

COVID-19: a review of current knowledge regarding exposure, quarantine, isolation and other preventive measures

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Abstract: Deeper understanding of the spread, morbidity, fatality, and development of immune response associated with coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, is necessary in order to establish an appropriate epidemiological and clinical response. Exposure control represents a key part of the combat against COVID-19, as the effectiveness of current therapeutic options remains partial. Since the preventive measures have not been sufficiently able to slow down this pandemic, in this article we explore some of the pertinent knowledge gaps, while overall looking to effective vaccination strategies as a way out. Early on, such strategies may need to rely on counting the convalescents as protected in order to speed up the immunization of the whole population.

Keywords: coronavirus disease 2019, epidemiology, exposure, infectivity, isolation, quarantine, severe acute respiratory syndrome coronavirus 2

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Introduction

Coronavirus disease 2019 (COVID-19) was first described based on a cluster of pneumonia cases starting in December 2019 in Wuhan, Hubei province, China.¹ By 7 January 2020, Chinese scientists isolated a novel betacoronavirus responsible for the outbreak, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By the end of January 2020, the disease had spread throughout Asia and the first cases were reported outside of the continent. The clinical characteristics, radiographic findings, and laboratory abnormalities of this primarily respiratory illness producing severe outcomes in some were described for adults² and in children³ shortly thereafter. The phylogeny of SARS-CoV-2 and its place among similar species has also been rapidly determined.⁴ As of mid-May 2021, we approached almost 170 million cumulative cases of laboratory-confirmed diagnosis of COVID-19 and exceeded 3.3 million deaths globally.⁵

The aim of this review is to summarize current knowledge influencing the definitions of exposure,

as well as the development of recommendations for the implementation of quarantine, isolation, and other preventive measures.

Epidemiology

Important parameters to consider for the development of appropriate epidemiological measures include the infection fatality rate (IFR) and the basic reproduction number [(R₀) and its effective current equivalent (R_t)],⁶ both of which can be influenced by epidemiological⁷ and therapeutic interventions.

As a way of introduction, IFR is defined by the proportion of deaths among all infected individuals including asymptomatic and, therefore, undiagnosed cases. The IFR can vary across different locations and reflects the expected total mortality burden of COVID-19. On the other hand, case fatality ratio estimates the proportion of deaths among identified confirmed cases, which leads to overestimation of the fatality rate by neglecting a substantial proportion of the least affected

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(asymptomatic) individuals and individuals undiagnosed due to lack of access to timely testing.^{8,9}

At present, according to the World Health Organization (WHO), which refers to some serological studies that are currently being undertaken worldwide, estimates the IFR at approximately 0.5–1% globally, though the numbers vary by region due to differing epidemiological control measures, population age, comorbidity profiles, viral seasonality, and more recently, differing lethality of prevalent mutations, i.e. variants of interest, monitored for potential implications regarding the pandemic, and especially, variants of concern (VOC), confirmed to have serious implications in individual countries.^{9–13} Furthermore, the level of vaccination within the population has become the biggest driver of decreasing IFR as, despite varying degrees of protection against symptomatic and asymptomatic disease, the level of protection against death is particularly high and reaches close to 100%. The reasons include not only lowering the IFR in the small fraction of breakthrough infections within the most vulnerable age groups but also the prevention of healthcare system overload, maintaining high quality healthcare accessible to all those in need.¹⁴

The R_0 is an important parameter of transmission, which is defined as the average number of secondary cases that can be generated by one infected individual throughout the entire index illness. The R_0 is calculated in a population entirely susceptible to infection and thus estimates the initial value of infectivity before any countermeasures are taken. The R_t is the expected number of new infections in a population where some individuals may no longer be susceptible and some countermeasures may have been applied. Therefore the R_t is used to determine the evolution of the epidemiological situation in a population over time.^{15,16} Epidemiological measures become particularly important in situations where the capacity to treat infected people according to the best available principles is limited.¹⁷ People needing mechanical ventilation and extracorporeal membrane oxygenation would not survive without these advanced measures as often, which influences the IFR. People also need to be properly advised and isolated once diagnosed with COVID-19 in order to drive down the R_t , and this could not be performed to the same degree if the healthcare system is overwhelmed.

