World Health Organization

Update on the development of Rapid Diagnostic Tests for meningitis

Olivier Ronveaux, WHO Geneva

London, MRF conference, November 2019

Meningitis in vitro diagnostics – three needs

1. **Global**. Key question on sick patient: is antibiotics/referral needed (yes/no). Point of care. Bacterial vs non bacterial infections

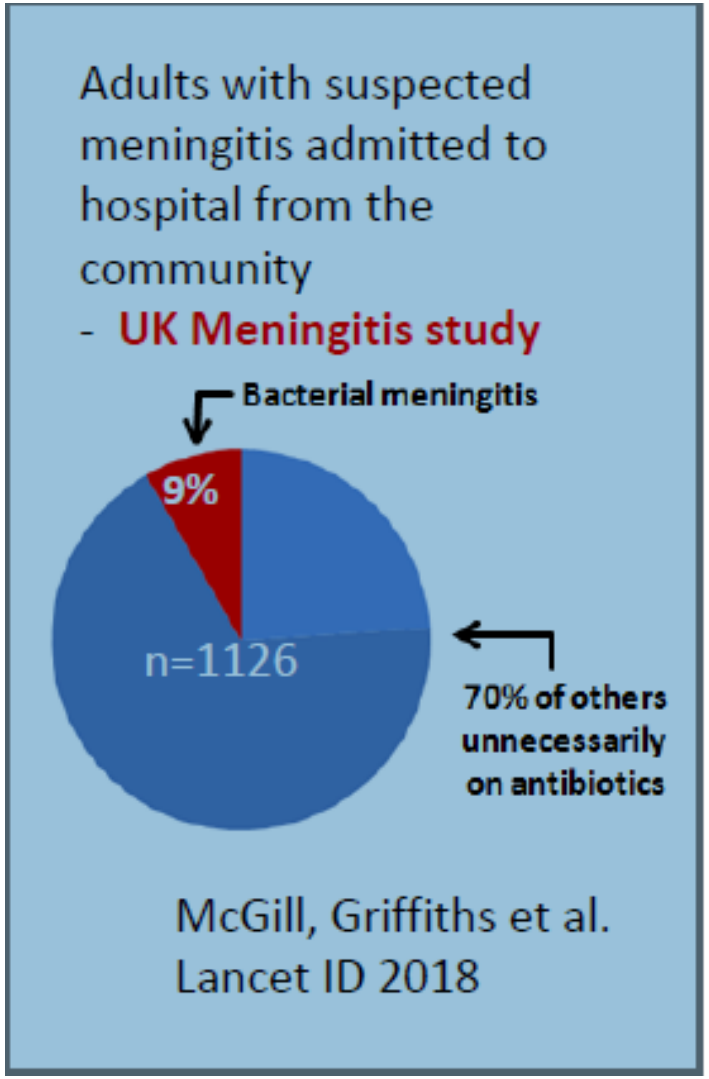
2. **Global**. Identify the pathogen –patient with meningoencephalitis syndrome- to determine the appropriate treatment, switch treatment or terminate inappropriate treatment.

3. **Meningitis belt.** Need to identify causative organism (Nm serogroup) rapidly at peripheral level for outbreak detection

https://www.who.int/emergencies/diseases/meningitis/en/

Meningitis in vitro diagnostics – Use case 1

1. **Global**. Key question on sick patient: is antibiotics/referral needed (yes/no). Point of care. Bacterial vs non bacterial infections
   - *Roadmap 2030*: by 2026, quality assured, affordable and accessible rapid diagnostic assay developed to rapidly detect invasive bacterial vs viral infection to support immediate medical decision-making at point of care



Challenge

Ideal biomarker/host marker not identified yet

Test profile

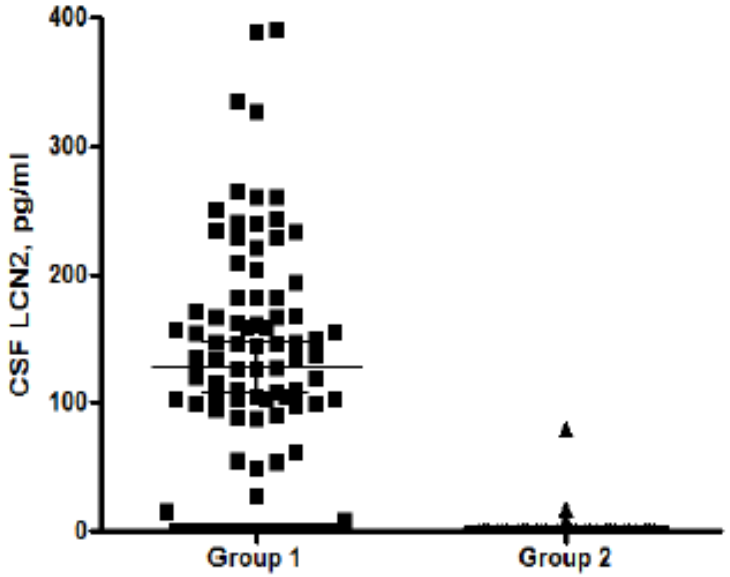
- No overlapping value between bacterial and viral
- Early detectable
- Blood or CSF without preparation
- Does not require highly trained staff
- High specificity – high negative predictive value
- Short time to result < 10 minutes

