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The detection of multiple meningitis pathogens, next-generation tools and new explorations

Brenda Kwambana-Adams

Meningitis Research Foundation's 12th International Conference

The British Museum, London

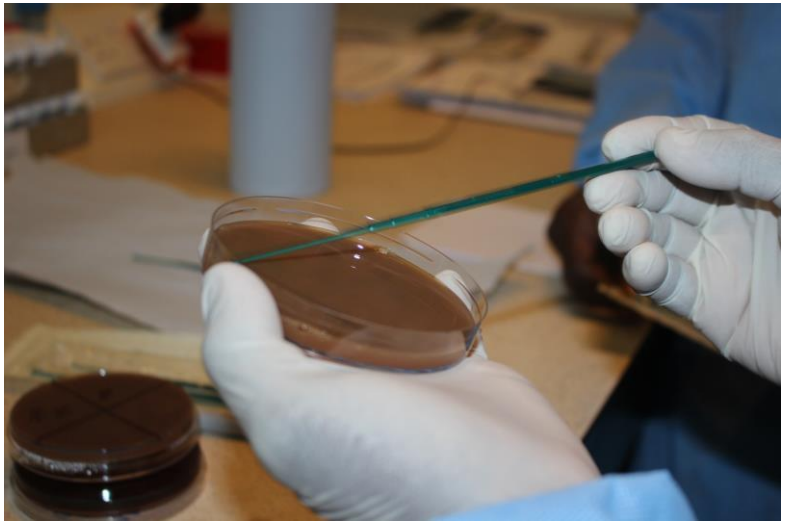
6th November, 2019

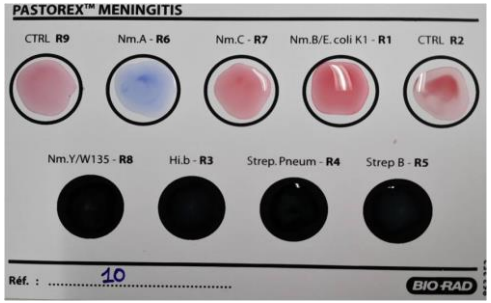
MPRU NIHR Mucosal Pathogens Research Unit

Meningitis laboratory confirmation

- Africa accounts for >50% of global meningitis cases and deaths
- Laboratory confirmation primarily based on culture and rapid tests (Latex & Binax)
- VP-IBD surveillance – qPCR targeting Nm, Spn and Hi is used
- Diagnostic yield among suspected cases remains very low

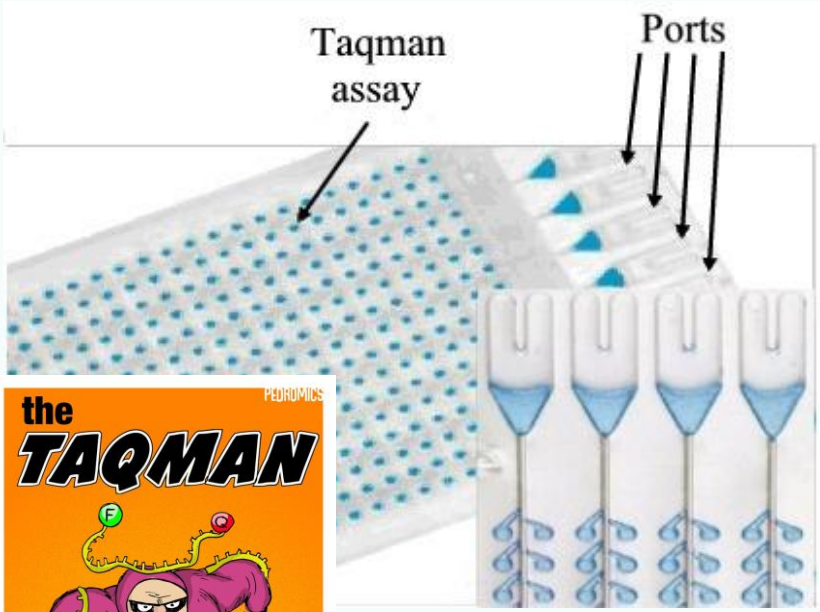
  e.g. **3.5%** **(1670/48,284**) for 26 AFRO IBD countries 2011-2016





Taqman Array Card (TAC)

- A custom compartmentalized probe-based qPCR system
- Thermocycling and data collection on the ABI QuantStudio instrument
- Previously used to increase case-level and population-level diarrhea case ascertainment among African and Asian children <5 years old, **Liu *et al.* 2016, Lancet**



