



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 Blueprint to Control the SARS-CoV-2 Pandemic

John C. O'Horo, MD, MPH; Amy W. Williams, MD; and Andrew D. Badley, MD



From Department of Infectious Diseases (J.C.O., A.D.B.), Department of Medicine (A.W.W.), and Mayo Clinic College of Medicine, (A.D.B.), Mayo Clinic, Rochester, MN.

After a year of pandemic status, remarkable progress has been achieved in understanding SARS-CoV-2 biology, developing accurate diagnostics, testing therapies, and validating vaccination approaches. Unfortunately, translating these into effective public health interventions has been—at best—uneven. Although the pandemic still rages, many are discussing how and when to reopen businesses, society, and economies. These decisions must be informed in a science-based understanding of how control of the pandemic can be achieved.

A basic principle of understanding the spread infectious diseases is the concept of infectious dose 50 ( $ID_{50}$ ) or the number of pathogens (in this case, number of SARS-CoV-2 viruses) that causes infection in 50% of those persons who are exposed. The  $ID_{50}$  for a given pathogen depends on the basic reproduction number ( $R_0$ , or the expected number of cases directly generated by 1 case) and host susceptibility. Those variables are not static; for example, the B.1.1.7 (United Kingdom) variant of SARS-CoV-2 is believed to have a higher  $R_0$  than the original SARS-CoV-2 strains. The number of human conditions that appear to affect host susceptibility to infection (for example, diabetes, obesity, and intrinsic errors in type 1 interferon signaling pathways) continues to grow as the outbreak continues. Although those variables may explain, in part, heterogeneity in disease outcomes on an individual basis, within large populations, they are generally stable, and understanding their influence can inform policy for reopening of societies.

Implicit in the concept of  $ID_{50}$ , is the understanding that if the number of pathogens is greater than  $ID_{50}$ , more hosts will become

infected, and if the number of pathogens is less than  $ID_{50}$ , fewer hosts will become infected. In other words, infectious rates follow a dose-response relationship.

In the case of SARS-CoV-2, at least 5 lines of evidence suggest that infection follows that dose-response relationship. In vivo models of infection, with closely related coronaviruses SARS-CoV-1 and murine coronavirus strain, 1 exhibit dose responsiveness.<sup>1</sup> The probability of SARS-CoV-2 infection following exposure to an infected person is inversely proportional to proximity of exposure, and recovery of droplets in the environment decreases with increasing distance, according to Stoke's law.<sup>2</sup> Efficacy of respiratory transmission of SARS-CoV-2, estimated by modeling, indicates that risk decreases both with increasing room size and increased frequency of air changes per hour,<sup>3</sup> consistent with a dose-response effect. Clinical success of antiviral agents for SARS-CoV-2 demonstrates that treatment success is associated with reduced viral load.<sup>4</sup> Higher viral loads, as measured by cycle threshold values, are associated with increased infectiousness in cell-culture models.<sup>5</sup>

The practical significance of SARS-CoV-2 following a dose-response relationship is seen at 2 levels: first in terms of symptoms and second in terms of transmissibility (Figure 1). Emerging data suggest that higher SARS-CoV-2 viral loads are associated with worsened severity of disease,<sup>6</sup> which align with previous observations that disease is more severe with higher viral loads in cytomegalovirus, herpes simplex virus, hepatitis B virus, and hepatitis C virus infections. Congruently, asymptomatic carriers of SARS-CoV-2 appear to be less efficient at transmitting SARS-CoV-2,<sup>7</sup> possibly because

