To: Subcommittee on Oversight and Investigations, February 12, 2016

"Outbreaks, Attacks and Accidents: Combatting Biological Threats

Question from:

The Honorable Michael C. Burgess, MD

1. **As a physician, I understand that the development and validation of precise diagnostics for emerging outbreaks is crucial to combating biological threats such as Zika virus. We need to quickly develop diagnostics for these purposes and work to ensure that public health laboratories and hospital laboratories throughout the country are able to screen people for the disease and that patients have access to these tests. I'm concerned that the CDC is creating barriers for laboratories to quickly disseminate the test and by not enabling competing tests, there's no way to assess whether or not the CDC test is adequate. Please describe the process CDC engages in for sharing necessary information, test reagents, and reference materials to laboratories to develop tests for emerging infectious diseases. I've also heard that despite the lack of cooperation from the CDC, some physicians have already developed tests for Zika virus at Texas Children's Hospital and Stanford University. Have you considered collaborating with these academic medical centers on developing diagnostics?**

ANSWER:

Thank you for the question, Congressman. Accurate diagnostic tests are essential tools for rapidly identifying and quenching epidemics of infectious disease. The strategic importance of diagnostic tests is not well recognized, and not reflected in government funding for infectious disease, and there are multiple, significant market issues which discourage the private sector from developing diagnostics for infectious disease, in spite of a wealth of technologies which could be utilized. Some of these impediments include regulatory hurdles – particularly regulatory uncertainty; poor return on investment for diagnostics compared to therapeutics; significant hurdles associated with getting new tests approved for payment by layers of insurers; and even hospital resistance to using new tests because billing practices are "locked-in" to electronic health records and difficult to change.

I am not familiar with the details of CDC's efforts to develop and disseminate diagnostic tests for Zika virus. Typically, CDC – which is, at heart, a reference laboratory – seeks to develop highly accurate tests that serve as the standard for all other tests and then disseminates the procedures and reagents for conducting such tests to state public health labs and other reference laboratories around the country. It takes time to develop and validate such tests and to procure and distribute the necessary instructions, reagents, etc. These tests may diffuse into clinical care settings or other test processes may be developed by diagnostic companies, achieve FDA approval and become the usual method of diagnosis in clinical labs because they are deemed sufficiently accurate and seen as cheaper, easier, faster, etc.

Sophisticated clinical laboratories, including for-profit labs and many hospital labs, have sometimes developed their own diagnostic tests, to provide faster results, reduce costs or to address specific clinical questions. Over time, the number of such tests has grown. This is not necessarily a bad development, but it does make it difficult to compare the results of different tests across institutions.

As I know you recognize, Congressman, the usefulness and performance characteristics of a diagnostic test, known as the Positive Predictive Value (PPA), varies depending on the "use case" and setting in which it is employed. The PPA of a test measures the percentage of the time a test accurately reports a "positive" result when the infection or condition of interest is actually present. PPA, and its counterpart, the Negative Predictive Value (the percent of time a Negative test result accurately reports that the infection being tested for is truly not present), are measures of the sensitivity and specificity of the test and the prevalence of the disease or condition in the population being tested.

The dilemma with Zika virus is that CDC – and the country – have a legitimate and pressing interest in ensuring that the reference diagnostic tests in use are accurate and reliable. Meanwhile, patients and their physicians are desperate for a diagnosis and clamoring for an acceptable diagnostic in the absence of a commercially available test, thus putting pressure on hospitals to develop their own methods. Different tests being developed by different hospitals, without careful standardization and comparison, guarantees differences in performance – i.e. differences in False Positive, False Negative results from test to test. Without an understanding of how "bespoke" tests compare to a "gold standard", clinicians cannot make informed judgments of test results, and CDC will be unable to assemble a clear picture of the incidence or prevalence of Zika in the population. The stakes on both sides are quite high, but in the long term, it is clearly in the public interest to have a reliable reference diagnostic as well as other diagnostic tests designed for specific use cases.

In-Q-Tel is not in a position to develop diagnostic tests, but as part of our BiologyNext Initiative, we are examining new diagnostic technologies – especially how new tools might enable the rapid design and manufacture of cheap diagnostics that deliver results within an hour – and market issues associated with private sector development. One can imagine the West Africa Ebola outbreak might have been controlled faster and with fewer victims had we had such diagnostic tools at hand or were able to develop them quickly. Thank you for noting the efforts at Stanford and Texas Children's Hospital to develop Zika diagnoses. My colleagues and I are interested in learning more about their work and will pursue.

It is important to recognize that diagnostic tests for infectious disease are **strategically** important to attempts to achieve early recognition and containment of disease outbreaks. Without clear diagnostic confirmation of cases, decision makers almost always delay action until a large number of cases have accumulated, erasing any doubt of an outbreak – and by then, the challenge of quenching the outbreak is more challenging. Lots of effective diagnostic technologies are available, some offering rapid read-outs. Major impediments to developing such tests include regulatory uncertainty, the difficulty of obtaining curated samples of the infectious agent in question to validate tests, poor return on investment due to billing practices, and the US government's failure to recognize the importance of and provide support for (e.g. through BARDA) rapid, reliable clinical diagnostic tests that could be used at point-of –care.

Submitted by: Tara O'Toole, MD, MPH

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