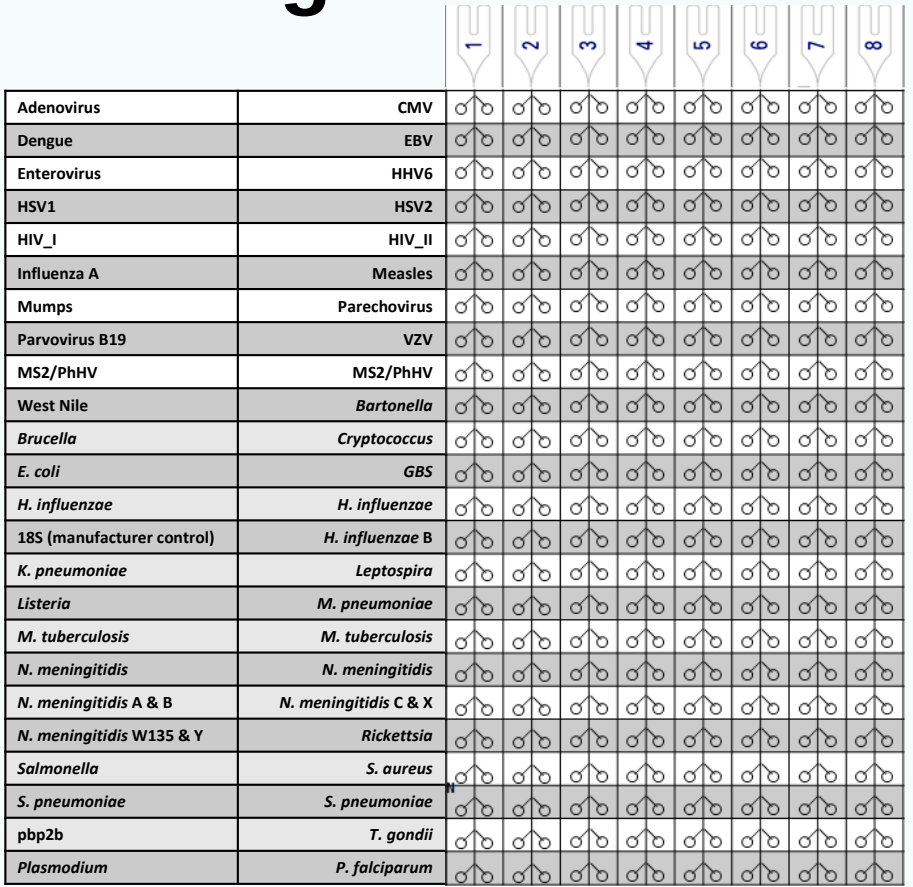
Objectives of the pilot

To leverage the existing surveillance to identify other aetiologies of meningitis with broad testing of pathogens using quantitative PCR via TaqMan Array Cards (TAC)

To determine the feasibility of using TAC to test for a broader set of aetiologies among paediatric meningitis cases enrolled through the surveillance

Paediatric meningitis TAC

- Simultaneous detection of 35 pathogens including:
  - -15 bacteria, 17 viruses, 1 fungus and 2 protozoans
  - -sub-typing of Nm, HIV, HSV, Hi



Suspected meningitis cases

- Children < 5 years old with suspected meningitis
- A total of 1088 CSF specimens were collected from sentinel sites in 5 West African countries
- 717/1088 (65%) had sufficient volume to perform TAC analysis

Characteristics of patients

		Ghana	Nigeria	Niger	Senegal	Togo
CSF specimens received# CSF specimens tested by TAC*		349 205	165 139	79 31	166 31	329 305
Sex	Male (%)	115 (56%)	82 (59%)	18 (58%)	19 (61%)	176 (58%)
Age	Median (months)	0.6	23	36	11	16
	<1 month (%)	123 (60%)	10 (7.2%)	0	8 (26%)	77 (25%)
	1-23 months (%)	59 (29%)	55 (40%)	11 (36%)	13 (42%)	100 (33%)
	24-59 months (%)	22 (11%)	74 (53%)	20 (65%)	10 (32%)	128 (42%)
Antibiotic usage		Yes	137 (71%)	0	0	12 (40%)
Antibiotic usage	No	56 (29%)	121 (100%)	1	18 (60%)	56 (35%)
CSF White blood count	<10	179 (90%)	139 (100%)	23 (74%)	8 (27%)	104 (65%)
CSF White blood count CSF glucose	10-100	10 (5.0%)	0	6 (19%)	9 (30%)	270 (89%)
Outcome at discharge	Died	5 (2.4%)	22 (16%)	5 (16%)	4 (13%)	50 (19%)
Outcome at discharge	Discharged alive	196 (96%)	103 (75%)	13 (42%)	22 (71%)	23 (11%)
	Transferred	1 (0.5%)	0	13 (42%)	3 (9.7%)	164 (82%)
	Left against medical advice	1 (0.5%)	12 (8.8%)	0	0	0
	Pending discharge	2 (1.0%)	0	0	2 (6.5%)	14 (7.0%)

