



# Perspective

## Defining the Epidemiology of Covid-19 — Studies Needed

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The epidemic of 2019 novel coronavirus (now called SARS-CoV-2, causing the disease Covid-19) has expanded from Wuhan throughout China and is being exported to a growing num-

ber of countries, some of which have seen onward transmission. Early efforts have focused on describing the clinical course, counting severe cases, and treating the sick. Experience with the Middle East respiratory syndrome (MERS), pandemic influenza, and other outbreaks has shown that as an epidemic evolves, we face an urgent need to expand public health activities in order to elucidate the epidemiology of the novel virus and characterize its potential impact. The impact of an epidemic depends on the number of persons infected, the infection's transmissibility, and the spectrum of clinical severity.

Thus, several questions are especially critical. First, what is the full spectrum of disease severity (which can range from asymp-

tomatic, to symptomatic-but-mild, to severe, to requiring hospitalization, to fatal)?

Second, how transmissible is the virus?

Third, who are the infectors — how do the infected person's age, the severity of illness, and other characteristics of a case affect the risk of transmitting the infection to others? Of vital interest is the role that asymptomatic or presymptomatic infected persons play in transmission. When and for how long is the virus present in respiratory secretions?

And fourth, what are the risk factors for severe illness or death? And how can we identify groups most likely to have poor outcomes so that we can focus prevention and treatment efforts?

The table lists approaches to answering these questions, each of which has shown success in prior disease outbreaks, especially MERS and pandemic H1N1 influenza.<sup>1</sup>

Counting the number of cases, including mild cases, is necessary to calibrate the epidemic response. Conventional wisdom dictates that the sickest people seek care and undergo testing; early in an epidemic, case fatality and hospitalization ratios are often used to assess impact. These measures should be interpreted with caution, since it may take time for cases to become severe, or for infected persons to die, and it may not be possible to accurately estimate the denominator of infected people in order to calculate those ratios.<sup>2</sup> As in past epidemics, the first cases of Covid-19 to be observed in China were severe enough to come to medical attention and result in testing, but the total number of people infected has been elusive. The esti-

Types of Evidence Needed for Controlling an Epidemic.	
Evidence Needed	Study Type
No. of cases, including milder ones	Syndromic surveillance plus targeted viral testing
Risk factors and timing of transmission	Household studies
Severity and attack rate	Community studies
Severity “pyramid”	Integration of multiple sources and data types
Risk factors for infection and severe outcomes, including death	Case-control studies
Infectiousness timing and intensity	Viral shedding studies

mated case fatality ratio among medically attended patients thus far is approximately 2%, but the true ratio may not be known for some time.<sup>2</sup>

Simple counts of the number of confirmed cases can be misleading indicators of the epidemic’s trajectory if these counts are limited by problems in access to care or bottlenecks in laboratory testing, or if only patients with severe cases are tested. During the 2009 influenza pandemic, an approach was described for maintaining surveillance when cases become too numerous to count. This approach, which can be adapted to Covid-19, involves using existing surveillance systems or designing surveys to ascertain each week the number of persons with a highly sensitive but nonspecific syndrome (for example, acute respiratory infection) and testing a subset of these persons for the novel coronavirus. The product of the incidence of acute respiratory infection (for example) and the percent testing positive provides an estimate of the burden of cases in a given jurisdiction.<sup>3</sup> Now is the time to put in place the infrastructure to accomplish such surveillance. Electronic laboratory reporting will dramatically improve the efficien-

cy of this and other public health studies involving viral testing.

