Rapid Diagnostic Tests for Bacterial Meningitis Pathogens: where we are now and what’s next.

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I have no conflict of interest in relation to this presentation

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Rapid Diagnostics for Meningitis

- Meningitis is a life-threatening disease
- Rapid detection of meningitis pathogens is critical for case management, outbreak response, and surveillance
- Poor accessibility of diagnostics remains to be addressed, especially in resource limited countries
  - insufficient funding
  - limitations of existing diagnostic tests
  - lack of trained staff members
  - low priority
  - Ineffective supply chain management
- Despite advances in diagnostic technology, an empirical antimicrobial treatment provided, rather than a treatment based on pathogen identification
Diagnostics: a Key Component in the Global Road Map to Defeat Meningitis by 2030

Pillar 2 Diagnosis and treatment
Achieved through improve diagnosis at all levels of health care, health worker training and prompt and effective case management

• Strategic goal 6: Improve diagnosis of meningitis at all levels of care
• Strategic goal 7: Develop and facilitate access to diagnostic assays at all levels of care to increase confirmation of meningitis
Three Use Cases To Improve Global Meningitis Detection

Use case 1 (Epidemic/outbreak settings, Africa)
• Identification of Nm serogroup at peripheral level (health center or district hospital) for appropriate vaccine response

Use case 2 (Epidemic and endemic settings, worldwide)
• Identification of bacterial meningitis/septicemia at peripheral level (health clinic or hospital) to initiate antibiotic treatment for case management

Use case 3 (Epidemic and endemic settings, worldwide)
• Identification of causative pathogens from syndromic meningitis panels (minimum 10 pathogens) at hospital level (district/regional hospital) for case management: stopping or changing antibiotics

https://www.who.int/emergencies/diseases/meningitis/meningitis-diagnostics-use-cases.pdf
Timelines for use case 3 development

May 2017: A call for action: global vision to defeat meningitis

March 2018: Expert group meeting to discuss development of next generation RDTs (use cases 1-3)

2019-20: Use case 3 TPP finalized

2020-21: Use case 3 landscape and Market analysis by PATH

2021: Identification of potential platforms for use case 3

2022-24: Development and validation of potential RDTs

2025-28: Pilot studies and RDT roll-out
Partnership and collaborations to accelerate use case 3 development

**Develop and finalize use case 3 Target Product Profile (TPP)**

**Conduct landscape analysis of meningitis diagnostics**
Use case 3
TPP

**Scope**
- Identify the causative meningitis pathogens
- Used in hospital or hospital laboratories
- Performed by trained clinical staff and lab technicians
- Inform appropriate treatment intervention

**Specific features**
- Multiplex technology allows detection of a wide spectrum of pathogens
- High performance (sensitivity, specificity, reproducibility, etc)
- Rapid and easy result interpretation
- Ideally, a portable and battery-operated device
- Easy to deploy and use
- Affordable

**Meningitis pathogen panel**
- Categories A, B and C
- Bacterial, Viral, Fungal, and Parasitic
Landscape analysis of meningitis diagnostics

Objectives
• Identify diagnostic gaps and obtain key stakeholders’ feedback on existing and pipeline technologies
• Review the diagnostic platforms and technologies currently available or under development with the potential for Use Case 3.
• Assess existing and emerging technologies, including their quality, cost, and relevance to Use Case 3

Methods
• Stakeholder interviews
• Literature review

Major Findings
• Existing Tests/platforms
• Potential platforms
• Advanced/Emerging technologies
# Existing Tests and Limitations

<table>
<thead>
<tr>
<th>Culture</th>
<th>Latex Agglutination Tests</th>
<th>Immunochromatographic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Specific species identification</td>
<td>• Target various meningitis pathogens and some meningococcal</td>
<td>• Sp and all meningococcal serogroups except B</td>
</tr>
<tr>
<td>• In-depth strain characterization</td>
<td>serogroups</td>
<td>• Rapid (&lt;15 mins)</td>
</tr>
<tr>
<td>• Serogrouping/typing</td>
<td>• Rapid (&lt; 20 mins)</td>
<td>• Cassette format expensive</td>
</tr>
<tr>
<td>• Antibiotic resistance</td>
<td>• High cost</td>
<td>• Cold chain for storage/distribution</td>
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<tr>
<td>• Molecular typing</td>
<td>• Cold chain for storage/distribution</td>
<td>• High sensitivity and specificity for specific targets</td>
</tr>
<tr>
<td>• Low cost</td>
<td>• Performance may vary</td>
<td></td>
</tr>
<tr>
<td>• Long turnaround</td>
<td>• lab verification: 33-100% sensitivity; 93-100% specificity</td>
<td></td>
</tr>
<tr>
<td>• Low recovery rates</td>
<td>• field evaluation: 69-80% sensitivity; 81-94% specificity</td>
<td></td>
</tr>
<tr>
<td>• Antibiotic use prior to specimen collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Improper storage &amp; transport conditions</td>
<td></td>
<td></td>
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<tr>
<td>• Suboptimal media quality</td>
<td></td>
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</tbody>
</table>
Existing Tests and Limitations: PCR-based Tests

- Quick turnaround (within several hours)
- Sensitive/specific for targets
- High throughput
- Multiple platforms available-commercial and lab developed tests (LDTs)
- LDTs implemented in many countries with External Quality Assurance in place

- High cost (expensive equipment)
- Require cold chain for key reagents
- Require technical trainings and lab infrastructure (freezer, fridge, separate rooms etc)
- Decentralization to regional/district levels is challenging in resource limited regions
## PCR tests for meningitis pathogens

