Systematic review of Rapid Diagnostic Tests for the diagnosis of meningitis in outbreak response in sub-Saharan Africa

Report for WHO Meningitis guideline revision

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Contents

1. INTRODUCTION

Rapid diagnostic tests have been defined as any test that yields a result in the same clinic visit as diagnosis (Pai et al 2012) or which can be used in healthcare settings with little infrastructure or trained personnel, preferably without electricity (Yansouni et al 2013).

For rapid diagnosis of bacterial meningitis, latex agglutination tests have been the techniques most commonly used. More recently, a pair of duplex dipsticks using immunochromatography have been developed in order to enable identification of four different serogroups of N. *meningitidis* (A, C, W and Y) using a cerebrospinal fluid (CSF) sample obtained by lumbar puncture. A similar technique has been developed for S. *pneumoniae*.

Rationale for review

It is ever more critical to ensure that the causal pathogen in outbreaks of meningitis is confirmed rapidly, particularly since the epidemiological shift brought about by the introduction of the MenAfriVac for N. *meningitidis* serogroup A (NmA). In many instances, reactive vaccination may occur too late to effectively reduce the size of outbreaks and epidemic presumptive case management may be less appropriate. RDTs are useful to support urgent decision-making for outbreak management. However, latex agglutination tests (LATs) e.g. Pastorex, are expensive, not easy to use and not always reliable. Immunochromatographic tests have not yet been widely deployed. A review of the sensitivity and specificity of different rapid diagnostic tests compared to the gold standards of culture or PCR was therefore commissioned by the WHO to summarise the diagnostic accuracy of RDTs, in turn supporting the development of revised WHO guidelines for outbreak response and management in sub-Saharan Africa.

Recommendation question:

What is the place of rapid diagnostic tests (RDTs) in decisions on outbreak management?

Aim:

To identify Rapid Diagnostic Tests (RDTs) for bacterial meningitis and determine the diagnostic accuracy (including the sensitivity and specificity) of each compared to the gold standard of culture or PCR.

Objectives:

This report presents preliminary data on the following study objectives:

1) To determine combined estimates of the sensitivity and specificity of each identified RDT for distinguishing between serogroups of N. *meningitidis*
2) To determine combined estimates of the sensitivity and specificity of each identified RDT for N. *meningitidis*
3) To determine combined estimates of the sensitivity and specificity of each identified RDT for S. *pneumoniae*
4) To determine combined estimates of the sensitivity and specificity of each identified RDT for *H. influenzae*

2. SEARCH METHODS AND TERMS

Details of search methods, terms used and databases searched are provided in the study protocol and are not repeated here. Quality assessment was undertaken using the QUADAS-2 tool for diagnostic test accuracy studies.

Results reported are limited to those test kits which are still in production and those which can both detect N. meningitidis serogroup W and then distinguish between serogroups A&W, as requested by the steering group.

3. RESULTS

The search identified 3004 records of which 2871 were excluded on the basis of title alone.

A further 70 papers were excluded on an abstract scan without obtaining full text.

Full text articles were requested for 56 papers. 54 were obtained; 36 papers were assessed as ineligible; for details see figure 1.

A total of 18 papers describing 16 observational studies and two laboratory validation studies are therefore included in this review.

Four different RDTs are assessed in this review. Their characteristics and the papers assessing each are summarised in table 1. 2 papers compare more than one test in all participants. Several papers employed alternative reference and index tests in selected subgroups, (for example only in PCR positive samples). We have considered in-country PCR the "ideal" reference standard for this review and only include studies where data comparing RDT and reference standard for the all patients in the study were available. The distribution of reference standard tests by RDT assessed is shown in table two.

The 16 observational studies reviewed were conducted in two different settings:

- "Field studies", in which the performance of the RDT at a district or regional health facility is assessed (e.g. close to the patient), by healthcare staff or local laboratory staff
- "Laboratory studies", in which the performance of the RDT when conducted in a central or national reference lab un

One observational study (Rose and Gerstl 2009) compared two different RDTs. One lab validation study compared four RDTs of which three are included in this review.

Two studies compared an RDT with two different reference standards (Rose and Mueller 2010, Collard 2014). These paper compared RDT results with both in-country PCR and WHO collaborating centre rt-PCR results for selected patients. For these papers, we have reported comparisons with in-country PCR.

Two papers describe concordance of RDT results from the same samples when performed in the field or in a reference laboratory (Boisier et al 2009, Collard 2014).