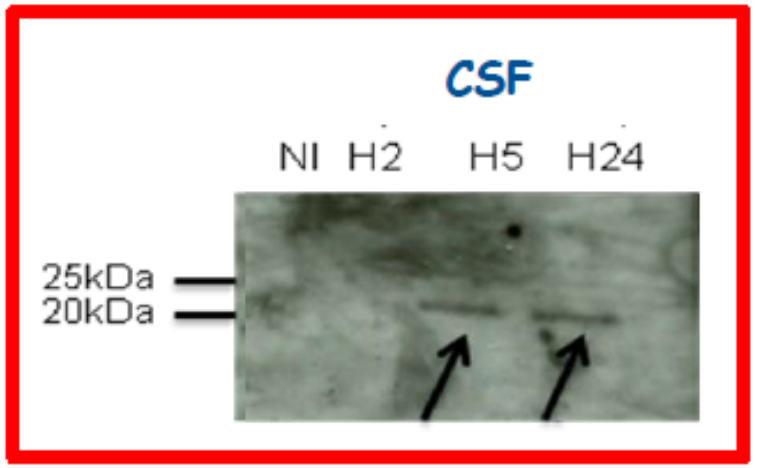
Host factors and biomarkers

- C-Reactive Protein
- Procalcitonin
- Lipocalin 2 (LCN2)
- Heparin Binding Protein
- Serum amiloid A Protein
- Cytokines / chemokines

Early detecting of LCN2 in CSF

	Confirmed acute bacterial meningitis n=90		Confirmed acute viral meningitis n=44		
CSF LCN2, pg/mL	127	108-146	2.4	0-6.2	<0.0001





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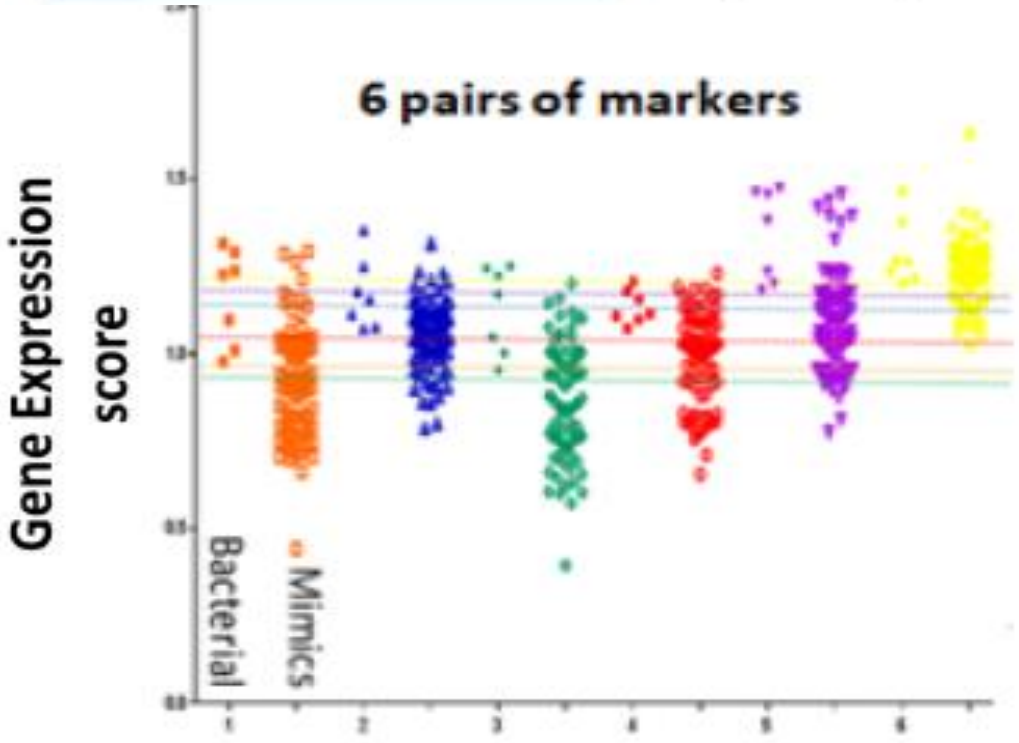
fast-track DIAGNOSTICS