Overview of TAC analysis

- 711/717 (99%) specimens yielded valid TAC results
- 19 pathogens in all detected, prevalence of 20%
  - 15.6% of specimens had 1 pathogen
  - 4.4% of specimens contained >1 pathogen

Performance comparison

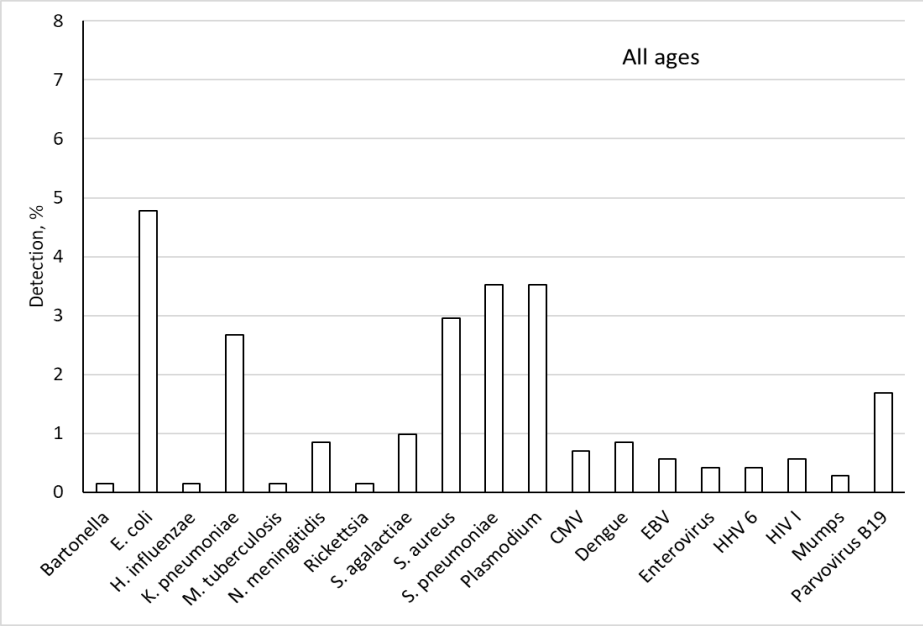
TAC vs. Culture

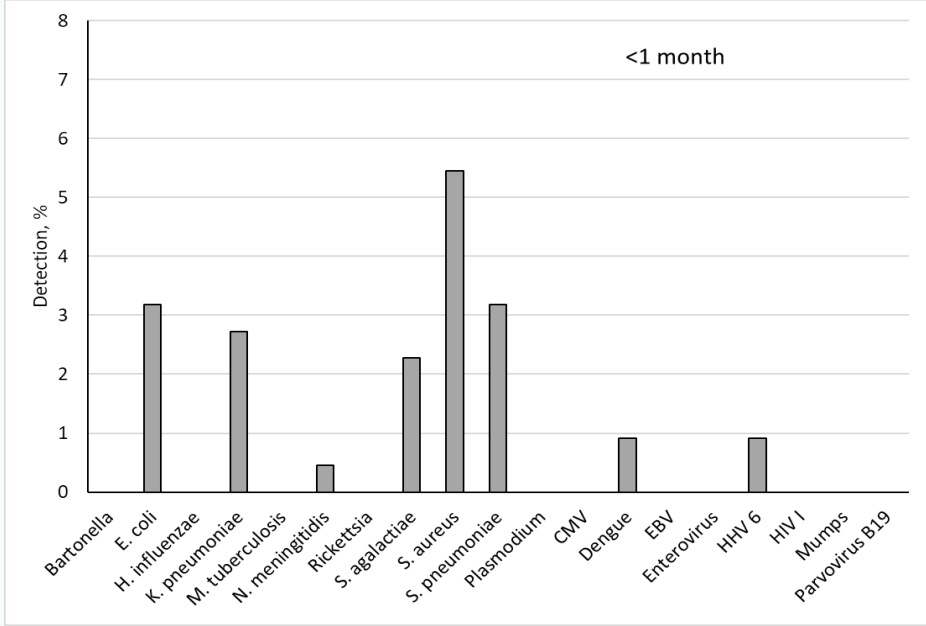
- Pathogen detection 20% vs. 2%
- TAC detected all cases confirmed by culture (1 Hi, 3 Spn, 2 Nm)
- TAC detected additional 22 Spn and 4Nm

