohorts, but there can be substantial variability in this proportion based on when the test was performed after infection (Figure 1). Pre-symptomatic transmission accounts for about 50% of all transmission, contributing to the worldwide pandemic spread. Last, there are individuals who display mild or non-severe symptoms and therefore choose to not engage with the healthcare system and fall beneath the threshold for detection by the system. These individuals are classified as paucisymptomatic. Importantly,
individuals who fall into all of these categories are capable of virus transmission to uninfected people.

The risk of transmission between an infected and uninfected individual is not only dependent on the person’s symptomatic classification but also on the infected person’s disease time course. July 2020, World Health Organization guidelines highlighted the importance of this clinical time course in SARS-CoV-2 because infected individuals can transmit the virus 1–2 days prior to onset of symptoms and maintain an infection burden high enough to permit infectivity up to 9 days after symptom onset. However, transmission of virus particles is also dependent on the severity of the individual’s clinical presentation because people with few upper respiratory tract symptoms, such as cough, would have less risk of transmitting virions to another individual. Thus, SAR-CoV-2 transmission can occur in the viral prodrome, pre-symptomatic period, and asymptomatic period with varying levels of success, depending on the environmental and behavioral factors of the infector and infectee.

The interval between initial exposure to SARS-CoV-2 and development of symptomatic infection is referred to as the incubation period. For SARS-CoV-2, the median incubation period is estimated to be 5 days and ranges from 4–11 days. This is in contrast to the latency period—the period between initial exposure and onset of the ability to transmit the virus. SARS-CoV-2’s median latency period is approximately 4 days and ranges from 1–24 days. The temporal discrepancies between the latent and incubation intervals partially contribute to the difficulty in disrupting pre-symptomatic transmission. Given the variability of SARS-CoV-2’s latency period, the serial interval is one useful measure for characterizing the rate of SARS-CoV-2 spread. The serial interval refers to the empirical estimate of the time from illness onset in the infector to illness onset in the infectee. The serial interval is a non-fixed range that could shorten based on implementation of non-pharmaceutical interventions, such as contact tracing and case isolation. The mean serial interval for SARS-CoV-2 is estimated to be 4 days early during the pandemic and around 5 days reported in a more recent meta-analysis; this estimate is essential for understanding the timing between case generation and the overall infectivity of the pathogen.
The serial interval distribution can be used as a proxy for non-observable generation intervals to further estimate other epidemiological parameters, such as the basic reproduction number ($R_0$) and the infectiousness of the pathogen.\textsuperscript{16,19} The incongruence between the serial interval and generation intervals means that, depending on which time interval is used in modeling, $R_0$ can be over- or underestimated. Figure 1 outlines the clinical course of infectiousness and transmission between two individuals infected with SARS-CoV-2.

Another important concept for understanding the literature on COVID-19 is the idea of diagnostic test performance. In medical diagnosis, test sensitivity is the ability of a test to correctly identify those with the disease (true positive rate), whereas test specificity is the ability of the test to correctly identify those without the disease (true negative rate). Positive predictive value (PPV) is the probability that a person with a positive test result is a true positive (has disease), whereas the negative predictive value (NPV) is the probability that a person with a negative test result is a true negative (does not have disease).\textsuperscript{20} Sensitivity and specificity are characteristics of the test, whereas the PPV and NPV depend on disease prevalence in the population. There are tradeoffs between test performance and implementation in SARS-CoV-2 diagnostics. Reverse-transcriptase polymerase chain reaction (RT-PCR), the current standard test for diagnosing and screening COVID-19, is highly sensitive and highly specific. One disadvantage of RT-PCR testing is that it can remain positive for much longer than the period that the person is infectious because it detects viral RNA (including prolonged shedding) rather than live virus.\textsuperscript{21} Because of the delays and long turnaround times of RT-PCR testing, which can take up to or more than 2 days, rapid antigen testing has been touted as an alternative globally even though it is less sensitive and less specific.\textsuperscript{22} Rapid antigen tests generally have lower sensitivity than RT-PCR but very high sensitivity for days with transmissible viral load.\textsuperscript{22} Frequent antigen testing has been suggested to quickly identify infected people who are more at risk for contagious spread.\textsuperscript{23} Additionally, rapid antigen testing has been suggested in geographic areas with unmet RT-PCR clinical testing demand. A caveat to low-sensitivity tests is that people who test false negative might incorrectly think they do not have disease and may not take proper preventative measures when they may actually have the disease. Thus, a negative rapid antigen test result with accompanying symptoms warrants further RT-PCR testing.\textsuperscript{22}

