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A Blueprint to Control the SARS-CoV-2 Pandemic

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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.[1] 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.[2] 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,[3] 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.[4] Higher viral loads, as measured by cycle threshold values, are associated with increased infectiousness in cell-culture models.[5]

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,[6] 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,[7] possibly because

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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_{50} 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.[8] 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%.[9] Thus, vaccination is very likely to reduce transmission, and early evidence supports that contention in a large population-based study in Israel.[10]

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 immune element assessed, but few, if any, confer protection against disease. In the case of SARS-CoV-2, monoclonal antispike antibodies alone are sufficient to prevent human infection,[11] 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

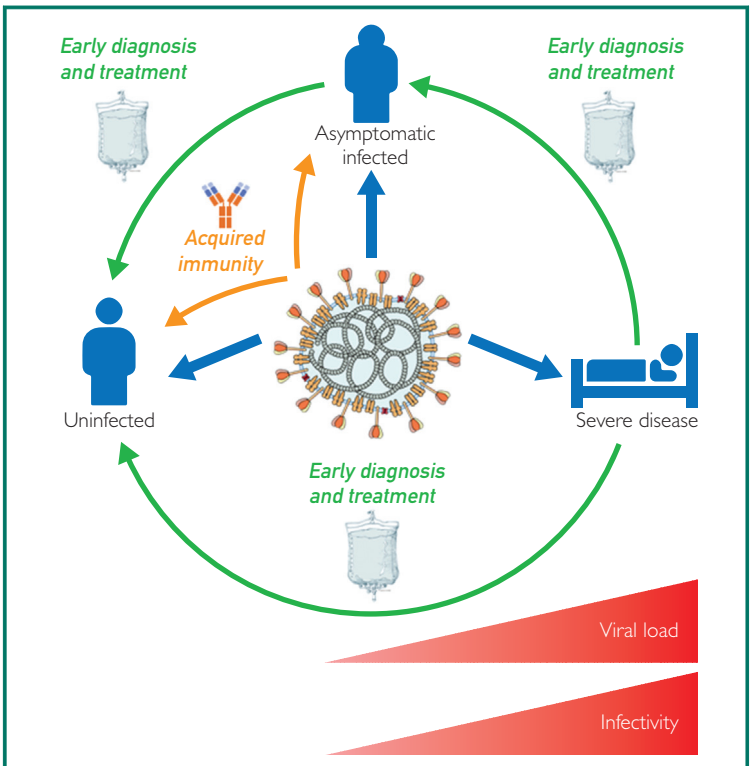

FIGURE 1. Exposure of humans to the SARS-CoV-2 virus may result in 1 of 3 outcomes: persons who are exposed but uninfected (left), infected but asymptomatic (top middle), or infected with severe disease (right). The amount of virus in these different hosts varies: with no virus in uninfected hosts, high 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.

over time in recovered patients with a half-life of ~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.[12] 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.[13] 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, nonpharmaceutical 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.[14]

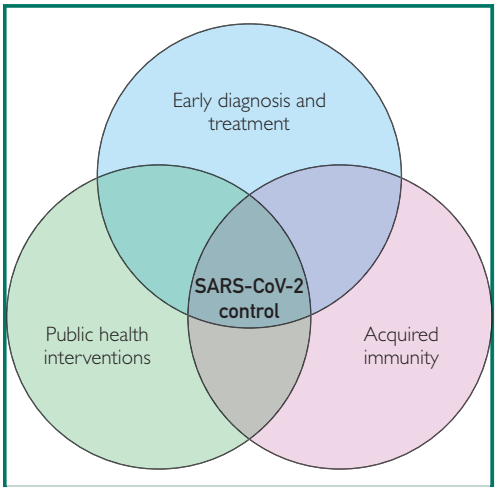

FIGURE 2. Maximal control of the SARS-CoV-2 pandemic will require a synergy of the effects of early diagnosis and treatment, public health interventions such as masking and social distancing, and the acquisition of immunity across a broad spectrum of society.

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.[15] 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.

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and Equilium; 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.

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