MRC Medical Research Council

TRanscripts Identifying Meningitis -TRIM test

Simple PCR assay
Developed from transcript data
(n> 500 samples)

lyophilised multiplex assay



Host transcripts in **blood** distinguish bacterial meningitis from clinical mimics

Sensitivity = 100%
Specificity = 90%
results of prototype assay

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fast-track DIAGNOSTICS

SIEMENS Healthineers

MRC Medical Research Council

- Trim Assay being validated in a multi-site study in UK and Europe
  - ensure it works in hospital setting
  - recruiting > 696 patients, started in April 2019
- Systems component ready for use on standard hospital equipment
- Baseline data on TRIM data accuracy in India, Indonesia, Malawi and Brasil*
- Funded by MRC and industry

Future Benefits

- Compatible with point-of-care devices.
- Compatible for syndromic detection of sepsis and other bacterial syndromes
- Potential for treatment monitoring
- Potential to integrate with pathogen specific PCR testing

More information on the TRIM study

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*supported by additional Newton and NIHR funded studies

Meningitis in vitro diagnostics – Use Case 2

2. **Global**. Identify the pathogen –patient with meningoencephalitis syndrome- to determine the appropriate treatment, switch treatment or terminate inappropriate treatment.
   - *Roadmap 2030*: by 2026, quality assured, affordable and accessible multiplex diagnostic test available to identify and distinguish the main pathogens responsible for meningitis

What do we want to have

- Cheap
- Reliable (high sensitivity and specificity)
- Capable of testing more and more pathogens
- Desk top machine that can be set up almost anywhere
  - Compact device, battery operated
  - Peripheral level
- Multi-pathogen detection in a single reaction or run

Multiplex PCR are already used…

- Commercially available: Xpert, Biofire, TAC etc
- In-house

Cape Town, 2017

- 6 pathogens
- Good performance compared to culture
- “potential to limit unnecessary therapy”

PLOS ONE

RESEARCH ARTICLE

Diagnostic accuracy of two multiplex real-time polymerase chain reaction assays for the diagnosis of meningitis in children in a resource-limited setting

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Devices are available…

Portable real-time PCR platforms

Platform	Features	Run Time	Power	Estimated Instrument Cost
Q-POC (UK)	Cassette Multiplex (up to 40 targets)	10-30 minutes	Battery powered	$3000
Anitoa Maverick compact qPCR system (US)	4-8 wells Multiplex (up to 4 targets)	~30 minutes	10V, battery backup option	$3500-6000
Coyote Mini8 Plus Real-Time PCR System (Germany)	8 wells Multiplex (up to 2 targets)	<2 hours	12V Battery pack	$6000-$8000
Bio molecular Systems Mic qPCR (Australia)	48 wells Multiplex (up to 4 targets)	~25 minutes	100-240V	$15000
Q160 Mini Real-Time PCR System (China)	16 wells Multiplex (up to 2 targets)	1-2 hours or less	85-265V	$4600
Handheld real-time PCR device (prototype)	4 wells	~35 minutes	?	?

Targets could be genes specific for pathogen and serotype/serogroup or associated with antibiotics

Table courtesy of Dr Xin WANG, US CDC

Meningitis multiplex test - developments

- WHO Expert meeting, September 2019 – Consensus on test specifications
  - Hospital, near-patient hospital laboratory which supports lumbar puncture and centrifugation, may support molecular testing
  - List A, universal, 13 pathogens, global level (bacterial, viral, parasite, fungi)
  - List B, Ideal, Regional specificities, 13 pathogens
- Target Product Profile to be published in December 2019
- Next steps:
  - Market review: identification of manufacturers in the pipeline
  - Define market size (demand): what is the global need
  - Access plan: Identification of barriers and incentives for assay development, production and accessibility
  - Design of a costing model: direct purchasing model versus alternate ones (need creative ideas to provide the machine/test/maintenance/reagents…access for LMICs)

Meningitis in vitro diagnostics – Use case 3

3. **Meningitis belt.** Need to identify causative organism (Nm serogroup) rapidly at peripheral level for outbreak detection
   - *Roadmap 2030*: Adopt, integrate and implement minimum standards for surveillance of the main meningitis pathogens at country level on epidemiology, laboratory capacity (including the use of up to date diagnostic and AMR tests), and data management (SG 10)