Unlike the R_t ,^{18,19} the fatality rate for COVID-19 is still not well established,^{20–22} which is not a surprise as the disease has at this point been present for just over 1 year. By definition, an infection epidemic starts to subside once the R_t is driven below 1, as below this level each subsequent cycle of secondary cases is less numerous than the previous one. Therefore the aim of all epidemiological measures for COVID-19 is to drive the R_t as far below 1 as possible. It is, however, important for any epidemiological measures not to replace the mortality and suffering caused by COVID-19 with worsening outcomes of other health conditions, including mortality caused by neglecting these conditions for fear of exposure. It is also important that the measures be balanced with economic security, which is also associated with health, mainly with mental health problems, increase in substance misuse, deterioration of interpersonal relationship, and even violence.^{23,24}

Lastly, an epidemic curve can be used to visually track the natural progression, as well as the effect of control measures on an epidemic.²⁵ Regarding COVID-19 specifically, this can be carried out with various degrees of precision, from simply monitoring the incidence of cases measured by virus detection methods,^{26,27} through inferences *via* combining data from virus detection methods with seroprevalence studies²⁸ to more granular attempts to forecast trends *via* viral load distributions.²⁹

SARS-CoV-2 infectivity

SARS-CoV-2 can be detected in the upper respiratory tract by reverse-transcriptase polymerase chain reaction (PCR) 2–3 days (previously reported maximum is 6 days) prior to the onset of symptoms.^{30–33} The duration of infectiveness cannot be measured by the current PCR testing, which can detect virus that is not replication competent. Recently, multiple investigators have attempted to address this insufficiency by trying to determine the probability of infectiousness from PCR cycle-threshold quantification (which somewhat varies from test to test), comparing it with successful viral cultures. A cycle threshold of >30 in patients at the end of their positivity (at least 10 days after the onset of positivity) has been proposed as a cut-off for presumption of noninfectivity, though a uniform consensus has not been conclusively provided as of yet.^{34,35} For obvious reasons, not using lower viral load as

evidence of infectivity is important during the window of rapid rise of replication at the end of the incubation period, hence the confirmation of symptoms duration or other clinical and/or epidemiological evaluations aimed at establishing the timeframe of SARS-CoV-2 infection are important. The duration of infectiveness is thought not to exceed 10 days in mildly to moderately ill individuals,³⁶ and up to 15–20 days in the minority of immunocompromised individuals and/or individuals with severe disease.³⁰ Prolonged expulsion of fragmented viral particles incapable of replication is hypothesized to be due to slow sloughing and decay of the infected cells resulting from immunological restriction of viral replication.^{30,37} Large observational studies, including PCR testing, contact tracing, and in some cases, viral cultures showed that prolonged (and/or recurrent) PCR positivity does not generate secondary infections after as few as 5–6 days of symptoms (see below).³⁸ Epidemiologically, there is some evidence that transmission generally does not occur outside of the approximately 10–14-day interval around the onset of symptoms, likely with the exception of the spread from the immunocompromised and severely ill individuals. A contact tracing report from Taiwan documented 22 secondary cases traced from an investigation of 2761 contacts of 100 primary cases.³⁹ In this report, the earliest transmission occurred on day 5 and the latest interval of exposure was on days 5–10. The review by Meyerowitz *et al.*³¹ (September 2020) suggests that the most dominant mode of transmission occurs through droplets and less so through aerosols, though physical proximity appears to play a role. In contrast a few studies showing persistence of viable viral aerosols in the air for prolonged periods of time and air travel of infectious particles well beyond 2 m⁴⁰ have recently supported the view that airborne transmission may actually be more important than previously thought.⁴¹ Dilution and environmental deactivation may play a role in the decreased infectivity at greater distance, though universal masking would certainly provide additional benefit.^{42,43} In fact, common cloth masks, in addition to surgical masks and higher-grade respirators appear to be effective for multiple reasons. Their filtration capacity, both barrier and electrostatic, seem to perform at a higher level than originally thought, especially when closely adhering to the facial contours.^{44,45} Other modes of transmission, though not entirely excluded, seem to play a smaller role in the spread of COVID-19.³¹ The modes discussed and rarely

confirmed have included contact with fomites, vertical trans-placental, fecal-oral, sexual, hematogenous, and transmission from animals (specifically minks to humans, though cats, ferrets, and dogs can contract the disease as well, yet no transmission to humans from these species has been documented to our knowledge to date). The relatively short half-life of SARS-CoV-2 on various surfaces⁴⁶ together with a need for a (yet unknown) critical infectious dose may thus interact in a way that prevents most contact (nonrespiratory) transmissions. Good hand hygiene is nevertheless an important part in preventing unnecessary exposure, especially where contact with concentrated sputum on various highly touched surfaces (e.g. handles, trays, seats) remains plausible.