Where more than one study exists for an RDT with the same reference standard, performed under the same conditions (laboratory or field) for the same serogroup or organism, pooled results have been used to provide sensitivities and specificities. This method allows for an overall measure to be presented in an interpretable manner; however care must be taken with results obtained in this manner. It would be more statistically accurate to present a full range of sensitivities and specificities for each set of conditions, each with a 95% CI however this is not easy to present and cannot be summarised.

Systematic review

Figure 1: Search for systematic reviews (undertaken by LT, TW and JS)

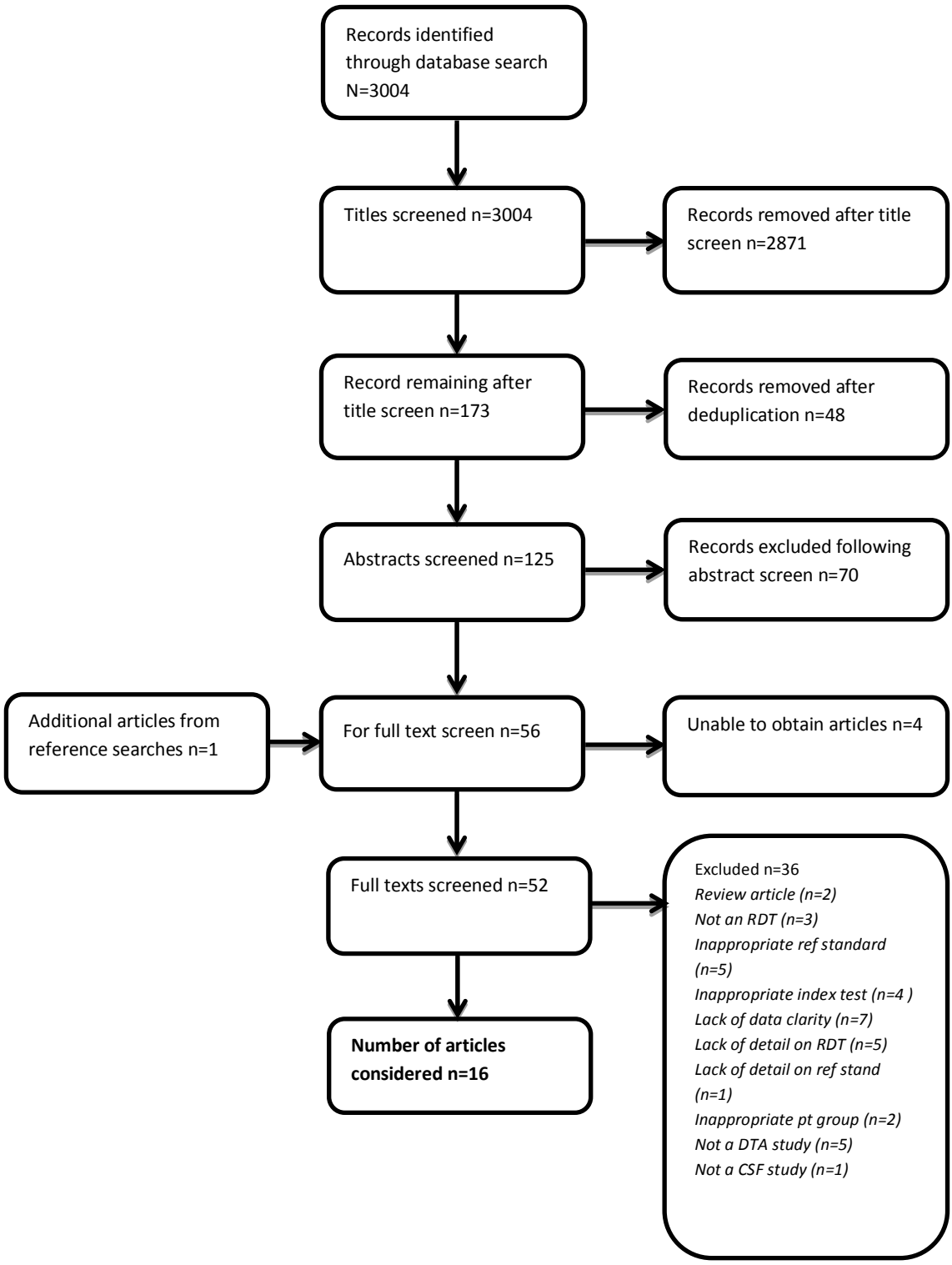


Table 1: RDTs included in this review, the antigens they detect and their component tests

