The SARS Coronavirus: Rapid Diagnostics in the Limelight

As the severe acute respiratory syndrome (SARS) epidemic spreads, specific, rapid, and practical diagnostic tests will become increasingly critical, both for the control of the epidemic and for the management of patients. At present, outside East and Southeast Asia diagnosis depends on a clinical case definition that includes travel to, or exposure to sick contacts who have traveled to, specific parts of the world *(1)*. As the epidemic matures, however, such epidemiologic connections will be increasingly difficult to demonstrate, and a clinical case definition that depends on this information will become increasingly irrelevant. In East and Southeast Asia, the rapidly expanding epidemic makes specific viral diagnosis even more essential. In such an evolving situation, the report by Poon et al. from Hong Kong *(2)*, in combination with the published diagnostic technologies of that group and others in Europe and the United States *(3–5)*, takes on extraordinary importance. Moreover, the development and publication of a rapid test for the SARS coronavirus in clinical samples, just weeks after the first reports of the emergence of the disease *(6)* is extraordinary.

As a historical footnote, this technologic tour de force is in extreme contrast to the diagnostic tests that led to the first descriptions of coronaviruses over 35 years ago. At that time, the most rapid diagnosis was by production of cytopathic effect after subpassage in tissue culture *(7)*, but most coronaviruses were recognized only with the use of human embryo tracheal organ cultures, and viral presence was detected by cessation of ciliary motion, by electron microscopy of nutrient media, or most cumbersome of all, by inoculation and production of colds in human volunteers *(8, 9)*. In fact, difficulty of diagnosis has dogged the field of human coronaviruses and hampered progress throughout its history.

The test described by Poon et al. *(2)* looks good. It appears to become positive before antibodies first appear, as we would expect from a sensitive test for virus. In the limited studies described, it performed quite well, although not as well as we could have hoped (sensitivity of 79% and specificity of 98% in relation to acute-to-convalescent seroconversion). From melting curves it was judged that the viral sequence did not vary from patient to patient, which bodes well for any PCR-based technique. Clearly the test requires validation in larger series of cases and non-cases to refine estimates of its performance. This is particularly critical with regard to its specificity, because rapid viral diagnosis is likely to play an extremely important role in areas where SARS is not actively epidemic. In such settings, false positives have the potential to fuel panic, and the test will be used much more often in those who do not have SARS coronavirus infection than in those who do. Of almost equal importance will be the demonstration that the test can be exported to other laboratories without loss of sensitivity or specificity.

To judge the real value of this test and therefore to use it optimally, we need much more information. What are the best specimens to obtain from patients? The Germans found that sputum contained a far stronger PCR signal than upper respiratory tract samples *(5)*; Poon and his colleagues *(2)* tested only nasopharyngeal aspirates. It could be that if sputum had been used instead, the sensitivity of the test would have been closer to 100%. When, during the course of illness and infection, do samples become positive? When do they become negative? What is the distribution of virus in the body? Is it in the blood? When? Is it in the urine? It appears to be present in the stool, but there is almost no information on either the quantity or the timing and duration of shedding.

A PCR-based diagnostic test for an infectious disease has advantages and disadvantages. It can be expected to be very sensitive. It allows a read-out in a matter of hours. It also has the potential to be quantitative. On the other hand, it is expensive, and it requires technology and trained technologists often not available in the locality of the disease. In addition, it says nothing about the infectiousness of the virus that is found. Like other tests for the virus, however, it can be anticipated that it will become positive early in the course of the illness, allowing the guidance of therapeutic and management decisions, as well as early institution of precautions to control contagion. If it turns out that it is very sensitive during the course of the disease, the value of a negative test may be even greater than that of a positive test, in its capacity to relieve patient, family, and community anxiety.

Moreover, a test for virus can give valuable information for those trying to contain the epidemic, both locally and globally. This test, as well as tests for infectious virus, need to be applied to a large number of cases in a prospective manner to make educated guesses about when during the course of the illness infected individuals are likely to be contagious. Case reports of SARS have described the presence of fever before the beginning of respiratory symptoms *(10, 11)*. Is virus in respiratory secretions at this stage? Is it there even before the fever begins? In studies of the "old" coronaviruses in human volunteers, virus could be isolated from nasal secretions before the onset of respiratory symptoms *(12)*. Is that true here? The same questions can and should be asked about fecal shedding.

We already know that antibody to the SARS coronavirus appears relatively late in the course of infection. There is no information available yet, however, on the time of appearance of IgM antibody, and this may prove to be an important adjunctive test in the early identification of infections.

An ideal test for virus will be not only rapid, sensitive, and specific, but also inexpensive and technologically simple, so that it is available at the point of care even in

small hospitals or in communities in the developing world. No tests designed to detect virus in clinical samples have satisfied all these criteria, but antigen detection tests probably come the closest. The academic, biotechnical, and epidemiologic forces around the world should be frantically working to create specific and sensitive mono- and polyclonal antibodies to this virus and assembling antigen detection tests that will move us quickly into the next era of diagnosis. Specific diagnosis will help to lessen fear. This test, and those that follow it, will make a major contribution to public health and the care of patients with respiratory infections as the SARS coronavirus spreads through the world.

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