Asymptomatic, presymptomatic and symptomatic spread of COVID-19

Based on various estimates, there is little doubt that containing the adverse economic impact of this pandemic is a high priority.⁴⁷ From that perspective, studying behavioral patterns that increase the risk of viral transmission is important for the development of a staged response, allowing essential and lower risk businesses to continue operations at the time when broader lockdowns are more economically detrimental than epidemiologically useful.^{48,49} A cruder differentiation between travel restrictions and local lockdowns has shown that travel restrictions, albeit perhaps useful early on, may no longer be as valuable once the disease has reached the community.^{50,51} Granular mobility data and attempts at determination of disease spread among various types and models of businesses, however, appear to be needed in order to further balance and boost health security with economic security. The transmission from the asymptomatic/presymptomatic individuals, which may be responsible for a substantial proportion of secondary infections,⁵² was the main reason for the US Center for Disease Control and Prevention (CDC) (4 April 2020) and later also the WHO (5 June 2020) recommendation for universal masking (masks worn by everyone, except children <2 years of age, during contact with others). Gandhi *et al.*^{53,54} have suggested that lowering the infectious inoculum by universal masking may play a role not only in curbing COVID-19 transmission but also in decreasing the disease severity, resulting from a lower starting infectious dose. This theory leans among other things on findings from an animal

model,⁵⁵ and various data showing plausible circumstantial evidence, including the significant difference between the rate of asymptomatic infections on two cruise ships, one with universal masking⁵⁶ and the other one without this measure.⁵⁷ Implementation of universal masking at a major academic medical center in the USA has been reported to effectively flatten the epidemiological curve within healthcare personnel.⁵⁸ Further evidence supporting the benefit of proper personal protective equipment use was reported in the 4 September 2020 MMWR (Morbidity and Mortality Weekly Report) from the CDC. This report showed that in 8 out of 13 sites comparing the seroprevalence of SARS-CoV-2 antibodies between local healthcare professionals and their surrounding communities, the seroprevalence was lower among the healthcare professionals despite a significantly higher likelihood of being exposed to COVID-19.⁵⁹ On 13 February 2021 the CDC recommended improved mask fitting by double masking and/or improving snug mask fit as this leads to significantly improved filtration of outgoing and incoming airborne particles by >60% compared with prior level of protection.^{60,61} This recommendation stems from the concerning findings regarding higher infectivity of the new mutant versions of SARS-CoV-2, some of which are also capable of at least partial escape from previously acquired immunity.⁶²

Previously positive cases

Evidence so far suggests that the majority of previously positive individuals tested by PCR have been negative for replicable virus in cultures, as well as epidemiologically, since they did not produce secondary cases in traced contacts. A study of 619 patients discharged after COVID-19-related hospitalization in China found 87 previously positive cases 7–14 days after all patients had a negative PCR test twice with at least 24 h in between.⁶³ Viral cell cultures were negative in all patients and a complete genome could not be sequenced, suggesting that the positive PCR was triggered by viral debris. Similarly, the Korean CDC reported on 285 patients, who had tested negative after their illness but then positive again 8–82 days later.⁶⁴ Contact tracing revealed 790 contacts including 351 family members and no secondary cases were found. Furthermore, in 108 of these patients, a viral cell culture was performed and did not find any growth. According to official CDC recommendations regarding

the isolation of infected persons, detection of replication-competent virus typically does not exceed 10 days in immunocompetent patients, and can be occasionally found at 10–20 days range after symptoms onset in some adults with severe COVID-19 infection. Some of these cases were to some degree immunocompromised. For these reasons and due to the potentially confusing prolonged presence of SARS-CoV-2 RNA fragments, routine ‘test of cure’ is not generally recommended. However, recovery of replication-competent virus in severely immunocompromised patients has been reported beyond 20 days, and as long as 143 days after first test positivity; in these cases, test of cure may still be important.³⁸

High risk versus low risk of exposures

The definition of prolonged exposure [>15 min (cumulatively over 24 h⁶⁵) or any amount of time during aerosol-generating procedures] has been set as a reasonable estimate, as the evidence to rigorously determine such a timeframe is lacking.⁶⁶ The CDC also acknowledges a similarly insufficient level of evidence for the recommendation of 2 m (6 ft) for interpersonal distancing,⁶⁷ and an 12 October 2020 update on certain recommendations lists close contact as within 1 m (~3 ft) based on a similar definition of high-risk exposure by WHO. New evidence is currently accumulating that indoor airborne transmission arises through the inhalation of small, micron-scale aerosol droplets exhaled by an infected individual, which is now considered as the dominant mode of transmission of COVID-19, especially for so called ‘superspreading events’.⁴¹ We can assume that high-risk exposure can imply a potentially higher infectious inoculum. Although it is very difficult to determine the association between viral dose and disease severity, existing data support that a greater inoculum at the time of SARS-CoV-2 exposure might determine a higher risk of severe COVID-19 infection.^{68,69}

Importantly, despite sophisticated vaccination efforts, the majority of the global population remains susceptible to SARS-CoV-2 infection, which despite a high degree of vaccination in several high-income countries, places everybody at risk for further development and propagation of mutated variants, and particularly VOC.⁷⁰ Therefore, unvaccinated individuals are more vulnerable to consequences of high-risk exposure opposed to fully vaccinated individuals.