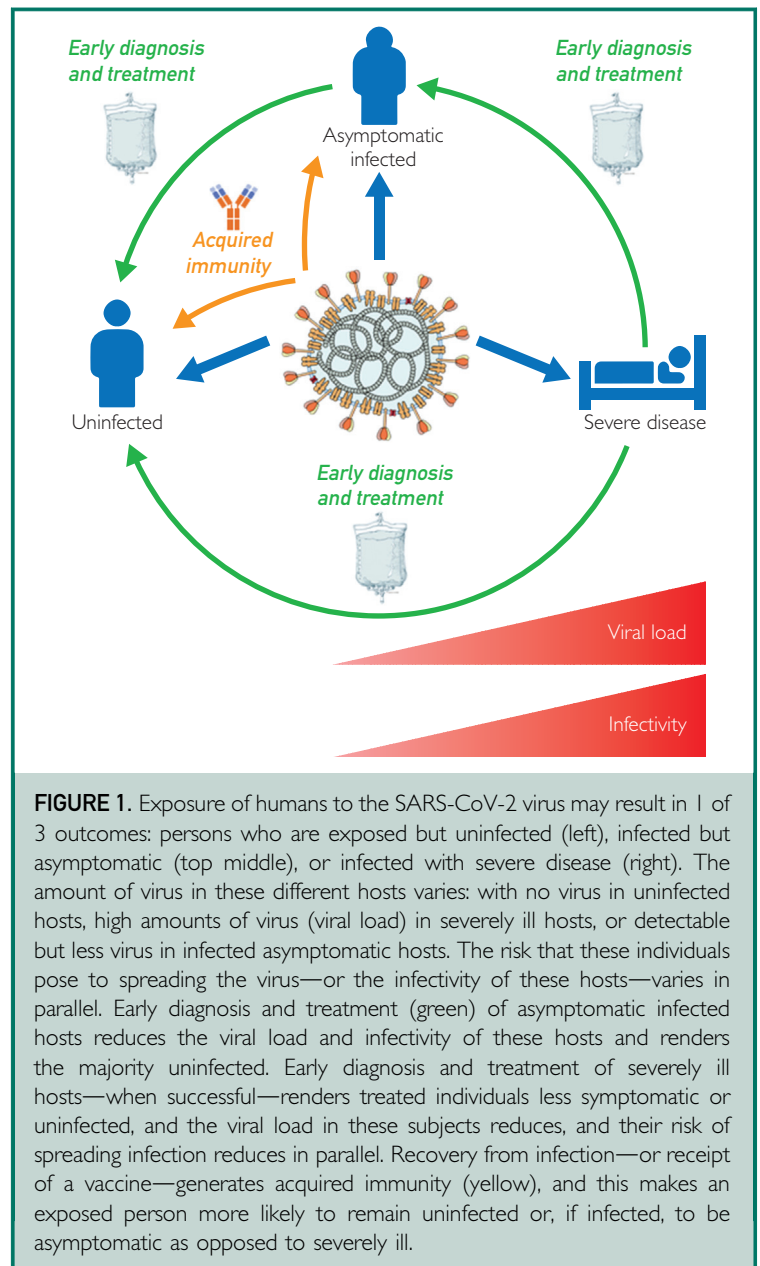
of reduced viral loads but also likely as a result of fewer symptoms, by definition, in asymptomatic persons. Because the symptoms of COVID-19 (coughing, in particular), increase effective droplet spread, fewer symptomatic cases translate to fewer droplets produced at or above the ID<sub>50</sub> over shorter distances.

It is good news that SARS-CoV-2 follows a dose response because any intervention that reduces virus copy number in infected hosts—or reduces the proportion of exposed persons who shed virus—will also reduce viral spread within populations. Knowing this, how can societies control the spread of the pandemic maximally? We posit that the following 3 interventions will be required in concert to achieve maximal control of the SARS-CoV-2 pandemic.

### ACQUIRED IMMUNITY

SARS-CoV-2 vaccines in humans have been shown to reduce the incidence of symptomatic infections by as much as 95%. Less is known about the impact of such vaccines of SARS-CoV-2 viral loads and consequent shedding. Rhesus macaques vaccinated with Ad26, then challenged with high-dose SARS-CoV-2, were followed for disease and viral load; vaccinated monkeys had fewer symptoms, less pathology, and greatly reduced viral loads (>3.0 log reductions) in both bronchoalveolar lavage samples and nasopharyngeal swabs.<sup>8</sup> Humans vaccinated with the ChAdOx1 nCoV-19 (AZD1222) vaccine, and prospectively monitored for proportion that shed virus by nasopharyngeal swab, showed that even a single dose of vaccine reduced viral shedding by 67%.<sup>9</sup> Thus, vaccination is very likely to reduce transmission, and early evidence supports that contention in a large population-based study in Israel.<sup>10</sup>

