Laboratory Response to Hepatitis Outbreak: Detection and Sequencing Aids Remediation Effort

Association of Public Health Laboratories Annual Meeting 2018
Michigan Department of Health and Human Services
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Preventing disease, promoting wellness and improving the quality of life of Michigan residents
Hepatitis A Virus Review

Picornavirus
- Humans are only known reservoir
- Stable at low pH and in freezing to moderate temps
- Inactivated by high temperature, formalin, chlorine
- Can survive in the environment for months

Pathophysiology
- Replicates in the liver and is excreted in feces
- Low infectious dose (10-100 virus particles)
- Person-to-person transmission >> contaminated food or water
- Incubation: 15-50d (average 28d)
- Infectious: 14d prior and 7d after onset of jaundice
Course of hepatitis A

Timeline for hepatitis A manifestations.

Official reprint from UpToDate® Graphic 57931 Version 4.0
Epidemiology of the MI outbreak

**Primary**
- Meets 2012 CSTE acute hepatitis A definition
- Case specimen matches one of outbreak strains

**Secondary**
- Meets primary case definition
- Epidemiologic link to a primary case

In support of efforts, MDHHS has a website for the hepatitis A outbreak that has important and timely information, available at:

- [www.mi.gov/hepatitisAoutbreak](http://www.mi.gov/hepatitisAoutbreak)

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### Hepatitis A Southeast Michigan Outbreak

Public health officials and the Michigan Department of Health and Human Services (MDHHS) are continuing to see an elevated number of hepatitis A cases in Southeast Michigan. Since the beginning of the outbreak in August 2016, public health response has included increased healthcare awareness efforts, public notification and education, and outreach with vaccination clinics for high-risk populations. No common sources of food, beverages, or drugs have been identified as a potential source of infection. Transmission appears to be through direct person-to-person spread and fecal drug use. Those with history of injection and non-injection drug use, homelessness, or transient housing, and incarceration are thought to be at greater risk in this outbreak setting. Notably, this outbreak has led to a high hospitalization rate.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Hospitalizations</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>610</td>
<td>501 (82.1%)</td>
<td>20 (3.3%)</td>
</tr>
</tbody>
</table>

*Table will be updated weekly by 4:00pm each Friday*

Please note: Table does not include all reported hepatitis A cases in the SE MI outbreak region, only those cases that are identified as outbreak-related. More detailed data on the current outbreak can be found within the Comprehensive Summary.

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### Hepatitis A is in Michigan communities.

Hepatitis A is a liver disease caused by the hepatitis A virus (HAV). Hepatitis A is spread through contaminated food or water and close contact with persons who are infected. Hepatitis A can affect anyone. Frequent hand washing with soap and warm water after using the bathroom, changing a diaper, or before preparing food can help prevent the spread of hepatitis A.

#### The best way to prevent against hepatitis A is to get the hepatitis A vaccine.

Talk to your health care provider to get the two doses you need for protection. Need help paying for vaccines? Your local health department or a Federally Qualified Health Center may have hepatitis A vaccine available for little cost.

#### Stop the spread. Get vaccinated today.

**Wash Your Hands**

1. Wet your hands with clean, running warm water and apply soap.
2. Lather your hands by rubbing them together with the soap. Be sure to lather the backs of your hands, between your fingers, and under your nails.
3. Scrub your hands for at least 20 seconds.
4. Rinse your hands well under clean, running warm water.
5. Dry your hands using a clean towel or air dry them. Rinse your hands with soap and water before feeding or caring for a child, using or handling baby items, or preparing food. Alcohol-based hand sanitizers are not effective against the hepatitis A virus. Wash your hands with soap and water after using the bathroom, changing a diaper, before eating food, and after handling an animal.
Geographic Distribution of Cases

Incidence rate of hepatitis A per 100,000 population

- 0
- 1 to 5
- 5 to 9
- 10 to 19
- >20

* indicates 1 to 5 cases

Prevent Disease • Promote Wellness • Improve Quality of Life
<table>
<thead>
<tr>
<th><strong>Number of Confirmed Cases</strong></th>
<th><strong>815</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>734</td>
</tr>
<tr>
<td>Secondary</td>
<td>81</td>
</tr>
<tr>
<td><strong>Hospitalized, n (%)</strong></td>
<td><strong>657 (80.6)</strong></td>
</tr>
<tr>
<td><strong>Deaths, n (%)</strong></td>
<td><strong>25 (3.1)</strong></td>
</tr>
<tr>
<td>Median age (range) years</td>
<td>40</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>286 (35.1)</td>
</tr>
</tbody>
</table>

*Data below excludes secondary cases*

| **Documented substance use, n (%)** | 371 (50.5) |
| **Coinfection with hepatitis C, n (%)** | 196 (26.7) |
| **Coinfection with hepatitis B, n (%)** | 20 (2.7) |
| **MSM, n (%) – data includes men only** | 72 (14.6) |
| **Homeless/transient living, n (%)** | 98 (13.4) |
| **Recently incarcerated, n (%)** | 56 (7.6) |
| **Healthcare worker, n (%)** | 21 (2.9) |
| **Food Worker, n (%)** | 35 (4.8) |
| **Lost to follow up, n (%)** | 141 (19.2) |
| **Non-substance use, non-homeless, n (%)** | 293 (39.9) |
# Hepatitis A Vaccine Coverage Estimates