Finally, when assessing case numbers, it is important to consider the types of tests being offered because these can affect who is eligible to be included as a case. Tests can be used for clinical and surveillance purposes and have fundamental differences. Clinical tests are generally reserved for symptomatic people and require high sensitivity to provide a definitive clinical diagnosis with less testing. Surveillance tests are conducted on a routine basis for testing individuals in a population who may or may not have COVID-19 symptoms and are used to understand the current incidence of disease in a population. Given the importance of clinical testing for management of disease, the willingness to pay for a test with a higher test sensitivity may be greater. Clinical testing is therefore typically done using RT-PCR. Mass population screening, on the other hand, may only be achievable with rapid antigen testing. In this instance, we may be willing to accept a lower test sensitivity at a lower cost to include mass access. To reduce community spread, testing regimens that will capture the most infections while they are still infectious are needed, such as rapid antigen tests.\textsuperscript{23} One disadvantage of mass tests is the increased amount of false positives (low PPV and high NPV) in the context of low disease prevalence, such as in COVID-19.\textsuperscript{24}
INFECTIONOUS DISEASE MODELING

Because infectious disease can be transmitted, mathematical models need to take into account the spread of disease between individuals. There is an abundance of COVID-19 literature based on mathematical modeling, and clinicians may not be familiar with the terminology required to understand these models. We briefly describe the important parameters in infectious disease modeling. \( R_0 \) is the number of cases produced, on average, by an infected individual where all contacts are potentially susceptible. This measure is usually used in the early stages of the epidemic, prior to the population gaining immunity or non-pharmaceutical interventions being implemented in the population. \( R_0 \) describes the contagiousness and transmissibility of pathogens and is a function of contact rates among individuals, transmission probability, and number of infective individuals. Thus, \( R_0 \) estimates are not determined exclusively by the pathogen, and variability in \( R_0 \) depends on local sociobehavioral and environmental settings. \( R_0 \) for COVID-19 is currently estimated to be 2.63 and ranges from 0.4–4.6, but other studies have estimated \( R_0 \) to range as high as 5 or 6.\(^3,25\)

Another important measure is the time-varying effective reproduction number (\( R_e \), \( R_a \), or \( R_t \)). This measure is the number of people in a population who can be infected by an individual at any specific time; it reflects the changing levels of immunity in the population and the effect of control measures limiting transmission.\(^26\) \( R_0 \) and \( R_e \) are population averages, and some individuals may infect more people than others. This individual-level variability depends on overdispersion parameter (K). K affects the distribution of the number of secondary transmissions, and a high K creates superspreading events, where one individual infects most of the secondary cases, and the pathogen is more likely to spread in clusters. Evidence has slowly emerged that K is an important driver of the COVID-19 pandemic because the disease is an overdispersed pathogen that causes large outbreaks to occur and spread faster.\(^27,28\) One of the key targets of modeling papers for COVID-19 has been an assessment of herd immunity. Herd immunity is the idea that there is a threshold of infection within a population where the fraction of susceptible individuals is too few to continue productive infection. Herd immunity depends on properties unique to the pathogen, such as \( R_0 \). In general, pathogens with higher \( R_0 \), which have greater transmissibility and are more infectious, need a larger proportion of the population to be immune to achieve herd immunity. With establishment of herd immunity, spread of infection is limited, and there is now a benefit of reduced viral transmission to the remaining proportion of the population that has no immunity. Assuming an \( R_0 \) of 3, models suggest establishment of herd immunity when approximately 67% of individuals in a population have immunity to the virus.\(^5\) This estimate, however, assumes that all individuals have an equal probability of infectiousness and susceptibility. The overdispersed nature of SARS-CoV-2 would lower the number of individuals needed to be immune to establish herd immunity.\(^29\)

