

## COVID-19: Time for precision epidemiology

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The global COVID-19 (SARS-CoV2, COVID-19) tsunami caused by SARSCoV2 is inundating and often-overwhelming health care systems in most countries and regions. Numbers of infected people and the death toll are increasing, with the fortunate exception of the first hit or the best prepared regions of East Asia. While some governments have had success in containing the spread of the virus, the global situation is constantly changing, usually for the worse, and the measures applied by different countries have often been ineffective.

Are we responding too slowly or are our measures too mild or too generic to contain the virus? It is clear that we are missing something, as most of our attempts have been unable to stop the spread of infection. SARS-CoV2 is a new virus and we are missing much key information that is vital to develop and implement fast and appropriate interventions.

Data-driven action is needed to improve the effectiveness and efficiency of interventions at all phases of this pandemic. The present commentary addresses a few of the key—(and we sincerely hope), obvious issues to blunt the trajectory of COVID-19—not just in this early phase of the pandemic, but also during the subsequent more pervasive and quiescent phases of spread and viral mutation.

At present, we do not doubt that isolation and social distancing are the most effective measures to contain the virus, but it is critical that we define at the finest granularity what virus variants are infecting what populations. What genetic, developmental, and environmental cofactors modulate the severity of COVID-19 diseases? Can we gain enough information in the next three months to triage and ultimately to vaccinate the most critical subgroups within each population?

Isolation will be far more effective if we know who we need to isolate, who is infected with which SARS-CoV2 variant (and there are already many), and the precise locales of infections. We need to identify both those who have been exposed and those who are infected to be

efficient to mitigate and possibly eliminate the COVID-19 pandemic.

Authors of this article propose the following seven points for immediate action:

1. The first goal should be identification of all or almost all those infected and to achieve effective isolation against a backdrop of tremendous variation in social setting and housing space. Regardless of social context, to achieve this goal will require a great deal more testing than has been typical even in wealthy and nominally well-prepared European and North American countries. In areas outside of hot spots, we need to test samples using a variety of selection parameters: (1) those entering from areas of high risk, (2) individuals working in health care, (3) individuals with high mobility within a community, (4) a systematic random sample by age, sex, ancestry, and social setting. There is hard evidence that COVID-19 infection is contagious 2–3 days before any symptoms and that a large proportion of infected people are symptomless.<sup>1–3</sup> This finding explains why the simple isolation based on clinical symptoms does not work for the present pandemic. In addition, there is also evidence that the regions with significant testing activity (South-Korea, <https://news.sky.com/story/coronavirus-experiment-in-northern-italian-town-halts-all-new-infections-after-trial-11959587>) have been successful in isolating the infection and stopping the spread.
2. Why is it important to identify those infected and isolate them? The best way to think of this infection right now is to consider the domino model. One single infected individual, with a transmission rate of 2 (one person infecting two people, it is  $R_0 = 2$ ) will give a total infected population of over a million people in just two weeks. However, if half of these

dominos were to be taken out (isolated) every three days, leaving the remainder to continue infecting at the same rate, the total number of infections after two weeks will be less than 5000. In case of the COVID-19, the  $R_0$  value could be as high as 4.5 and this means much wider spread, causing the difficulties to contain it.<sup>4</sup> There is no substitute for social isolation of infected persons, but we have to know who these subjects are that we need to isolate. If testing of very large sections of the whole population on a regular basis is not feasible for logistic or economic reasons, social isolation of very large sections of the population is the only effective means of containment. Ideally, in a scenario that protects the most vulnerable sections in the population, slow progression of the infection amongst the least vulnerable sections of the population could contribute to the development of herd immunity. Once an effective vaccine has become available, of course mass vaccination will achieve population-based immunity. The success of this approach will depend on our efficiency to detect the infected persons by repeated and mass-based testing, until an efficient assay for the identification of persons resistant to infection or re-infection becomes available.

3. We need a global mobilization to support much higher and faster testing that is necessary to fulfill the goal of identifying the journey of the virus in the population and targeting the most at risk areas in the community. We need to engage researchers and available resources across the globe. This includes diagnostic laboratories, hospital systems, universities, research institutes, and potentially any group who can perform validated reverse transcription polymerase chain reaction (RT-PCR) or polymerase chain reaction (PCR) tests in areas farther removed from diagnostic and health care facilities. The governments need to provide resources to run the tests and to organize the custody of collected samples. After identifying the infected persons, we need to trace back their whereabouts and isolate the infected persons. This is the only way to stop the COVID-19 pandemic in the foreseeable future.
4. Systematic retesting of individuals, especially in the vicinity of hot spots, should be performed within a week or 10 days to identify the fraction of cases who had virus, but with undetectable levels upon initial testing. We also need to start testing for seroconversion to detect those who developed immunity. These could be infected people, symptomatic or otherwise, who developed neutralizing antibodies, thus developing possible resistance to re-infection.
5. Intensive testing and identification of virus carriers help us to minimize risk to those working on the health care frontlines. These are health care professionals, law and immigration officers, those in the energy, transportation, and utility service sectors,

social workers, food and other service providers, and any group with high mobility between areas. Even in lockdown, our societies have to maintain essential functions and we have to protect those who are key to these core functions.

6. We need an intensive global collaborative research effort to describe the clinical course and virus cycle based on highly diverse patient populations. Why do some individuals not develop symptoms, why are children relatively inured to clinical disease? How do genetic variants in genes such as *ACE2* modulate the infection cascade, influence the susceptibility to SARS-CoV2? What is the duration and efficacy of immunity after initial infection? What is the comparative virulence of different variants of SARS-CoV2 and how do these variants interact with genetic and environmental factors of host humans?
7. Research results related to COVID-19 should be submitted, reviewed, published quickly, and made freely available. We need to maximize the amount of information we have, which is the best way to outrun and overcome COVID-19 and subsequent pandemics.

We encourage the governments and research communities to initiate immediate global molecular testing for the SARS-CoV2 infection, as using only the clinical symptoms to detect infected persons is too slow ( $R_0 = 4.5$ ).<sup>4</sup> We call for the initiation of precision epidemiology that is a modernized workflow taking into account the viral genome, the host genome and response, exposure history, and the disease trajectory. Precision epidemiology will help us to overcome the ongoing pandemic and would protect our communities from potential outbreaks in the future. Extensive testing combined with appropriate data interpretation is a fundamental requirement to stop the ongoing pandemic. The testing needs to be repeated several times as persons with negative tests could become positive the next day as a result of a new infection or the replication of the virus. In either case, the individual testing negative could still transmit the infection and the false assurance of negative results could have severely negative impacts. Repeated testing will reduce the risk of missing these events. These would be the first steps to stop the propagation of the virus. Additional molecular tests for re-infection resistance, immunological response or clinical prognosis are required in the next phase of the fight against COVID-19. These are some of the most important steps we are required to take in order to overcome this pandemic and to be better prepared for any similar outbreaks in the future.

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