Kit	Antigens detected	Observational studies	Lab validation studies
Latex Agglutination Tests			
Pastorex meningitis kit ("Pastorex")	*H. influenzae b* *S. pneumoniae* *N. meningitidis A* *N. meningitidis C* *N. meningitidis Y,W135* *N. meningitidis B*	Borel 2006 (Nm A) Djibo et al 2006 Rose and Gerstl 2009 (Nm A) Ouedraogo 2012	*NICD*
BD Directigen Meningitis Combo Kit ("Directigen")	*H. influenzae b* *S. pneumoniae* *N. meningitidis C, W135* *N. meningitidis A,Y* *N. meningitidis B*	Cuevas 1989 Hoban et al 1985 Hossein (unpublished results)	*NICD*
Immunochromatographic Tests			
BinaxNOW S. pneumoniae	S. *pneumoniae*	Moisi 2009 Saha 2005 Samra 2003	*NICD*
CERMES duplex dipstick ICT NB: *no trade name*	*N. meningitidis A, W135/Y* *N. meningitidis C,Y*	Boisier et al 2009 (Nm A&W) Chanteau 2006 (Nm A or W/Y) Collard et al 2014 (NmA&W) Rose and Gerstl 2009 (Nm A) Rose and Mueller 2010 (Nm A)	*Terrade 2014*

An overview of the number of observational studies assessing each RDT type using CSF culture, PCR or other is shown at table 2.

Table 2: A comparison of reference test by RDT type – ICT=Immunochromographic Test, LAT=Latex Agglutination Test – NB some studies assessed more than one RDT

RDT	Reference Test		
	Local CSF Culture	**Local CSF PCR**	**Culture +/- PCR**
BinaxNOW (ICT)		**1** Saha 2005	**2** (Moisi 2009, Samra 2003)
CERMES Dipstick (ICT)		**2** (Boisier 2009, Collard 2014)	**3** (Chanteau 2006, Rose & Gerstl 2009, Rose & Mueller 2010[local and WHOCC])
Directigen (LAT)	**3** (Cuevas 1989, Hoban 1985, Gambia unpublished data)		
Pastorex (LAT)		**1** (Djibo 2006, Ouedraogo 2012)	**2** (Borel 2006, Rose & Gerstl 2009)

Sensitivities and specificities for each RDT are illustrated on the following pages. Where applicable, these are accompanied with pooled results along with calculations for true and false positive and negative results for a theoretical population of 1000. Each of these uses an assumed disease prevalence of 20%, to fit the conditions thought to occur during epidemic seasons. These results are therefore extrapolated from the results reported in individual studies, for which prevalence by serogroup and organism varies from c.1% to over 80% by paper (see appendix one; summary of study characteristics).

IMMUNOCHROMOGRAPHIC TESTS

CERMES Duplex ICT for N. meningitidis

FIELD CONDITIONS

Four papers assessed the diagnostic accuracy of the CERMES duplex ICT under field conditions. Two of these assessed the accuracy in diagnosing N. meningitidis serogroup A; two papers assessed the accuracy in diagnosing serogroups A & W.

Two of these papers used local PCR alone as a reference standard. Two used local CSF culture and PCR.

As the antibody used to NmA has been replaced since the dipstick was initially assessed, results below distinguish between assessments of the "old" and "new" test kits.

Results for serogroup A are shown in Table 3. Example calculations at an assumed disease prevalence of 20%, based on the pooled results for the original test kit can be seen in Table 4. Results for serogroup W are shown in Tables 5 and 6 respectively.

Serogroup A

Table 3: Diagnostic accuracy of CERMES ICT under field conditions for N. meningitidis serogroup A

	Paper	Participants	Results
Sensitivity	Rose and Gerstl (2009)	126	87% (95%CI 77-93%)
	Boisier et al (2009)	517	91% (95%CI 84-96%)
	Rose & Mueller (2010)	265	70% (95%CI 55-82%)
		908	**Pooled sensitivity: 83% (95%CI 77-87%)**
	Collard (2014) *(new NmA antibody)*	1632	87% (95%CI 84-89%)
Specificity	Rose and Gerstl (2009)	126	64% (95%CI 51-76%)
	Boisier et al (2009)	473	97% (95%CI 94-98%)
	Rose & Mueller (2010)	265	97% (95%CI 93-99%)
		864	**Pooled specificity: 95% (95%CI 93-96%)**
	Collard (2014) *(new NmA antibody)*	1632	79% (95%CI 76-82%)

Table 4: Example calculations for N. meningitidis serogroup A using the CERMES duplex dipstick ICT with an *assumed disease prevalence of 20%*.

