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Editorial

The Role of Community Molecular Diagnostics Laboratories in the H1N1 Pandemic

Ten weeks after the virus first appeared, the initial H1N1 influenza pandemic episode appears to be waning in the United States. Everyone involved is breathing a bit more easily knowing that this novel virus is not as virulent as we had originally feared. This episode tested our preparedness for a more virulent outbreak, which has been the subject of numerous planning meetings since the arrival of SARS and Avian Flu several years ago. It is now time to ask the hard questions: How prepared were we? Was our public health response adequate? Was our clinical response appropriate?

This H1N1 pandemic episode has particular significance for those of us who work in molecular diagnostics laboratories, as it is the first pandemic in the age of molecular diagnostics. To be sure, the traditional methods of the virology laboratory are still important, but now the primary focus is on the viral sequence, including the evolution of the virus, its identification, screening tests, diagnosis, and even drug resistance when it emerges. This episode is ours.

So how have molecular diagnostics laboratories performed during this pandemic? Very well, we believe. In the Chicago area, during the first 4 weeks of the pandemic, 62% of nearly 8000 patients were first screened for H1N1 by community molecular diagnostics laboratories (both academic and non-academic labs, not affiliated with public health laboratories). Indeed, more than half of the total cases of H1N1 (or probable H1N1) in Illinois were first diagnosed in community molecular diagnostics laboratories. It is reasonable to ask how this came about. What elements were in place that made this rapid, effective laboratory response possible? We can point to several key factors without which this kind of response could not have occurred.

First, we need to acknowledge that there exists in this country a large network of well-developed molecular diagnostics laboratories. Some of these are located in academic centers, but others are in the community hospital setting. Characteristically, these laboratories are staffed by directors and personnel trained in molecular diagnostics with expertise in the development and validation of clinical tests. This rich resource, the foundation of modern molecular medicine, is generally undervalued, unappreciated, and, as evidenced in this most recent public health emergency, underutilized.

The 2009 College of American Pathologists Survey for molecular testing for influenza boasts an enrollment of more than 100 laboratories, a 50% increase over the 2008 enrollment. This is a reasonable benchmark for the number of laboratories capable of routine molecular testing for influenza. An informal survey of Association for Molecular Pathology member laboratories during the first week of the H1N1 episode showed that 93% of the 43 respondents had a molecular assay that could detect and distinguish influenza type A from type B. Those laboratories had an aggregate test capacity of 3000 to 4000 specimens per day, and could expand their capacity to as much as 12,000 specimens per day within 30 days if needed. Thirty-six percent of the laboratories reported having the capability of distinguishing the novel H1N1 strain from seasonal H1 strains. During the first week of the outbreak, those laboratories had an aggregate test capacity approaching 2500 specimens per day, with a potential for expanding within 30 days, handling nearly 8000 specimens daily. Even with a disease incidence as low as 5%, this test capacity could have easily accommodated all of the testing that identified the nearly 28,000 infected patients in the United States that the Centers for Disease Control and Prevention has documented at this time. This is only a fraction of our true test capacity.

It is important to note that reports from these laboratories are largely available within 24 hours of specimen collection, a degree of timeliness not likely to be matched by any public health laboratory. There can be no argument that accurate, timely data are crucial for making public health decisions in the first hours and days of an emerging pandemic. By the end of the first week of the H1N1 episode, our own laboratory had identified 39 cases of "probable H1N1 infection" (our laboratory initially reported cases of influenza A, not seasonal H1 or H3, as "probable H1N1, pending confirmation by the public health laboratory"), only a fraction of which had been corroborated by our state public health laboratory, and confirmed only sometime after day 8. The Centers for Disease Control and Prevention tally for all of Illinois at the end of that week was still only three cases confirmed, a number widely reported in the media, misinforming the

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public and the medical community of the true nature of the pandemic.

The ability of clinical laboratories to respond as they did was very much tied to their ability to develop and validate their own assays, ie, laboratory-developed tests. This ability to develop new analytical procedures in response to clinical need is deeply rooted in the tradition of the pathologist as the clinical scientist. This role, this responsibility, is now shouldered primarily by us, molecular pathologists and laboratory directors who bring molecular diagnostics to patient care. The Association for Molecular Pathology survey respondents used more than five different commercial assays, both analyte-specific reagent and *in vitro* diagnostic tests, in their laboratories, and 18% had noncommercial laboratory-developed tests in use. Whether or not they were cleared by the US Food and Drug Administration, none of these existing assays had been approved for the detection of the novel virus. Adaptation for this use could only be accomplished by validation as a laboratory-developed test in the performing laboratory.

This rapid adaptation only occurred due to the availability of the H1N1 sequence data, which is as important to the manufacturer of *in vitro* diagnostics as it is to the developer of a laboratory-developed test. These data need to be accessible, quickly and without limitation. Analyte-specific reagent manufacturers, prone to invoking proprietary restrictions when it comes to releasing sequence information, need to provide sequence, concentration, and purity information for their products as a matter of routine. *In vitro* diagnostics manufacturers, however, may encounter a dilemma in providing information that could promote unauthorized use of their products. This problem could be readily addressed through an Emergency Use Authorization as was issued by the US Food and Drug Administration for the H1N1 confirmatory assay developed by the Centers for Disease Control and Prevention; however, policies and mechanisms to follow any such course of action need to be in place beforehand.

None of these arguments should be construed as calling for diminished standards with regard to laboratory testing. Test validation, as always, needs to be rigorous and thorough, but it need not be slow. Indeed, the vast majority of molecular diagnostic tests for infectious agents originate as clinical laboratory-developed tests in response to clinical need, and it is exactly that nimbleness afforded the clinical laboratory that is called for during a public health emergency. Leveraging that capability for the benefit of the public's health, however, does call for forethought and planning.

Communication and collaboration with local public health laboratories are essential. The primary functions of the community molecular diagnostics laboratory and the public health laboratory are not the same. The former is focused on rapid diagnosis for patient care, and in a pandemic, for effective infection control and possible allocation of limited resources. The public health laboratory necessarily takes a broader view to understand the epidemiology of the pandemic, with an eye to formulating public policy. Both activities are necessary, but they are not independent. Understanding and coordinating their different roles not only enhances their respective values, but results in an efficiency that cannot be achieved otherwise. Preparations are currently underway within the public health laboratory network for the coming influenza season, with projections that H1N1 will be a significant player. This is an opportune time for the laboratory response network to engage the community molecular diagnostics laboratories in a dialogue to develop cohesive testing strategies. Our experience in the Chicago area suggests that the impetus to do this will not likely come from Washington or Atlanta but needs to start locally.

In the next pandemic, as in the next H1N1 wave to visit this country, it is reasonable to expect that most infected individuals will be diagnosed with a test performed in a community molecular diagnostics laboratory. Appropriate treatment decisions, effective infection control measures, and prudent use of antiviral agents, all demand accurate and timely diagnoses and will drive the further implementation of molecular assays. We believe that community molecular diagnostics laboratories offer an unprecedented resource to our public health pandemic planning efforts and suggest that they be an integral part of future strategic planning.

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