Final report 12 April 2018

WHO Meeting Report

Developing a new generation RDTs for Meningitis
Geneva, 9 March 2018

Introduction

Olivier Ronveaux (Chair) welcomed participants (Annex A). He outlined the agenda and purpose of the meeting (Annex B). The objectives were to review the current status of RDTs for meningitis, to define the goal for new generation RDTs, to explore how to create market conditions and funding mechanisms, and to define actions needed to move forward.

Background

Katya Fernandez outlined the background to this meeting. In May 2017 an expert meeting was held at Wilton Park, UK to develop a vision for global meningitis control by 2030. One key message was that a new scalable RDT is crucial and long overdue. WHO has since agreed to produce a road map for a plan to defeat meningitis by 2030 that includes the development of point of care diagnostic tests. A Task Force will be set up to submit a resolution to the World Health Assembly in 2020.

Olivier summarised challenges of effective outbreak control in the African meningitis belt, with identification of the responsible organism and reactive vaccination often coming late in the outbreak. In this situation RDTs are needed to for rapid identification of serogroup in outbreaks of meningococcal meningitis to guide vaccination response. There is no need to confirm all cases.

Another potential objective use of meningitis RDTs is rapid identification of the causative organism to guide early case management. If bacterial meningitis, antibiotics should be started as soon as possible. If meningococcal meningitis, contact tracing of close contacts should be initiated. Knowing the serogroup would not affect clinical management.

Current status of RDTs

All existing RDTs have limitations. The most widely used RDT in the meningitis belt is a latex agglutination test (Pastorex). CSF is needed, and lumbar puncture depending on the setting may need to be done by doctors. The test is not thermostable and has a short shelf life, it is relatively expensive and needs centrifugation and training, but it can identify most organisms and serogroups that cause bacterial meningitis. Immunochromatographic tests such as those developed by CERMES in Niger have more potential but are not widely available.

WHO had invited expression of interest for an RDT with a target product profile designed for the meningitis belt, with a response from only one company, probably because of the limited potential market. With the Institut Pasteur, this company (BioSpeedia) has developed new lateral flow tests to identify meningococcal serogroups and *S.pneumoniae* that are currently under field evaluation. Scaling up production and cost of the tests will possibly be issues for the future.

Martine Guillerm presented a review of recent publications on RDTs for bacterial meningitis, that covered several tracks:

(i) Lateral flow assays. New monoclonal antibody tests for NmC and NmX. Evaluated on CSF apart from urine for pneumococci. No field evaluation as yet.
(ii) Biomarkers. Variety of tests. Mainly CSF, some plasma serum. None on whole blood, saliva, urine.
(iii) Nucleic acid based tests. Isothermal application. Near point of care tests available. Mainly CSF, some blood. Still need lab technicians, but new platforms being developed to standardise such as LAMP.
(iv) New platforms under investigation e.g. use of filter papers at low cost, no sample preparation, sensitive, can be combined with LAMP or microfluidics.

A number of technologies are in development to simplify, standardise, and miniaturise RDTs, aiming for point of care using a combination of different technical approaches. There is a need for prioritisation and coordination, communication between public health policy makers, academics and test developers, evaluation of the global market for point of care meningitis tests, and a review of target product profiles.

Cassandra Kelly commented that evaluations of biomarkers in non-CSF samples have mainly been done to date in healthy populations. LAMP is not the most robust technology for field use. It will be important to check performance and feasibility of new RDTs in low and middle income countries (cost, application).

Alicia Feagins presented on multiplex platforms for meningitis RDTs. They require a centralised laboratory and good transport, and have relatively high costs to date but they do have potential as meningitis RDTs. Examples include BioFire Film Array that can test for 17 meningitis pathogens, is rapid and simple to use with good performance, but high cost (c.$130 per sample). Other technologies include Atlas Genetics (for sexually transmitted infections) and Taqman array for multiple pathogens.

Cassandra agreed with Alicia that lateral flow tests have most potential for use in low and middle income countries, being cheap, thermostable, and simple to use. Digital readers are advantageous. Anita Sands commented that multiple lateral flow tests often have lower specificity.

