The Language of Zika Virus Testing

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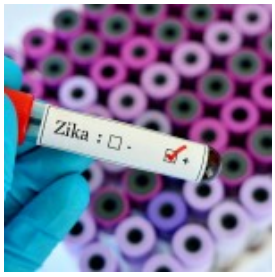

Abstract:

When a new virus emerges or an old one re-emerges, one of the earliest conversations is about whether there exist good tests to detect it. Laboratory testing takes different forms but remains key to understanding whether an emerging virus is or was present in a suspected case of infection. Testing is the first step in understanding how many cases have occurred, how long they have been occurring, the range of disease outcomes possible or whether there really is any link between detection of the virus and disease. Virus tests have indeed kept pace with the latest emerging virus outbreaks, but perhaps virus testing has not.

Main Article:

If a disease is thought to be caused by a virus, laboratory testing is usually needed to confirm the virus is there. Which patients are sampled for testing, what samples are collected, what tests are used and whether and how the results are reported are all affected by the same politics of life that are found in any human decision making process.

In recent years there have been lots of news stories about scary-sounding outbreaks of new viruses we knew about, but ignored. Sometimes the commentary describes the lack of any test for the virus. This may be true when the outbreak occurs in a region of the world with few resources, limited experience or testing expertise. Sometimes the message is just confused, misleading or plain wrong.

A primer on human virus testing

Laboratory virus testing usually involves the polymerase chain reaction (PCR) which can detect small amounts of the virus' genetic code in a sample from a sick person. Different testing involves finding evidence that the person was infected previously, by showing a change in their immune response (antibodies) to the virus. A "routine" lab can return a single result in six to eight hours if the specimen is appropriate, no technical problems occur, no repeat or add-on testing is required, and if result reporting is straightforward. There is a third group of tests – which can cover virus, antibody or other chemistry - that can be done at the point of care (POC) – these aim to be fast, inexpensive and more simple to interpret.

Routine lab tests can be performed in the clinic, as they are created or assembled by the laboratory, or they may come in ready-to-use commercial kits. Which type of test is used depends on local guidelines and regulations (which vary around the world) and on the skills and capacity of the laboratory to create, optimise, validate and oversee in-house testing. A major benefit of using a commercial kit is that reliability is assured. All the hard work of validating the test for

a range of different sample types and conditions has already been done by the company. There can still be a few issues with kits. For example, supply when demand is high, cost, and requirements for supporting reagents and equipment. Kit validation should also (but sometimes does not) consider and account for the impact of region-specific co-circulating pathogens. For example dengue and chikungunya viruses in areas where Zika virus (ZIKV) transmission is active.

Recent testing times

When Middle East respiratory syndrome (MERS) emerged, the narrative often focussed on the absence of good testing for its causal coronavirus (MERS-CoV). In reality, a reliable and robust PCR-based test, still widely used today, was described almost immediately.[1] Testing was available, but understanding of the importance of testing may have been the more critical shortfall.[2] Faster POC testing may have helped contain early spread from the very first, or index, case that triggers an outbreak in a healthcare setting.[3]

Understanding Of The Importance Of Testing May Have Been The More Critical Shortfall

The Zaire ebolavirus (EBOV) epidemic took place in a part of the world where modern testing was not resourced and unable to cope with the unexpected speed and ferocity of EBOV transmission.[4] Many good PCR-based tests were in use or in readiness around the world, but could not be used in West Africa, which lacked the supporting infrastructure of laboratories, equipment and trained personnel. Here, ready-to-go rapid, inexpensive, sensitive and specific POC tests would have been very useful for improved triage of suspected cases.[5]

Zika virus tests us more than we test for it

Forty countries have confirmed local ZIKV transmission since 2015 and once again we see claims that testing is inadequate.[6, 7] But precisely what about the testing is inadequate?

Whether because of limited resources, habit, mindset or simply the scale of the epidemics, some countries have reported ZIKV-positive lab results on only a small fraction of suspected positive patients. It is presumably hoped that these limited data will accurately represent the rise and fall of the epidemic. Clinical assessment is relied upon to document ZIKV presence. Clinical diagnosis is not accurate because the symptoms are indistinguishable from those due to other co-circulating viruses such as dengue, chikungunya and others that can cause rash and fever. We also know from a study in 2007, that up to 80% of ZIKV infected people may not have any signs of acute disease.[8]

ZIKV persists for a shorter time in serum than other viruses, yet serum is the commonly used sample for ZIKV testing. ZIKV is reportedly found for longer periods in whole blood and urine.[9] So PCR tests need to be performed fairly early on in the infection. There are good, highly specific ZIKV PCR tests that can detect infection [10, 11] and new ones that are being developed.[12]

There is a known issue of cross-reactivity in testing antibody responses to infection by flaviviruses, the family of viruses that ZIKV is part of.[13] A person who has high levels of antibodies against dengue virus [14] or West Nile virus [8, 15] for example, may show a positive result in a ZIKV antibody test. It is often hard to be sure whether that is because of true cross-reaction (the antibodies to different viruses both bind the same substrate used in the test) or because the person has been infected by both of the viruses, either at the same time, or consecutively. Collecting two serum samples, two weeks apart is essential. Different antibody detection tests, protocols, laboratories and approaches all perform differently. Specific ZIKV antibody test results are possible, but they require a good quality method that has

been well validated, ideally with additional testing for other mosquito-borne viruses likely to be in the same geographic region.[16]

It is hard to tell how often or exactly which of these tests are being used in the current epidemics because testing methods or findings are not always reported. There is no POC testing available for ZIKV.

What we need more of

When we read about a lack of tests or testing, what can be meant is that the tests we have are not easily available in sufficient quantities for the demand, they are not in kit form, they are not rapid, sensitive and specific, competitively priced or are simply not used. POC testing is a tool ideally suited to help contain outbreaks because it can be used when and where needed, to inform public health decisions and to aid infection control; for viruses the reality of POC testing has to date fallen far short of the promise.[17, 18]

That said, we do have the technology for slower but very sensitive and specific testing and a world of expertise in that space. The major roadblock to improve testing is us; humans make the call as to whether innovative new or trusted traditional tests for a new or emerging virus are developed, deployed and funded for sufficient use to make it possible to truly understand a new or emerging disease.

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