EVALUATING LITERATURE

Epidemiologic studies include not only descriptive studies of infectious disease cases or characteristics but also assessments of treatments, vaccines, or other preventive interventions for reducing morbidity and mortality from a disease. Epidemiologic studies, especially those conducted using observational data, can be complicated and require specialized knowledge to conduct and evaluate. Here we elucidate some of the most common issues that can arise in these studies to help clinicians understand and evaluate the COVID-19 literature.
A simple starting point for evaluating research papers is to use an existing quality evaluation tool. For observational epidemiology studies that are designed to assess preventive or treatment interventions, we recommend the ROBINS-I toolset, which provides a framework to assess risk of bias in clinical studies. For randomized trials, we recommend the similar ROB-2 tool from the same group. These tools first specify the research question and its relevance based on existing literature. For many COVID-19 interventions of interest, biological rationale is established by looking at similar studies, including other coronaviruses, infectious diseases like influenza, and/or use of the intervention for other inflammatory conditions or diseases. These tools assess seven biases that assess confounding and selection bias at pre-intervention, misclassification bias at intervention and any deviation from intervention, missing data, measurement, and publication or selective reporting bias after intervention. Confounding measures the effect of an exposure on an outcome based on an association of exposure with other factors that influence the occurrence of the outcome. Confounding bias can be evident when confounding factors are not considered or not properly accounted for in the study. Selection bias refers to distortions in the effect of outcome and exposure based on the procedures used to select individuals in the study, shown in a large cohort study. Measurement bias refers to systematic error arising from inaccurate measurement of subjects on study variable(s). Similarly, misclassification bias occurs when the exposure or outcome is classified incorrectly in studies. Misclassification can introduce differential bias when the probability of misclassification is different for those with and without disease or among all groups. Conversely, non-differential misclassification bias is the same probability of misclassification among all groups and can distort measures of association. In general, differential misclassification can bias the measure of association toward or away from the null, and non-differential misclassification biases toward the null. With COVID-19, measures of misclassification have mainly revolved around test performance, such as sensitivity and specificity, outlined in Key Terms and Concepts. For example, the number of positive tests confirmed from Quidel’s rapid SARS-CoV-2 antigen test performed on students at the University of Arizona would be different, as a result of lower test sensitivity and specificity, in comparison with the number of positive tests at other universities where RT-PCR testing was performed (https://www.nytimes.com/2020/11/02/health/coronavirus-testing-quadel-sofa.html). Last, publication bias or selective reporting bias is the tendency to submit and publish “positive” novel results that reaffirm hypothetical assumptions rather than results that are not statistically significant or “positive.” This bias distorts available scientific literature and downstream meta-analysis studies.

Box 1. RCT example

In this case study, we describe the sources of bias in the RCTs of the use of combined Hydroxychloroquine (HCQ) and azithromycin (AZ).

A French open-label randomized trial reported a 50-fold benefit of the HCQ and AZ treatment compared to standard care. However, this odds ratio is likely to be inflated given the study’s small sample size of 42 across 3 subgroups. The lack of confidence interval with this underpowered effect estimate makes it particularly difficult to evaluate this finding.