Defining the goal

Elias Kumbakumba, a paediatrician from Uganda, explained that in his clinical setting there was a lack of diagnostic facilities with consequent delays to diagnosis of meningitis and a high case fatality. The main bacterial causes of meningitis were *S.pneumoniae, H.influenzae* type b and non-typhoidal Salmonella. Suspected cases are often treated for both malaria and meningitis unless or until laboratory results were available. RDTs for malaria are successfully used at community health worker level, but CSF sampling is only carried out at district and regional hospitals. Desired attributes for a RDT are a simple, rapid, low cost bedside test for a range of pathogens including malaria. He emphasised the need to compare costs of unnecessary treatment vs cost of test. Costs and difficulties of equipment maintenance must not be forgotten.

Anne-Laure Page agreed that objectives for an RDT will differ between surveillance/epidemic response and clinical case management. If the aim is to change antibiotic or other treatment, will it do this? If few organisms tested and uncertain test performance, a negative test result may not change clinical management. A very high sensitivity and negative predictive values would be needed to stop antibiotics, and a high specificity to modify antibiotic regimens. This may be even more important in future with decreased risk of pneumococcal meningitis due to pneumococcal conjugate vaccine programmes, and less risk of meningococcal meningitis outbreaks after introduction of a pentavalent conjugate vaccine.

Discussion points were that we may need to test for multiple organisms to influence case management. At peripheral level, illness severity markers or ability to identify bacterial infection would be useful. Clinicians also want to know local causes of meningitis, and as do public health policy makers for evaluation of vaccine programmes. It was noted that RDTs provide insufficient information for surveillance needs and that laboratory confirmation remains essential. In general, development of new point of care tests is expanding and costs are reducing.

A need was identified for three different meningitis RDTs:

1. In the epidemic setting of the Meningitis belt where a pentavalent conjugate is expected within the next few years and where the market is anyway limited. Here the need is to identify the **causative organism (meningococcal serogroup**) rapidly at peripheral level (heath centre/district hospital) to determine vaccine response. A target product profile is in existence, and lateral flow tests from one company are on field trial. Specimens should still be referred to the regional/national reference laboratory.

2. Globally in epidemic and endemic settings for individual case management **at peripheral level** (first contact with the patient)**.** The key question for a sick patient with possible meningitis/septicaemia is to identify **bacterial infection** in order to give antibiotics immediately or not. A blood test would be ideal. Results would be integrated into clinical algorithms for treatment and referral.

3. Globally in epidemic and endemic settings for individual case management **at hospital level**. RDT to identify **multiple meningitis pathogens** such as *N.meningitidis, S.pneumoniae, H.influenzae* type b, Salmonella, Listeria, Group B streptococci, Echovirus, Coxsackievirus, Herpes Simplex, Cryptococcus. Ideally as point of care test, could be CSF or blood. The RDT needs to be highly sensitive and specific to influence case management (stopping /changing antibiotics).

How to get there

Mike Bond explained about the work of LifeArc, a medical research charity translating biomarker research. Intellectual Property position is key and may not be simple to obtain as natural phenomena are not patent eligible and additional technical steps are required. An early understanding of the potential path from marker to a diagnostic technology is key to developing an effective IP position and validation strategy. Early industry engagement can be vital in developing this strategy.

Rosanna Peeling stressed the importance of raising the profile of meningitis RDTs, for example, by official recommendations for use of RDTs in official guidelines, including RDTs on WHO essential diagnostic lists, emphasising the potential size of the global market. Clarification would be useful on advance purchase commitment by funders, need for provision for surge capacity or stockpiling, expected seasonal changes in demand, presence of a training plan and infrastructure in place to distribute tests through national programmes.