<table>
<thead>
<tr>
<th>Test</th>
<th>Platform</th>
<th>Targets</th>
<th>Specimen Type</th>
<th>Sen/Spec</th>
<th>Instrument/Cost</th>
<th>Time</th>
</tr>
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<tr>
<td><strong>BioFire Film Array</strong></td>
<td>Multiplex</td>
<td>Bacterial/viral/fungal meningitis pathogens</td>
<td>CSF</td>
<td>&gt;90%</td>
<td>Biofire FilmArray Systems/High ($45K for 2.0)</td>
<td>~1 hr</td>
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<tr>
<td><strong>Xpert® EV</strong></td>
<td>Multiplex</td>
<td>Enteroviral meningitis pathogens</td>
<td>CSF</td>
<td>&gt;95%</td>
<td>Genexpert system/Medium-High ($11K-64K)</td>
<td>&lt;2.5 hrs</td>
</tr>
<tr>
<td><strong>QIAstat-Dx</strong></td>
<td>Multiplex</td>
<td>Bacterial/viral/fungal meningitis pathogens</td>
<td>CSF</td>
<td>NA</td>
<td>QIAStart-Dx analyzer/Medium (~$25K)</td>
<td>~1 hr</td>
</tr>
<tr>
<td><strong>HG Meningococcus/ Sp (Ireland)</strong></td>
<td>LAMP</td>
<td>Nm Serogroups (A, B, C, E, W, X, Y, and Z)/Sp serotypes</td>
<td>Blood, CSF, Swab, Direct CSF</td>
<td>NA</td>
<td>LAMP instrument/$9.7 (main or battery power)</td>
<td>&lt;1 hr</td>
</tr>
<tr>
<td><strong>Lab Developed Tests</strong></td>
<td>Direct PCR, triplex</td>
<td>Bacterial meningitis pathogens and capsule types</td>
<td>CSF, serum</td>
<td>&gt;95%</td>
<td>ABI, AriaMx (&gt;25K)</td>
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Potential diagnostic platforms (for other pathogens)

<table>
<thead>
<tr>
<th>Platform</th>
<th>Feature</th>
<th>Run Time</th>
<th>Power</th>
<th>Instrument cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-POC</td>
<td>Multiplex, up to 40 targets</td>
<td>&lt; 30 mins</td>
<td>Main/battery power</td>
<td>$28K</td>
</tr>
<tr>
<td>Anitoa Maverick compack qPCR</td>
<td>Multiplex, up to 4 targets</td>
<td>~30 mins</td>
<td>Main/battery power</td>
<td>~3.5K-6K</td>
</tr>
<tr>
<td>VERI-Q PCR</td>
<td>Multiplex, up to 10 targets</td>
<td>&lt; 1 hr</td>
<td>Main power</td>
<td>~10K</td>
</tr>
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</table>
Advanced diagnostic platforms

• Growing interest in next generation sequencing in past 10 years
• Used for detection of various pathogens (bacterial, viral etc)
• Various platforms (MinION, Illumin supported platforms, Ion Torrent, BGISEQ etc) and analysis tools available
• Higher cost and lower sensitive compared to PCR-based tests
• Targeted approaches offer better sensitivity, reduced cost, and decreased complexity of bioinformatic analysis
CRISPR/Cas system: an emerging technology for diagnostics

- Isothermal amplification technology, relying on Cas protein, an endonuclease that cleave complementary sequences
- Cleavage induces nonspecific cleavage of single stranded DNA or RNA, which can be modified with reporter/quencher, allowing signal detection
- Applied to viral pathogen detection

Next-generation diagnostics with CRISPR | Science (sciencemag.org)
Future Diagnostics for Meningitis

Existing platforms for meningitis pathogens
- Most Category A pathogens
- High sensitivity and specificity
- Expensive

Platforms with the potential for Use Case 3
- Not developed for meningitis pathogens
- Meet many features outline in Use Case 3 TPP
- Lower cost

Advanced and emerging technologies for Use Case 3
- Sequencing or CRISPR/Cas based
- Early development for diagnostics
What’s next?

1. Assess various platforms—existing/potential and estimate market size
   - Identify suitable platforms for validation
   - Develop and validate tests for meningitis pathogens
   - Estimate market size for meningitis diagnostics

2. Pilot studies to inform global deployment strategies
   - Evaluate RDT field performance and lab capacity at local levels in selected countries
   - Assess LP rate, supply chain/specimen transport systems, and data reporting

3. Develop region/country-specific rollout strategies
   - Country’s risk level for meningitis and prevalence of pathogens
   - Impact on surveillance, testing algorithm, data flow etc
   - Shift in the roles of laboratory at national/subnational levels
   - Procurement process/trainings
Conclusion

- RDTs are important for rapid meningitis detection at local hospitals and laboratories; culture remains important for AMR and genomic surveillance
- Strong partnership and innovations in technology and informatics accelerate the development of next generation rapid tests
- Deployment of new RDTs requires engagement of multi-stakeholders and may lead to a paradigm shift in the roles of clinical and public health laboratories
- Partner/country’s commitment and investment ensures sustained access to RDTs
Acknowledgement

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• PATH landscape analysis team
• Meningococcal Working Group (GAVI, Bill and Melinda Gates Foundation, UNICEF, WHO and CDC)
• CDC Meningitis and Vaccine Preventable Disease Branch (lab/epi members)
Thank you for your attention