More generally, it is useful to synthesize data from simultaneous surveillance studies, epidemiologic field investigations, and case series.<sup>1</sup> Conducting cohort studies in well-defined settings such as schools, workplaces, or neighborhoods (community surveys) can help in describing the overall burden and the household and community attack rate; perhaps most important, it can permit rapid assessment of the severity of the epidemic by counting the number of illnesses, hospitalizations, and deaths in a well-defined population and extrapolating that rate to the larger population.<sup>4</sup> Understanding transmissibility remains crucial for predicting the course of the epidemic and the likelihood of sustained transmission. Several groups have estimated the basic reproductive number  $R_0$  of SARS-CoV-2 using epidemic curves, but household studies can be superior sources of data on the timing and probability of transmission and may be useful in estimation of  $R_0$ .<sup>5</sup>

Household studies can also help define the role that subclinical, asymptomatic, and mild infections play in transmission to inform evidence-based decisions

about prioritization of control measures; measures that depend on identification and isolation of symptomatic persons will be far more effective if those persons have the primary role in transmission. On the other hand, if persons without symptoms can transmit the virus, more emphasis should be placed on measures for social distancing, such as closing schools and avoiding mass gatherings. To evaluate whether the risks that school closure poses to children’s well-being and education — and to productivity if working parents are needed for child care — are justified, we must learn whether children are an important source of transmission. Household studies can also be used to conduct viral shedding studies that can help determine when patients are most infectious and for how long they should be isolated.

A key point of these recommendations is that viral testing should not be used only for clinical care. A proportion of testing capacity must be reserved to support public health efforts to characterize the trajectory and severity of the disease. Although this approach may result in many negative test results and therefore appear “wasteful,” such set-aside capacity will permit a far clearer understanding of the spread of the epidemic and wiser use of resources to combat it. Testing in unexplained clusters or severe cases of acute respiratory infections, regardless of a patient’s travel history, may be a sensitive way to screen for chains of transmission that may have been missed. Such findings are relevant particularly in light of evidence that even Singapore, with one of the world’s best public health systems, has found

cases that have so far not been linked to known cases or to Chinese travel. If such undetected introductions are happening in Singapore, it is prudent to expect they are happening elsewhere as well.

Early investments in characterizing SARS-CoV-2 will pay off handsomely in improving the epidemic response. If sustained transmission takes off outside China, as many experts expect, the urgency of the epidemic will necessitate choices about which interventions to employ, under which circumstances, and for how long. Starting these epidemiologic and surveillance activities promptly will enable us to choose the most efficient ways of controlling the epidemic and help us avoid interventions that may be unnecessarily costly or unduly restrictive of normal activity.

Many urban centers in China are or will soon be overwhelmed with the treatment of severe cases.

It may be difficult for many of them to perform the kinds of studies described here. One exception is systematic surveys of persons who are not suspected to have Covid-19 or who have mild respiratory illness, to assess whether they are currently subclinically infected (viral testing), have been infected previously (serologic testing), or both. These studies, which will inform estimates of the severity spectrum, will be most informative in the settings that have the most cases.

Fortunately, the numbers of detected cases outside China remain manageable for public health authorities — and too small for the conduct of such studies. But it is vital for jurisdictions outside mainland China to prepare to perform these studies as case numbers grow.

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1. Lipsitch M, Finelli L, Heffernan RT, Leung GM, Redd SC. Improving the evidence base for decision making during a pandemic: the example of 2009 influenza A/H1N1. *Biosecur Bioterror* 2011;9:89-115.
2. Lipsitch M, Donnelly CA, Fraser C, et al. Potential Biases in Estimating Absolute and Relative Case-Fatality Risks during Outbreaks. *PLoS Negl Trop Dis* 2015;9(7):e0003846.
3. Lipsitch M, Hayden FG, Cowling BJ, Leung GM. How to maintain surveillance for novel influenza A H1N1 when there are too many cases to count. *Lancet* 2009;374:1209-11.
4. Janusz KB, Cortes JE, Serdarevic F, et al. Influenza-like illness in a community surrounding a school-based outbreak of 2009 pandemic influenza A (H1N1) virus — Chicago, Illinois, 2009. *Clin Infect Dis* 2011;52: Suppl 1:S94-S101.
5. Cauchemez S, Donnelly CA, Reed C, et al. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. *N Engl J Med* 2009;361:2619-27.

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