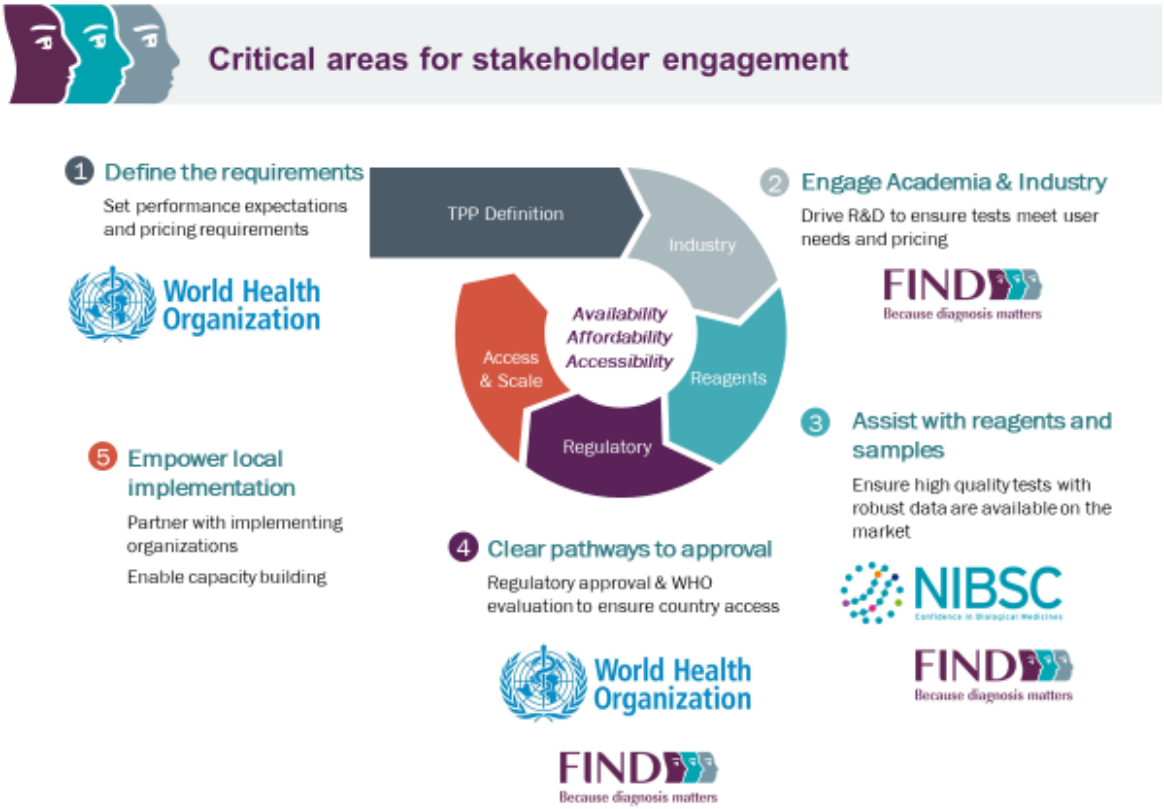
It may cost half a billion dollars to develop a new test. Improving existing test is easier and cheaper. Tests should ideally be ASSURED: Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment free, Deliverable. A pyramid showing the health service level at which the tests would be used is helpful to identify potential demand. There is a trade-off between access and performance.

The technology is expanding rapidly. New molecular technologies that can be performed at the point-of-care offer accurate and more accessible diagnostic tests but most remain costly. Open platform technologies offer the potential to test for multiple pathogens using a single specimen or multiple samples for a single target. Smart phone based diagnostics offer opportunities to reach remote areas, with connectivity solutions linking data from diagnostic laboratories and test readers for automated surveillance systems, quality monitoring and stock management systems. Point of care technologies can be adapted for meningitis but need to develop an investment case for a suite of diagnostics for different levels of the health care system.

Vinny Smith emphasized (i) the importance of collaboration between multiple partners and stakeholders, not just manufacturers and scientists and (ii) the size of underlying problem. Meningitis and neonatal sepsis are a major global cause of death (9% of deaths due to infectious disease) in under 5 year olds, yet meningitis is absent from most global health plans. We know that meningitis is a major concern among parents. Given the wider opportunities for funding, it is time to drive this initiative forward.

Cassandra Kelly discussed the critical areas for stakeholder engagement (Figure 1). Defining requirements through target product profiles, engaging academia and industry, driving R&D to ensure tests meet user needs and pricing, designing feasibility and evaluation studies, assisting with availability of samples for testing, ensuring regulatory approval, and partnering with implementing organisations.