Another trial used a large sample size of 412 symptomatic outpatients as the treatment group, yet 224 patients who refused treatment were used as controls in the study. This likely introduces confounding, since patients who refused the treatment are likely to have different baseline and disease characteristics compared to cases. This Brazilian study focused only on suspected outpatient COVID-19 cases with milder symptoms, thus lacking generalizability to confirmed or severe disease patients.

Source: adapted from Fox et al.
All of the aforementioned biases contribute to the internal validity of the study in determining whether the knowledge gained outweighs the potential biases. When internal validity is established, external validity should be considered. The two components of external validity are generalizability, which describes how well study results apply to a broader group or situation, and transportability, which describes how well study results apply to other settings including other countries. A study that lacks external validity fails generalizability to other COVID-19 cases having data sampled only from suspected outpatients with milder symptoms (Box 1).32 Early COVID-19 trials often had limited transportability because there were few international site collaborations;33 however, a more recent remdesivir study had 60 trial sites in 10 different countries.34

The types of biases assessed by the ROB-2 and ROBINS-I tools can occur in all types of studies, but each type of study design has particular challenges. We briefly review these with examples.

Randomized clinical trials (RCTs) are conducted with subjects allocated randomly into treatment and control/placebo groups. This randomization process guarantees no confounding bias at baseline for treatment assignment. Placebo groups are generally provided an inert medication with no pharmacological effects to give an individual the perception that they are receiving treatment or assistance for their complaints. RCTs are typically analyzed based on intention-to-treatment effect considering the initial randomization treatment, regardless which treatment was actually received.37 Non-adherence to treatment has a negative effect on the magnitude of estimation for intention-to-treatment effect and can lead to underestimated drug efficacy or safety. When trials have non-adherence, an alternative is to calculate the per-protocol effect. The per-protocol effect is not affected by adherence because it excludes individuals who did not follow the treatment regimen,
disregarding randomization, leading to introduced biases; estimating this effect without bias is complex and requires special statistical tools. Aside from the biases listed above, another challenge for randomized trials is that a study with a small sample size can provide weak evidence or power to determine significant effects or type II errors.

Many early COVID-19 clinical trials in the early spring of 2020 (Box 1) were non-randomized, single-arm, and open-label trials that lacked transportability. Single-arm trials, such as a case series, have no placebo or control group, making it harder to determine true drug efficacy, safety, and toxicity. Lack of randomization in assignment of treatments can lead to confounding in the characteristics of each group. Often during emerging infectious diseases outbreaks, these types of studies are a result of open-label compassionate use of drugs in clinical setting to provide some therapeutic interventions against a new disease that does not have approved or proven treatments. However, these types of studies may conversely hurt affected individuals and society more than help because they may promote use of therapeutics without reliable evaluation of efficacy. Open-label trials have no masking or blinding, and the doctor and affected individual know which treatment is being provided, possibly leading to reporting or selection bias. Clinicians may be influenced in recording data when the affected individual is known to have received treatment and may ask more questions about adverse effects. Additionally, the people in these studies, who know they were given the experimental treatment, may report fewer disease symptoms. Ideally, most trials have double blinding, where study participants and clinicians have details withheld regarding intervention to prevent biases to the study, but it is difficult to enforce this for procedure-based or surgical interventions.

When a treatment or exposure cannot be delivered randomly, an alternative study design is the cohort study. Cohort studies do not involve any intervention, usually following a designated study population over time with comparison of incidence rates in groups that differ in exposure levels. In addition to the biases described above, cohort studies can be subject to problems related to missing data and the table 2 fallacy. The table 2 fallacy occurs when all factors adjusted for in a model are interpreted as causal of the outcome but may not have direct causal effects attributed to the outcome of interest. An example of this is shown in a large cohort study factors related to COVID-associated death (Box 2). Characteristics described in the model require causal methods to explore whether different characteristics lead to altered risk of death.