<table>
<thead>
<tr>
<th>Michigan Children 19 through 35 months as of March 18, 2018 that have at least 2 doses of the Hepatitis A vaccine recorded in the Michigan Care Improvement Registry (MCIR)*</th>
<th>United States Children 19 through 35 months as of 2015 that have at least 2 doses of the Hepatitis A vaccine ever as reported to the National Immunization Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage Est., 19 through 35 months 2+ Doses</td>
<td>57.3 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Michigan Adults 19 years and older as of March 19, 2018 that have at least 1 or 2 doses of the Hepatitis A vaccine ever recorded in the MCIR</th>
<th>United States Adults 19 years and older as of 2015 that have at least 2 doses of the Hepatitis A vaccine ever as reported to the National Health Interview Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage Est., ≥19 yrs., 1+ Doses Ever</td>
<td>14.0 %</td>
</tr>
<tr>
<td>Coverage Est., ≥19 yrs., 2+ Doses Ever</td>
<td>8.5 %</td>
</tr>
</tbody>
</table>

*MCIR Reporting Rules: Health care providers who are required to report an immunization shall report: ALL immunizations administered to every child born after December 31, 1993 and less than 20 years of age within 72 hours of administration. Adult vaccination record submission to the MCIR is not required though highly encouraged. A 2006 change to the Michigan Public Health Code enabled the MCIR to transition from a childhood immunization registry to a lifespan registry including citizens of all ages in the MCIR.
Total Adult Hep A Vaccine Doses Administered in Outbreak Jurisdictions

- Health messaging
- Targeted vaccination
- VNA contract
- State funding ECC activation

Week of Illness Onset

Cases of hepatitis A

Total Adult Hep A Vaccine Doses Administered in Outbreak Jurisdictions

Michigan Department of Health and Human Services
Bureau of Laboratories
Timeline of the Lab Testing

• IgM offered for HAV
  – 2015 - only 3 requested vs. 2017 - limited to repeat testing if genotype negative

• CDC assisted with genotyping of specimens

• MDHHS validated genotyping on the ABI 3130xl platform and in Dec. 2017 MDHHS took over genotyping of all Michigan specimens

• April 2018; offers to provide extra space on sequencer runs to neighbor states
HAV Genotyping performed at MDHHS

Dec. 2017 through April 2018 specimens

<table>
<thead>
<tr>
<th>Result</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.B MI Outbreak Strain #1</td>
<td>60</td>
</tr>
<tr>
<td>1.B (one base different from Cluster 1)</td>
<td>1</td>
</tr>
<tr>
<td>1.B MI Outbreak Strain #2</td>
<td>117</td>
</tr>
<tr>
<td>1.B (one base different from Cluster 2)</td>
<td>1</td>
</tr>
<tr>
<td>1.A</td>
<td>6</td>
</tr>
<tr>
<td>1.B (sent to CDC for confirmation)</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>120</td>
</tr>
<tr>
<td>Duplicate Specimen Received</td>
<td>41</td>
</tr>
</tbody>
</table>
MI outbreak clusters are unrelated to other recent HAV genotype 1B outbreaks

Hepatitis A Outbreak Sequences (VP1/P2B region, 315 bp in length)

<table>
<thead>
<tr>
<th>Outbreak cluster comparison</th>
<th>NT variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between MI clusters</td>
<td>0.32%</td>
</tr>
<tr>
<td>Between MI and CA clusters</td>
<td>2.22–2.86%</td>
</tr>
</tbody>
</table>

MDHHS
Michigan Department of Health and Human Services
Bureau of Laboratories
• Full dendogram comparisons are provided by CDC regularly.
• Majority of MDHHS specimens are part of MI 1.B Cluster 1.
• Starting to find some specimens match outbreaks from other locations.
Budget and Staffing Challenges

- Budget - no set $ for this newly added testing and started after the start of a fiscal year
  - Epidemiology partners stepped in to help support some of the costs
  - FY19 state budgets will include a request for funding
  - Building an outbreak response requests through federal grants in case outbreak expands

- Staffing challenges: rotate instruments and staff for Norovirus and Flu testing needs

- Genotyping - multiple day process that entails PCR and sequencing of specific regions of interest
  - Approx. cost of $75-90 per specimen
  - Can run up to 22 specimens in a batch
  - More cost effective to fill runs and batch samples

- IgM - only repeat serology when samples found to be negative by PCR
  - Approx. cost of $20/test
Specimen Challenges

• Symptom onset vs Date of Collection
• Vaccination a week or two prior to collecting specimens & unknown status of vaccination
  – Some patients found to request boosters from out of state after they had already received two shot series in MI
  – Some providers would vaccinate then wait a week or more to send a specimen for IgM or genotyping
• Specimen volume issues
• Collection tubes that leak and we cannot perform test
  – MDHHS has started sending screw top tubes for serum transport to some hospitals and health departments
• MDHHS provides 6 days a week courier service to all lower-peninsula birthing hospitals & large local health departments
  – Pre-paid commercial shipping labels and Cat. B shipping materials being provided to all others sites
Assay Challenges

• Unknown lower limit of detection for the genotyping
  – Questions of if LOD would result in missing specimens that were positive via IgM assay

• IgM repeats are not always positive
  – As of end April:
    115 repeat HAV IgM specimens
    60 reactives
    45 nonreactives
    10 equivocals

• Outreach to clinical partners regarding which IgM kit was used, storage temperatures and times, shipping conditions
Future Planning and Solutions

• Specimens from neighboring states - provide assistance in genotyping to determine if they are related to the MI cases
• Store extra sample material to be able to provide to colleagues at other labs that are bringing testing methodologies online

• Assessing the potential of WGS in place of the Sanger sequencing genotypes
  – Cost difference
  – Data analysis pipelines (GHOST)
  – Timeliness of WGS and number of staff available