Figure 1: Stakeholder engagement



Philip Jordan explained that the Wellcome Trust had two approaches to funding (i) Response funding e.g. innovations in malaria, neglected tropical diseases where therapeutics have a higher priority than diagnostics. (ii) Portfolio approach e.g. CEPI vaccines for outbreaks, making vaccines affordable. If funding is requested for RDT development, it will be important to specify the test requirements, who will partner, how much funding is needed, success criteria.

Sebastien Quesney supported this RDT initiative. Training would be needed in clinical presentation of different manifestations of meningitis and invasive meningococcal disease, correct sampling and how to use RDT kits. He also highlighted that RDTs from several neglected diseases should be promoted.

Next steps

A. Global advocacy.

WHO actions:

- ensure RDTs included on global road map
- raise public profile of RDTs at the first meeting of the meningitis 2030 Task Force.
- raise profile of meningitis across WHO and global health plans
- request meningitis included on Essential Diagnostic lists at SAGE meeting April 2018
- define RDT requirements and forecast demand at each health service level by context

B. Specific steps to progress recommended RDTs (p3, Defining the goal).

1. RDT in meningitis belt to identify the causative organism (meningococcal serogroup) at peripheral level.

    - WHO to review performance of Biospeedia in June. If positive field evaluation, hold discussions with BioSpeedia about mechanisms of funding and production for surge capacity. Consider contingency plan to transfer technology to another company.

2. RDT in epidemic and endemic settings to identify bacterial infection for individual case management at peripheral level.

    - WHO to review other initiatives on RDTs to identify bacterial infection and to include meningitis in evaluation panels wherever feasible.
    - Cassandra to check if meningitis can be included in FIND evaluation of TPP for children with fever.
    - WHO to check with Rosanna about adding meningitis and septicaemia to validation panels for commercial RDTs (procalcitonin and CRP levels) that could be used.

3. RDT in epidemic and endemic settings to identify multiple meningitis pathogens for individual case management at hospital level

    - WHO and FIND to develop plan of action. Expert group to agree product specification, define demand forecast, make specimens available and help with clinical trials, set up forum with manufacturers. Ideally make use of existing platform.

C. Next meeting:

- WHO to convene another meeting on RDTs within or outside the Meningitis 2030 Task Force

Annex A

List of Participants

Organization	Participant	email
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Annex B

Developing a new generation RDTs for Meningitis - Geneva, 9 March 2018 – WHO, M205

Objectives

- Define the RDT goal : scope, type, target user, timelines for having a product
- Explore how to create market conditions
- Explore funding mechanisms
- Define the immediate next steps: what is needed to move forward

Chair: Olivier RONVEAUX Rapporteur: James STUART

Agenda

Welcome & introductions Planned meeting outcomes	Chair	9.15-9.30
Session 1 – define the RDT goal		
Context: 2017 Wilton Park meeting and global strategy 2030	WHO	9.30-9.40
Limitations of existing products	WHO	9.40-9.50
Literature review findings - Identification of new tracks related to: rapid diagnostic of bacterial meningitis, biomarkers, new technologies - Identification of gaps in the research agenda and avenues for lobbying the need for new meningitis tests.	Martine Guillerm	9.50-10.05
Translation of Biomarker Research	Michael Bond	10.05-10.15
Multiplex – a way forward?		10.15.10.25
Discussion		10.25-11.00
Coffee		**11.00-11.15**
Define the product of the future – introduction	WHO	11.15-11.25
Country perspective	Elias Kumbakumba	11.25-11.40
How does the diagnostic outcome change the patient management	Anne-Laure Page	11.40-11.50
Discussion		11.50-12.30
Lunch		**12.30-14.00**
Session 2 – define the market conditions		
Market definition: demand, supply – lessons learned from elsewhere	Rosanna Peeling	14.00-14.20
Diagnostic collaboration	MRF	14.20-14.45
Role of potential stakeholders	FIND	14.45-15.00
Discussion		15.00-15-30
Coffee		**15.30-15.45**
Session 3 – Funding opportunities		
Successful criteria for financing the public health need	Wellcome Trust	15.45-16.00
	Fondation Mérieux	16.00-16.15
Discussion		16.15-16-45
Review of recommendation & next steps	**Rapporteur**	**16.45-17.00**