Lateral flow immunochromatography

Two RDTs from Biospeedia

Thermostable

MeningoSpeed - PneumoSpeed

- Good performances under laboratory conditions: RDT vs PCR
  - Institut Pasteur Paris and Burkina Faso, CIV, CAR, Niger, Togo, Morocco
  - MeningoSpeed: sensitivity 95.6%, specificity 93.8% (545 samples)
- WHO: two levels of evaluation
  - Product suitability for procurement by WHO
    - Review of documentation, manufacturer practices, etc
  - External field validation
    - Burkina Faso and Niger, 2018-2019

Field validation study, Burkina Faso and Niger

- RDT at health centre level
  - Real situation. Districts in Alert -> staff immediately trained
- National Reference Laboratory (NRL): repeat RDT and PCR as gold standard
- Semi structured interviews and questionnaires
- Concordance : control photography by blinded reviewer
- Ethical approval: WHO and two national ethical committees

327 patients included: Niger (246) and Burkina Faso (81)

CSF positive - RDT health Centre	Neisseria (Nm)	106	32%
	NmA	9	3%
	NmC	56	17%
	NmW	2	1%
	NmX	40	12%
	NmY	1	0
	S. pneumoniae	28	9%

Final results (October 2019)

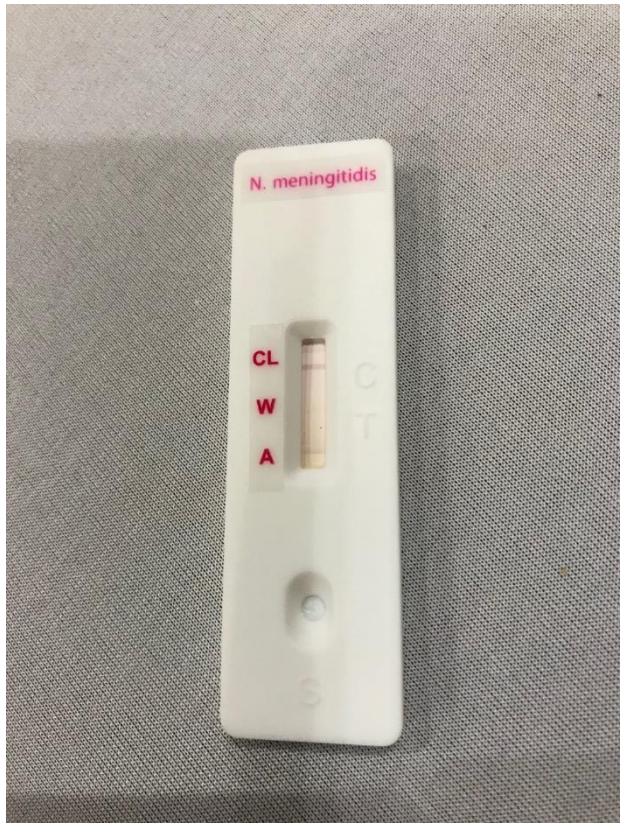
		N	Sensitivity (%)	CI 95%		Specificity (%)	CI 95%		PPV (%)	NPV (%)
Health center	All Nm	327	95.3	88	99	90	86	94	77	98
	Sp	334	92.9	77	99	99	97	100	87	99

NmA? Two by two tables

Health center

RDT \ PCR	+	-
+	0	9
-	0	329

2 out of these 9 tests positive also found positive by blind reviewers



NRL

RDT \ PCR	+	-
+	0	6
-	0	119

NmA migration line too close to the border of the device

- Manufacturer indicated that this has been fixed

Good training is necessary

easy

Less easy

Study limitations

- Field conditions challenging (security)
  - PCR confirmation: hampered in Burkina Faso (strike)
  - RDT repeat at the NRL challenged in Niger
- Nm distribution: mainly C and X serogroups
  - Small numbers with other serogroups

Results suggest

- Good performance of the RDT overall
  - in particular for NmC and NmX (Se: 93% and 91%, respectively)
- Interpretation issues, specially associated with NmA
  - all false negatives were on the AW cassette
- Conditions for use need to be carefully implemented

Conclusions

- Quick wins welcome!
  - Lateral flow has a place now in the meningitis belt
  - Finalize the RDT suitability for procurement
  - Deployment to be discussed 29 November
  - Exploration outside the belt
- Ambitious agenda (use case 1 and 2)
  - Development money to be identified
- Fast moving context
  - Support of all stakeholders needed

Thank you

Group B Strep – roadmap 2030

- By 2026, a quality assured, affordable and accessible diagnostic assay available to identify (i) maternal GBS carriage and (ii) invasive GBS disease

Concordance: high agreement between blind reviewer and RDT reading at the Health centre

		Total	Percentage of agreement (%)	Coefficient Kappa
RDT at the health centre	All Nm	65	82	61
	NmA	73	90	32
	NmC	75	96	39
	NmW	73	95	32
	NmX	70	94	83
	NmY	71	100	
	Sp	73	97	82