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 heath 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

Defeating meningitis by 2030: a global road map (who.int)

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)

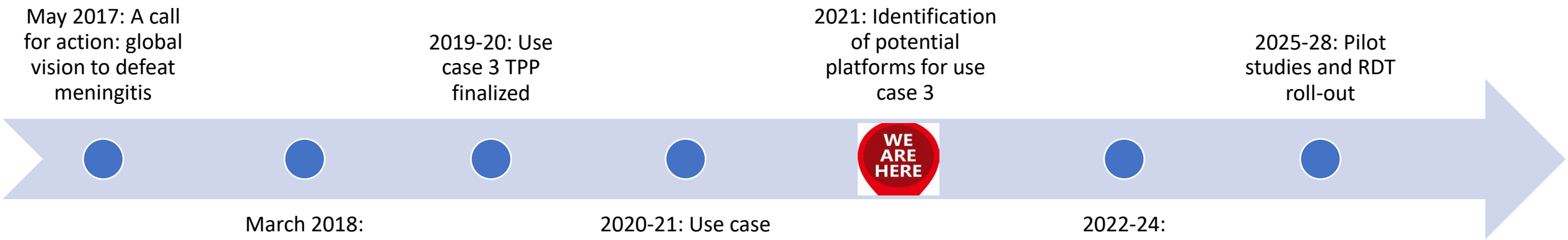
- Identification of bacterial meningitis/septicemia at peripheral level (health clinic or hospital) to initiate antibiotic treatment for case management

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



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

Culture

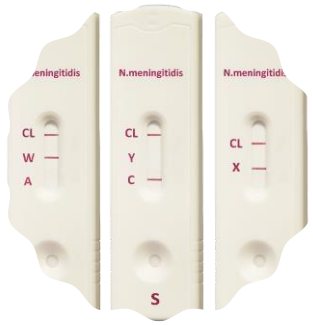
- Specific species identification
- In-depth strain characterization
  - Serogrouping/typing
  - Antibiotic resistance
  - Molecular typing
- Low cost
- Long turnaround
- Low recovery rates
  - Antibiotic use prior to specimen collection
  - Improper storage & transport conditions
  - Suboptimal media quality

Latex Agglutination Tests

- Target various meningitis pathogens and some meningococcal serogroups
- Rapid (< 20 mins)
- High cost
- Cold chain for storage/distribution
- Performance may vary
  - lab verification: 33-100% sensitivity; 93-100% specificity
  - field evaluation: 69-80% sensitivity; 81-94% specificity

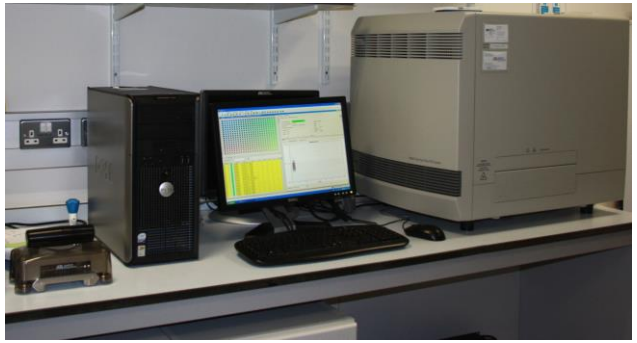
Immunochromatographic tests

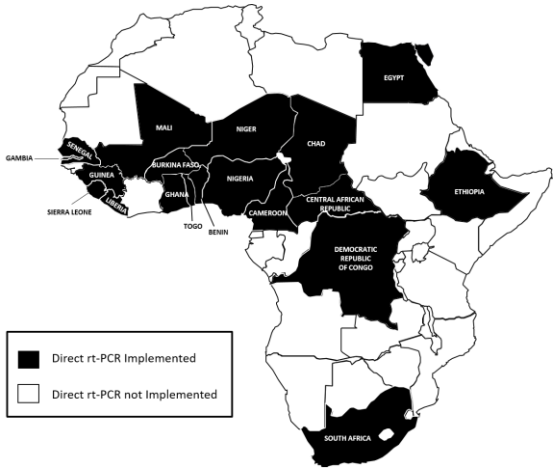
- Sp and all meningococcal serogroups except B
- Rapid (<15 mins)
- Cassette format expensive
- Cold chain for storage/distribution
- High sensitivity and specificity for specific targets



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



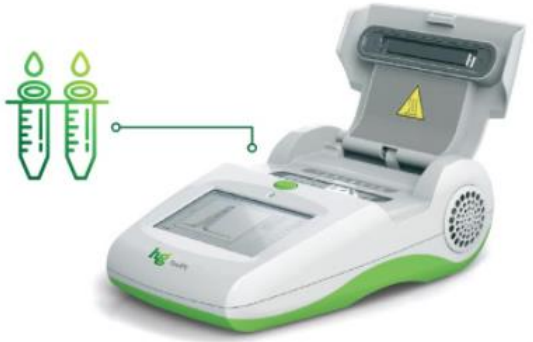


- High cost (expensive equipment)
- Require cold chain for key reagents
- Require technical trainings and lab infrastructure (freezer, fridge, separate rooms etc)
- Decentralization to regional/district levels is challenging in resource limited regions