A second type of observational study design is the case-control design. Case-control studies involve comparing cases with a suitable control group of individuals without the disease. These studies are good for studying rare outcomes and risk factors for disease but have some particular challenges. The most important methodological challenge for case-control studies is use of a reasonable control group. Controls should be selected in a way that is independent of their exposure or treatment status and should include individuals who would be eligible to be cases in the study if they had developed the disease of interest. Ideally, the cases and controls should have similar baseline characteristics to minimize potential biases. Another potential bias that is common in case-control studies is recall bias. This can occur when participants have trouble remembering details pertinent to the study, especially when cases and controls remember different levels of details. Finally, it is important to remember that case-control studies cannot typically be used to estimate the frequency of disease occurrence. For example, in a study exploring serum antibodies in SARS-CoV-2
cases and controls, the relative risk and incidence of SARS-CoV-2 in the population cannot be estimated because the number of cases and controls are pre-selected in case-control studies.42

Another common type of observational study is the cross-sectional study. Cross-sectional studies examine relationships between diseases and other variables of interest in a defined population at a particular time. The main challenge for cross-sectional studies is that temporality of cause and effect or causality generally cannot be established because prevalence, the measure of disease occurrence at a particular time, is reported rather than the period incidence reported in other types of studies where people are followed over time.

Finally, ecological studies have been common in assessing COVID-19. Ecological studies are less resource intensive than other studies, making them popular for exploratory analyses or hypothesis generation. Ecological studies are distinct from other observational studies because they use populations rather than individuals as units of analysis. This population focus makes them a useful tool for evaluating the effects of group-level exposure, such as policies (Box 3). However, these studies are particularly prone to bias and should be interpreted with caution. Many ecological studies are cross-sectional and, thus, prone to the same problems as cross-sectional studies for evaluating cause and effect. In addition, ecological studies are often used inappropriately to hypothesize about individual-level exposure-outcome relationships. However, these studies generally cannot be used in this way—doing so risks the ecological fallacy; however, ecological studies can play an important role when group-level processes are of interest. The converse of the ecological fallacy is known as the aggregation fallacy—erroneous inference observed at an individual level in non-ecological studies is applied to the group level.

CONCLUSIONS

A greater understanding of the emerging SARS-CoV-2 epidemiological literature is essential to inform clinical practice and improve outcomes. This review aimed to clarify the terms and types of studies commonly used in infectious disease epidemiology. Clinicians need familiarity with basic epidemiological concepts to critically
appraise the large influx of COVID-19 studies and be proficient in the vocabulary necessary to contribute to the COVID-19 evidence base.

ACKNOWLEDGMENTS
E.J.M. was partially supported by NICHD (R21HD098733).

DECLARATION OF INTERESTS
The authors declare no competing interests.

REFERENCES

1. World Health Organization. (2021). WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/.

2. Randolph, H.E., and Barreiro, L.B. (2020). Herd Immunity: Understanding COVID-19. Immunity 52, 737–741.

3. Ragor, D.D., Lee, M.H., Archuleta, S., Bagdasarian, N., and Quek, S.C. (2020). The many estimates of the COVID-19 case fatality rate. Lancet Infect. Dis. 20, 776–777.

4. Bajema, K.L., Wiegand, R.E., Cuffe, K., Patel, S.V., Iachan, R., Lim, T., Lee, A., Moyse, D., Havers, F.P., Harding, L., et al. (2020). Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020. JAMA Intern. Med. e207976.

5. He, J., Guo, Y., Mao, R., and Zhang, J. (2020). Proportion of asymptomatic coronavirus disease 2019: A systematic review and meta-analysis. J. Med. Virol. 93, 820–830.

6. Buitrago-Garcia, D., Egi-Dany, D., Councotte, M.J., Hossmann, S., Imeri, H., Ipekci, A.M., Salanti, G., and Low, N. (2020). Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLoS Med. 17, e1003346.

7. Oran, D.P., and Topol, E.J. (2020). Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review. Ann. Intern. Med. 173, 362–367.