Proper use of personal protective equipment by healthcare professionals is considered highly effective despite the risk of high exposure regardless of the distance or duration of contact.⁷ Surgical masks are enough for most exposures, particularly when worn by all parties, while higher-level respirators are needed only for aerosol-generating procedures, or when the COVID-19 infected party is being examined at close distance.

Quarantine, isolation, and pharmacological preventive measures

High-risk exposures then lead to quarantine, which can be imposed for anywhere from 7 days to 14 days with supplementary testing if the shorter interval is chosen.⁷² People who have been in close contact should monitor themselves for the development of symptoms and may consider testing at an appropriate time interval, especially if working or living with particularly vulnerable individuals.

At present, clinical trials with combinations of monoclonal antibodies casirivimab plus imdevimab are very promising. Preliminary data showed 81% reduced risk of symptomatic SARS-CoV-2 infection and also faster clearance of virus resulting in a shorter duration of symptoms. Very important and desirable is the additional finding that casirivimab and imdevimab can reduce the risk and burden of COVID-19 infection among household contacts of SARS-CoV-2-infected individuals, which can be very important in postexposure prophylaxis of the disease.⁷³ Persons who develop COVID-19 symptoms and/or test positive begin medical isolation for a minimum of 10 days (from a positive test for asymptomatic individuals,³³ or from the development of symptoms). Immunocompromised individuals and those with a severe course of illness can be isolated for up to 20 days instead of 10 days, since a limited number of these individuals may produce replication-competent virus beyond 10 days.⁷⁴ Repeat testing with currently used PCR techniques is not needed and may not be appropriate given the potential for ongoing positivity with viral debris shedding as discussed above. However in severely immunocompromised persons, a test-based strategy may need to be considered in order to prevent spread beyond 20 days of isolation.⁷⁴ On the other hand, new evidence about mutant variants is emerging. A new study by Kissler *et al.*⁷⁵ suggests that the mutations in B.1.1.7, commonly

known as the British variant, can not only cause longer clearance of the virus from the nasopharynx, but also longer infectivity. This and similar facts will need to be taken into account when recommending the length of isolation for emerging variants, as well as for various testing implications (e.g. detection problems).

Quarantine is not currently needed in people who have overcome the disease within the past 3 months and recovered unless they develop new symptoms. Also, persons who are already fully vaccinated and have been in contact with infected individuals do not need quarantine if they are not symptomatic.⁷⁶ Among other things, recent case studies show that some immunocompromised individuals may shed replication-competent virus for much longer than previously recognized. Prolonged SARS-CoV-2 replication along with ineffective immune pressure may be associated with viral evolution leading to the development of new mutant strains of the virus.⁷⁷⁻⁷⁹

Conclusion

From a broader epidemiological perspective, the unique feature of asymptomatic and presymptomatic spread COVID-19 requires multiple layers of security. Under these circumstances, even diligent self-quarantining or monitoring for symptoms would not prevent all transmissions, which was recently documented in one modeling study.^{80,81} From this perspective, to further minimize the need for unnecessarily broad lockdowns, various models propose screening approaches, in which the speed of testing, determined by the capacity and turn-around time of the results, appears more important than the sensitivity of the test (allowing for utilization of cheaper tests more frequently for greater effect).⁸² Specifically, tests with turn-around time of only minutes, capable of ideally capturing only currently infectious individuals would also provide an added benefit of targeting contact tracing only toward individuals within or immediately after the incubation period (i.e. before the majority of transmissions has occurred), which is another multilayered safeguard of cost-effectiveness.⁸³

Ultimately, however, it would appear that for now only rapid global vaccination effort could stop this pandemic, and the speed of vaccine rollout is all the more important, as it may be the only effective way of preventing further development

of escape mutations (lowering the effectiveness of postinfectious, as well as vaccine-derived immunity. Vaccination also currently appears to be the only effective way of reducing not only short-term morbidity and mortality, but also long-term sequelae and disability from organ damage and prolonged immune activation currently known as the postacute sequelae of COVID-19.^{81,84}

Author contributions

All authors contributed equally to this manuscript and reviewed its final version.

Conflict of interest statement

The authors declare that their results have not been published previously, are not under submission elsewhere, and that coauthors have reviewed and agreed upon this version of the submitted text. All authors declare no conflicts of interest, and claim full standards for reporting of scientific research.

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