PCR tests for meningitis pathogens

Test	Platform	Targets	Specimen Type	Sen/Spe	Instrument/Cost	Time
BioFire Film Array	Multiplex	Bacterial/viral/fugal meningitis pathogens	CSF	>90%	Biofire FilmArray Systems/High ($45K for 2.0)	~1 hr
Xpert® EV	Multiplex	Enteroviral meningitis pathogens	CSF	>95%	Genexpert system/Medium-High ($11K-64K)	<2.5 hrs
QIAstat-Dx	Multiplex	Bacterial/viral/fugal meningitis pathogens including Nm/Hi capsule types	CSF	NA	QIAStart-Dx analyzer/Medium (~$25K)	~1 hr
HG Meningococcus/ Sp (Ireland)	LAMP	Nm Serogroups (A, B, C, E, W, X, Y, and Z)/Sp serotypes	Blood, CSF, Swab, Direct CSF	NA	LAMP instrument/$9.7 (main or battery power)	<1 hr
Lab Developed Tests	Direct PCR, triplex	Bacterial meningitis pathogens and capsule types	CSF, serum	>95%	ABI, AriaMx (>25K)	~ 2 hrs

Potential diagnostic platforms (for other pathogens)



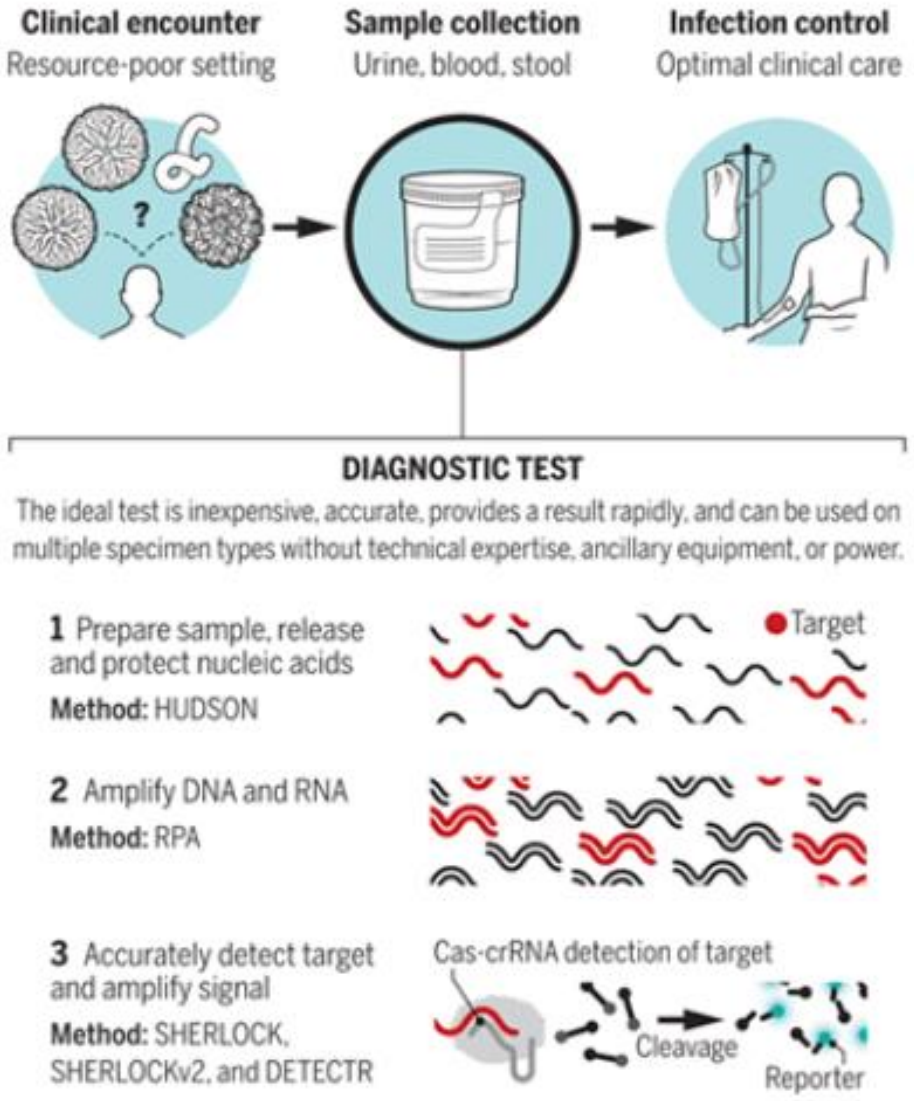
Platform	Feature	Run Time	Power	Instrument cost
Q-POC	Multiplex, up to 40 targets	< 30 mins	Main/battery power	$28K
Anitoa Maverick compack qPCR	Multiplex, up to 4 targets	~30 mins	Main/battery power	~3.5K-6K
VERI-Q PCR	Multiplex, up to 10 targets	< 1 hr	Main power	~10K

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

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Thank you for your attention