One of the enigmas of understanding immune-mediated protection is the concept of immune correlates of protection, or which element of the immune response is associated with protection from disease. An extreme example is seen with prophylactic HIV vaccines; most vaccines tested generate robust immune responses of virtually any



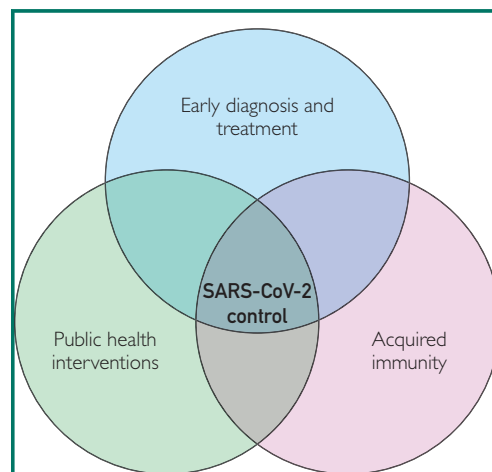
**FIGURE 1.** Exposure of humans to the SARS-CoV-2 virus may result in 1 of 3 outcomes: persons who are exposed but uninfected (left), infected but asymptomatic (top middle), or infected with severe disease (right). The amount of virus in these different hosts varies: with no virus in uninfected hosts, high amounts of virus (viral load) in severely ill hosts, or detectable but less virus in infected asymptomatic hosts. The risk that these individuals pose to spreading the virus—or the infectivity of these hosts—varies in parallel. Early diagnosis and treatment (green) of asymptomatic infected hosts reduces the viral load and infectivity of these hosts and renders the majority uninfected. Early diagnosis and treatment of severely ill hosts—when successful—renders treated individuals less symptomatic or uninfected, and the viral load in these subjects reduces, and their risk of spreading infection reduces in parallel. Recovery from infection—or receipt of a vaccine—generates acquired immunity (yellow), and this makes an exposed person more likely to remain uninfected or, if infected, to be asymptomatic as opposed to severely ill.

immune element assessed, but few, if any, confer protection against disease. In the case of SARS-CoV-2, monoclonal antispikes alone are sufficient to prevent human infection,<sup>11</sup> demonstrating de facto that 1 immune correlate of protection is antibody. That, in turn, informs our understanding of the protection conferred after recovery from natural infection. Recent data demonstrate that although antibody levels decay

over time in recovered patients with a half-life of  $\sim 83$  days, memory B cells, including those producing receptor-binding domain antibodies, increase over the first 4 to 5 months postinfection, strongly suggesting that natural infection produces lasting immunity to reinfection.<sup>12</sup> Indeed, although reinfections with SARS-CoV-2 have been reported, the rate of infection in subjects who are seropositive as a result of natural infection is significantly less than in seronegatives.<sup>13</sup> Accordingly, recovery from natural infection, affects disease susceptibility and will contribute to control of the pandemic.

### PUBLIC HEALTH INTERVENTIONS

For most of the pandemic, without a vaccine and with limited treatment options, non-pharmaceutical interventions (NPIs) have been the backbone of the response. These are public health interventions that reduce exposure to SARS-CoV-2 and, based on the dose-response principle, reduce infections and subsequent transmission. Analyses have shown efforts that reduce crowds by canceling public events and limiting private gatherings reduced rates of infection, as did restrictions on schools and workplaces.<sup>14</sup>



**FIGURE 2.** Maximal control of the SARS-CoV-2 pandemic will require a synergy of the effects of early diagnosis and treatment, public health interventions such as masking and social distancing, and the acquisition of immunity across a broad spectrum of society.

However, for these to be effective, the population has to adhere to the measures meticulously. Compliance with NPIs has reduced over time, and the impact of enacting and discontinuing them can lag for weeks, leading to the “seesaw” pattern of infections seen last year. As the impact of NPIs becomes increasingly apparent, it is critical to maintain this jointly with the other interventions described.

### TREATMENT AS PREVENTION

The concept of treatment as control reached maturity in the HIV epidemic, and we now know, definitively, that identifying and treating patients for HIV reduces the ability of an infected person to spread infection.<sup>15</sup> So, too, this is likely the case for SARS-CoV-2. Returning to the concept of infectiousness operating on a dose-response curve, and given that treatments with remdesivir and spike monoclonal antibodies reduce SARS-CoV-2 viral load, early and effective treatments are likely to reduce the ability of infected persons to spread virus by 2 means: by implementing quarantine and other isolation interventions and by reducing the viral load in treated persons, thereby reducing their ability to spread virus (Figure 2).

