Quality Challenges During the Spring 2009 Swine-Origin Influenza A Outbreak

The Clinical Laboratory Perspective

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Core Laboratory for 70 Not-for-Profit Hospitals
> 12,000 beds
Virologists notified about the outbreak at the Clinical Virology Symposium in Daytona Beach.

Warde Pandemic Flu plan activated when Texas cases were announced.
Our Approach

- Respiratory specimens are screened for influenza A by PCR prior to being inoculated into cultures.
  - Includes respiratory specimens submitted for chlamydia cultures
- Flu A positive specimens were not cultured
- Flu A negative specimens are cultured as our standard protocols.
An Early Success

- Early posting of Swine Flu sequences (GenBank) allowed laboratories to check PCR primer and probe sequences used in their LDAs.
- Some labs had to re-formulate and re-validate due to base mis-matches, especially under the probe.
- ASR Vendor problems. Sequences not available, no clinical claims, no way to check.
Shortages

- Clinical Laboratories depend upon standing orders and just-in-time deliveries to manage cash flow and keep inventories low. (LEAN/Six Sigma principles)
- Federal purchases of large quantities of supplies caused havoc in the supply chain.
- Facing uncertain supply sources, Labs responded by increasing inventories.
- These practices only made the problem worse.
Shortages affected many aspects of clinical testing, not just influenza.
Lab Impact of Product Shortages

- Rapid validation and stability studies across multiple analytes
  - Saline as a transport for respiratory viruses
  - In-house developed viral transport media
  - Different swab types
- Limit of Detection and Inhibition Profiles for PCR Master Mixes
- Education and training for
  - Nasal washes
  - Other little-used procedures
Specimen Collection

- EUA test protocols allowed testing of a limited number of specimen types, some of which are not used routinely by clinical laboratories.
- A number of specimens had to be recollected before they could be sent on for Swine Flu testing.
CDC published their PCR protocol on April 28, 2009.

- 6FAM-TCTAGTGTTACCGAGATATGCATTCGC-(TAMRA)
- 6FAM-CAGAATATACA(T)CCRGTCACAATTGGARAA
- 6FAM-CYACTGCAAGCCCCA(T)ACACACACAAGCAGGCA

Within days after these sequences were published, the special “T” residue was on back-order. Most of these bases went into the EUA kits sent to the State Labs.
“THESE MATERIALS AND PROTOCOLS ARE THE PROPERTY OF THE CENTERS FOR DISEASE CONTROL AND ARE MADE AVAILABLE UNDER AN EMERGENCY USE AUTHORIZATION (EUA) AS A SERVICE TO THE PUBLIC HEALTH COMMUNITY. THESE PROTOCOLS ARE NOT INTENDED TO BE USED FOR COMMERCIAL DEVELOPMENT OR FOR-PROFIT TESTING.”
Diagnostic Laboratories

- Not allowed to utilize a test with known performance characteristics
- Forced to develop LDA procedures that may have different performance characteristics
- Result quality is in question
- Test variability could confuse epidemiological surveillance data, school closings, etc.
Validating Swine Flu Protocols

- Laboratories were faced with increasing demands for Swine-origin influenza A testing.
- Requests to State Labs for assistance in validating PCR tests had to be referred to the CDC for “permission.”
- Slowed down the test development process.
- Doing it on our own increased testing and result variability.
- Michigan Lab agreed to assist with the test validation process in July 2009.
Why Is This Important?

<table>
<thead>
<tr>
<th>Antiviral Drug</th>
<th>Swine-Origin H1N1</th>
<th>Seasonal A/H1N1</th>
<th>Seasonal A/H3N2</th>
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<tbody>
<tr>
<td>Zanamivir</td>
<td>Sensitive</td>
<td>Sensitive</td>
<td>Sensitive</td>
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<tr>
<td>Osteltamivir</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Sensitive</td>
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<tr>
<td>Amantadine</td>
<td>Resistant</td>
<td>Sensitive*</td>
<td>Resistant</td>
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<tr>
<td>Rimantadine</td>
<td>Resistant</td>
<td>Sensitive*</td>
<td>Resistant</td>
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</tbody>
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0.5% of isolates are resistant to Amantadines
Why is This Important?

- Swine Flu Testing drives therapy.
- To have any impact, therapy must be started within 48 hours of symptom onset.
Unmet Needs

- Public Health laboratories were attempting to perform Diagnostic and Surveillance Testing.
- Testing requests had to be pre-approved and meet testing guidelines.
- Guidelines kept changing and fewer test requests were approved.
- Results were faxed to Laboratories.
Unmet Needs

- Testing results were not available within a timeframe that could support treatment.
- Economic downturn affected Public Health resources (decreased staff, furlough Fridays, etc.).
- Public Health Laboratories generally do not have the infrastructure to accommodate rapid viral testing that affects the treatment of an individual patient.
- Need clinical partners who have couriers, afternoon and midnight testing capabilities, and interfaced computer systems.
“Rapid tests may be used.”

Unknown sensitivity and specificity to detect human infection with S-OIV (H1N1) virus in clinical specimens.

Therefore, a negative rapid test could be a false negative and should not be assumed a final diagnostic test for swine-origin influenza infection.
One Hospital’s Experience

- Rapid tests were originally sequestered (mostly due to scarcity)
- Used to test high risk patients with a high index of suspicion
- Later, they were released to clinics and EC for routine use.
Learning Process

- Massive purchases disrupted the supply chain and adversely affected testing (and result quality) for a number of viral analytes.
- Setting up and administering the pre-approval program increased costs and delayed testing.
- Clinical partners should be brought in earlier.
- CDC could have provided more forceful guidance to limit the use of Rapid Tests.