8. World Health Organization. (2020). Transmission of SARS-CoV-2: implications for infection prevention precautions. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions.

9. Ferretti, L., Wymant, C., Kendall, M., Zhao, L., Nurtay, A., Abeler-Dörner, L., Parker, M., Bonsall, D., and Fraser, C. (2020). Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science 368, eabb9336.

10. Gandhi, M., Yokoe, D.S., and Havlir, D.V. (2020). Asymptomatic Transmission, the Achilles’ Heel of Current Strategies to Control Covid-19. N. Engl. J. Med. 382, 2158–2160.

11. He, X., Lau, E.H.Y., Wu, P., Deng, X., Wang, J., Hao, X., Lau, Y.C., Wong, J.Y., Guan, Y., Tan, X., et al. (2020). Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat. Med. 26, 672–675.

12. World Health Organization. (2020). Criteria for releasing COVID-19 patients from isolation. https://www.who.int/publications/i/item/criteria-for-releasing-covid-19-patients-from-isolation.

13. Petersen, E., Koopmans, M., Go, U., Hamer, D.H., Petrosillo, N., Castelli, F., Storgaard, M., Al Khali, S., and Simonsen, L. (2020). Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. Lancet Infect. Dis. 20, e238-e244.

14. Liu, Z., Magal, P., Seydi, O., and Webb, G. (2020). A COVID-19 epidemic model with latency period. Infect. Dis. Model. 5, 323–337.

15. Li, R., Pei, S., Chen, B., Song, Y., Zhang, T., Yang, W., and Shaman, J. (2020). Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science 368, 565–569.

16. Ali, S.T., Wang, L., Lau, E.H.Y., Xu, X.K., Du, Z., Wu, Y., Leung, G.M., and Cowling, B.J. (2020). Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions. Science 369, 1106–1109.

17. Du, Z., Xu, X., Wu, Y., Wang, L., Cowling, B.J., and Meyers, L.A. (2020). Serial interval of COVID-19 among publicly reported confirmed cases. Emerg. Infect. Dis. 26, 1341–1343.

18. Rai, B., Shukla, A., and Dwivedi, L.K. (2021). Estimates of serial interval for COVID-19: A systematic review and meta-analysis. Clin. Epidemiol. Glob. Health 9, 157–161.

19. Gostic, K.M., McCough, L., Baskerville, E.B., Abbott, S., Joshi, K., Tedijanto, C., Kahn, R., Niehus, R., Hay, J.A., De Salazar, P.M., et al. (2020). Practical considerations for measuring the reproductive number, Rt. PLoS Comput. Biol. 16, e1008609.

20. Rothman, K.J., Greenwood, S., and Lash, T.L. (2012). Modern Epidemiology, Third Edition (Lippincott Williams & Wilkins).

21. Cevik, M., Tate, M., Lloyd, O., Marao, A.E., Schafers, J., and Ho, A. (2021). SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe 2, e13–e22.

22. Guglielmi, G. (2020). Fast coronavirus tests: what they can and can’t do. Nature 585, 496–498.

23. Mina, M.J., Parker, R., and Larremore, D.B. (2020). Rethinking Covid-19 Test Sensitivity — A Strategy for Containment. N. Engl. J. Med. 383, e120.

24. Abbasi, K. (2020). Covid-19: Screening without scrutiny, spending taxpayers’ billions. BMJ 371, m1205.

25. Mahase, E. (2020). Covid-19: What is the R number? BMJ 369, m1891.

26. White, L.F., Moser, C.B., Thompson, R.N., and Pagano, M. (2020). Statistical Estimation of the Reproductive Number From Case Notification Data. Am. J. Epidemiol. kmw211.

27. Adam, D.C., Wu, P., Wong, J.Y., Lau, E.H.Y., Tsang, T.K., Cauchemez, S., Leung, G.M., and Cowling, B.J. (2020). Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong. Nat. Med. 26, 1714–1719.