The remarkable development of accurate diagnostics, effective therapies, and preventive vaccines for SARS-CoV-2 have positioned societies to think about reopening; however, to be safe and effective, we propose an approach that maximizes the synergy of the 3 individually successful interventions of early diagnosis and treatment, public health interventions, and acquired immunity. Once control is achieved—defined as a low steady state of new infections—it might then be possible to consider relaxing of behavioral interventions such as masking.




**Grant Support:** Dr Badley is supported by grants from NIAID (grants A110173 and A1120698), Amfar (#109593), and Mayo Clinic (HH Shieck Khalifa Bib Zayed Al-Nahyan Named Professorship of Infectious Diseases).

**Potential Competing Interests:** Dr O'Horo has received consulting fees from Elsevier, Bates College, and Nference, Inc. for COVID-19–related work. Dr Badley is a paid consultant for Abbvie and Flambeau Diagnostics; he is a paid member of the DSMB for Corvus Pharmaceuticals

and Equilibrium; has received fees for speaking for Reach MD; owns equity for scientific advisory work in Zentalis and Nference; and is founder and President of Splissen Therapeutics. Dr Williams reports no competing interests.

**Correspondence:** Address to Andrew D. Badley, MD, Mayo Clinic College of Medicine, Division of Infectious Diseases, 200 First Street SW, Rochester, MN 55905 ([badley.andrew@mayo.edu](mailto:badley.andrew@mayo.edu); Twitter: [@BadleyAndrew](https://twitter.com/BadleyAndrew)).

#### ORCID

John C. O'Horo:  <https://orcid.org/0000-0002-0880-4498>; Amy W. Williams:  <https://orcid.org/0000-0001-7824-2067>; Andrew D. Badley:  <https://orcid.org/0000-0001-7796-7680>

#### REFERENCES

1. Watanabe R, Matsuyama S, Taguchi F. Receptor-independent infection of murine coronavirus: analysis by spinoculation. *J Virol*. 2006;80(10):4901-4908.
2. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet*. 2020;395(10242):1973-1987.
3. Zhang X, Wang J. Dose-response relation deduced for coronaviruses from COVID-19, SARS and MERS meta-analysis results and its application for infection risk assessment of aerosol transmission. *Clin Infect Dis*. 2020. Online ahead of print, <https://doi.org/10.10093/cid/ciaa1675>.
4. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. 2021;325(7):632-644.
5. La Scola B, Le Bideau M, Andreani J, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. *Eur J Clin Microbiol Infect Dis*. 2020;39(6):1059-1061.
6. Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis*. 2020;20(6):656-657.
7. Liu Z, Chu R, Gong L, Su B, Wu J. The assessment of transmission efficiency and latent infection period in asymptomatic carriers of SARS-CoV-2 infection. *Int J Infect Dis*. 2020;99:325-327.
8. Abu-Raddad LJ, Chemaitelly H, Coyle P, et al. SARS-CoV-2 reinfection in a cohort of 43,000 antibody-positive individuals followed for up to 35 weeks. *medRxiv*. Available at: <https://doi.org/10.1101/2021.01.15.21249731>.
9. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet*. 2021;397(10277):881-891.
10. Rossman H, Shilo S, Meir T, Gorfine M, Shalit U, Segal E. Patterns of Covid-19 pandemic dynamics following deployment of a broad national immunization program. *medRxiv*. 2021. Available at: <https://doi.org/10.1101/2021.02.08.21251325>.
11. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med*. 2020;384(3):229-237.
12. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*. 2021;371(6529):eabf4063.
13. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med*. 2021;384(6):533-540.
14. Askitas N, Tatsiramos K, Verheyden B. Estimating worldwide effects of non-pharmaceutical interventions on COVID-19 incidence and population mobility patterns using a multiple-event study. *Sci Rep*. 2021;11(1):1972.
15. Cohen MS. Successful treatment of HIV eliminates sexual transmission. *Lancet*. 2019;393(10189):2366-2367.