TAC vs. VP-IBD PCR

- Pathogen detection 20% vs. 2.4%
- TAC detected (0/1 Hi, 4/5 Spn, 3/3 Nm)
- TAC detected additional 17 Spn and 4Nm

Prevalence of pathogens < 5yrs and neonates





Pathogen detection (%) by country

Pathogen	Ghana (n=205)	Nigeria (n=139)	Niger (n=31)	Senegal (n=31)	Togo (n=305)
E. coli	5 (2.4)	20 (14)	-	5 (16)	4 (1.3)
Plasmodium	3 (1.5)	5 (3.6)	2 (6.5)	-	15 (4.9)
S. pneumoniae	**13 (6.3)**	4 (2.9)	4 (13)	**3 (9.7)**	1 (0.3)
S. aureus	**8 (3.9)**	2 (1.4)	-	**3 (9.7)**	**8 (2.6)**
K. pneumoniae	7 (3.4)	**8 (5.7)**	**2 (6.5)**	2 (6.5)	-
Parvovirus B19	-	**8 (5.7)**	**1 (3.2)**	1 (3.2)	2 (0.7)
S. agalactiae	**6 (2.9)**	1 (0.7)	-	-	-
Dengue	3 (1.5)	-	-	1 (3.2)	2 (0.7)
N. meningitidis	1 (0.5)	1 (0.7)	3 (9.7)	-	1 (0.3)
CMV	2 (1.0)	-	-	1 (3.2)	2 (0.7)
EBV	-	2 (1.4)	1 (3.2)	-	1 (0.3)
HIV I	-	1 (0.7)	1 (3.2)	-	2 (0.7)
Enterovirus	3 (1.5)	-	-	-	-
HHV 6	2 (1.0)	-	-	-	1 (0.3)
Mumps	1 (0.5)	-	-	-	1 (0.3)
HIV II	-	-	-	-	1 (0.3)
Bartonella	1 (0.5)	-	-	-	-
H. influenzae	-	-	1 (3.2)	-	-
M. tuberculosis	-	1 (0.7)	-	-	-
Rickettsia	-	1 (0.7)	-	-	-
Total	**45 (22)**	**33 (24)**	**9 (29)**	**14 (45)**	**24 (8.0)**

Pathogen association with mortality

	Discharged alive (n=498)	Died (n=59)	Univariate OR	(P value)
CMV	3	1	2.8 (0.3, 27.8)	0.347
Dengue	5	0	-	-
E. coli	23	5	1.9 (0.7, 5.2)	0.200
Enterovirus	3	0	-	-
HHV 6	2	1	-	-
HIV	**2**	**2**	**8.7 (1.2, 63.0)**	**0.010**
K. pneumoniae	12	3	2.2 (0.6, 7.9)	0.230
N. meningitidis	5	0	-	-
Parvovirus B19	9	1	0.9 (0.1, 7.5)	0.951
Plasmodium	**12**	**5**	**3.8 (1.3, 11.0)**	**0.010**
S. agalactiae	6	1	1.4 (0.2, 12.0)	0.749
S. aureus	17	2	1.0 (0.2, 4.4)	0.992
S. pneumoniae	19	4	1.8 (0.6, 5.6)	0.279

Summary

- Ten-fold increase in diagnostic yield of paediatric meningitis with TAC assays
- Pneumococcus remains a leading cause of paediatric meningitis in West Africa
- Large proportion of paediatric meningitis is attributed to Gram Negatives such as *E. coli and K. pneumoniae* as well as *S. aureus*
    - Particularly important for neonatal infections
    - Gram negatives associated with antimicrobial resistance
- Importance of viruses such as enterovirus, parvovirus, dengue and

Towards WHO Defeating Meningitis 2030

TAC platform has potential to be implemented in routine surveillance to:

1. Identify “new” priority pathogens with high burden of disease e.g. Gram-negatives, *S. aureus,* GBS
2. Used to monitor vaccine-preventable meningitis e.g. Spn and Nm
3. Used to monitor genetic markers of antimicrobial resistance

Acknowledgements

MRCG @ LSHTM

Martin Antonio

Catherine Okoi

Archibald Worwui

Peter Ndow

Nuredin I. Mohammed

University of Virginia

Eric Houpt

Jie Liu

Jean Gratz

WHO

Jason Mwenda

Adam L. Cohen

Fatima Serhan

Richard Mihigo

Country Ministries of Health (Nigeria, Niger, Togo, Senegal and Ghana)

Enyonam Tsolenyanu

Beckie Tagbo

Mohamadou A. Sonko

Lorna Awo Renner

Muhammad F. Bashir

Daniel Ansong

Mamadou Kourna