28. Endo, A., Abbott, S., Kucharski, A.J., and Funk, S.; Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group (2020). Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. Welcome Open Res. 5, 67.

29. Gomes, M.G.M, Corder, R., King, J., Langwig, K., Souto-Maior, C., Carneiro, J., Goncalves, G., Penha-Goncalves, C., Ferreira, M., and Aguas, R. (2020). Individual variation in susceptibility or exposure to SARS-CoV-2 lowers the herd immunity threshold. medRxiv. https://doi.org/10.1101/2020.04.27.20081893.

30. Sterne, J.A., Hernán, M.A., Reeves, B.C., Savovíc, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., et al. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919.

31. Sterne, J.A.C., Savovic, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Broun, I., Cates, C.J., Cheng, H.Y., Corbett, M.S., Eldridge, S.M., et al. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4989.

32. Fox, M.P., D’Agostino McGowan, L., James, B.D., Lessler, J., Mehta, S.H., and Murray, E.J. (2020). Concerns About the Special Article on Hydroxychloroquine and Azithromycin in High Risk Outpatients with COVID-19 by Dr. Harvey Risch. Am. J. Epidemiol. 189, 1423–1425.

33. Hsiehchen, D., Espinosa, M., and Hsieh, A. (2020). Deficiencies in the Designs and Interventions of COVID-19 Clinical Trials. Med (N Y) 1, 103–104.

34. Beigel, J.H., Tomashek, K.M., Dodd, L.E., Mehta, A.K., Zingman, R.S., Koll, A.C., Hohmann, E., Chu, H.Y., Luetkemeyer, A., Kline, S., et al.; ACTT-1 Study Group Members (2020). Remdesivir for the Treatment of Covid-
35. Gautret, P., Lagier, J.C., Parola, P., Hoang, V.T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V.E., et al. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int. J. Antimicrob. Agents 56, 105949. Published online Mar 20. https://doi.org/10.1016/j.ijantimicag.2020.105949.

36. Barbosa Esper, R., Souza da Silva, R., Costa Oikawa, F.T., Machado Castro, M., Razuk-Filho, A., Batata, P.B., Jr., Lotze, S.W., Nunes da Rocha, C., de Sá Cunha Filho, R., Barbosa de Oliveira, W.E., et al. (2020). Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine, https://pgibertie-files-wordpress-com.ezproxy.bu.edu/2020/04/2020.04.15-journal-manuscript-final.pdf. Accessed January 17, 2021.

37. Williamson, E.J., Walker, A.J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C.E., Curtis, H.J., Mehrkar, A., Evans, D., Inglesby, P., et al. (2020). Factors associated with COVID-19-related death using OpenSAFELY. Nature 584, 430-436.

38. Tennant, P.W.G., and Murray, E.J. (2021). The Quest for Timely Insights into COVID-19 Should not Come at the Cost of Scientific Rigor. Epidemiology 32, e2.

39. Gupta, S.K. (2011). Intention-to-treat concept: A review. Perspect. Clin. Res. 2, 109–112.

40. Hernán, M.A., and Robins, J.M. (2017). Per-Protocol Analyses of Pragmatic Trials. N. Engl. J. Med. 377, 1391–1398.

41. Bhadelia, N., Sauer, L., Cieslak, T.J., Davey, R.T., McLellan, S., Iyeki, T.M., and Kortepeter, M.G., National Ebola Training and Education Center’s Special Pathogens Research Network (SPRN)’s Medical Countermeasures Working Group (2019). Evaluating Promising Investigational Medical Countermeasures: Recommendations in the Absence of Guidelines. Health Secur. 17, 46-53.

42. Caturegli, G., Materi, J., Howard, B.M., and Caturegli, P. (2020). Clinical Validity of Serum Antibodies to SARS-CoV-2 : A Case-Control Study. Ann. Intern. Med. 173, 614-622.