		PCR (local)		
		NmA present	*NmA absent*	
CERMES ICT	*Positive*	TP **166(154-174)**	FP **40(32-56)**	
	Negative	FN **34(26-46)**	TN **760(744-768)**	
Prevalence: **20 %**		**200**	**800**	**1000**

Serogroup W

Table 5: Diagnostic accuracy of CERMES ICT under field conditions for N. meningitidis serogroup W			
	Paper	**Participants**	**Results**
Sensitivity	Boisier et al 2009	517	89% (95%CI 52-100%)
	Collard et al 2014 (unpublished data)	1200	92% (95%CI 88-94%)
		1717	**Pooled sensitivity: 92% (95%CI 88-94%)**
Specificity	Boisier et al 2009	517	99% (95%CI 98-100%)
	Collard et al 2014 (unpublished data)	1200	92% (95%CI 89-93%)
		1717	**95% (95%CI 93-96%)**

Table 6: Example calculations for N. meningitidis serogroup W using the CERMES duplex dipstick ICT with an *assumed disease prevalence of 20%*.

		PCR (local)		
		NmW present	*NmW absent*	
CERMES ICT	*Positive*	TP **184 (176-188)**	FP **40 (32-56)**	
	Negative	FN **16 (12-24)**	TN **760 (744-768)**	
Prevalence: **20 %**		**200**	**800**	**1000**

Multiple Testing

With a prevalence of Nm W of 20%, the theoretical Positive Predictive Value (PPV) of the CERMES duplex dipstick ICT would be 184/224 = 0.82 (i.e. 82% of all dipstick positives are truly NmW). Based on this PPV the expected values of the number of true NmW cases in a given number of samples (within a certain time frame) are shown in table 7 below:

Table 7: Expected true positives for given numbers of positive RDT results

Number of positive RDT results	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Expected true positives[1]	4.1	4.9	5.8	6.6	7.4	8.2	9.0	9.9	10.7	11.5	12.3
Rounded true positives[2]	4	4	5	6	7	8	9	9	10	11	12

* Expected number of real cases

[1] Expected number of real cases
[2] Rounded down to a complete number (partial tests not possible)

CERMES Duplex ICT for N. meningitidis

LABORATORY CONDITIONS

Three papers assessed the diagnostic accuracy of the CERMES duplex ICT for serogroups A&W under laboratory conditions.

Two of these papers used local PCR alone as a reference standard (Boisier 2009, Collard 2014). One (Chanteau 2006) used local CSF culture and PCR.

As the antibody used to NmA has been replaced since the dipstick was initially assessed, results below distinguish between assessments of the "old" and "new" test kits.

Results for serogroup A are shown in Table 8 with example calculations for at a prevalence of 20% based the pooled results for the original test kit at Table 9; results for serogroup W are shown in Tables 10 and 11 respectively.

Serogroup A

Table 8: Diagnostic accuracy of CERMES ICT under laboratory conditions for N. meningitidis serogroup A

	Paper	Participants	Results
Sensitivity	Boisier et al 2009	517	87% (95%CI 80-93%)
	Chanteau et al 2006	57	94% (95%CI 71-100%)
	Collard et al 2014	1616	86% (95%CI 84-89%)
		2190	**Pooled sensitivity: 87% (95%CI 84-89%)**
Specificity	Boisier et al 2009	517	94% (95%CI 91-96%)
	Chanteau et al 2006	57	97% (95%CI 87-100%)
	Collard et al 2014	1616	77% (95%CI 74-79%)
		2190	**Pooled specificity: 82% (95%CI 80-84%)**

Table 9: Example calculations for N. meningitidis serogroup A using the CERMES duplex dipstick ICT under laboratory conditions with an *assumed disease prevalence of 20%*.

		PCR (local)		
		NmA present	*NmA absent*	
CERMES ICT	*Positive*	TP **174(168-178)**	FP **144(128-160)**	
	Negative	FN **26(22-32)**	TN **656(640-672)**	
Prevalence: **20 %**		**200**	**800**	**1000**

Serogroup W

Table 10: Diagnostic accuracy of CERMES ICT under laboratory conditions for N. meningitidis serogroup W			
	Paper	**Participants**	**Results**
Sensitivity	Boisier et al 2009	517	89% (95%CI 52-100%)
	Chanteau et al 2006	57	100% (95%CI 16-100%)
	Collard et al 2014	1177	97% (95%CI 95-98%)
		1751	**Pooled sensitivity: 97% (95%CI 95-98%)**
Specificity	Boisier et al 2009	517	99% (95%CI 98-100%)
	Chanteau et al 2006	57	100% (95%CI 94-100%)
	Collard et al 2014	1177	91% (95%CI 89-93%)
		1751	**Pooled specificity: 95% (95%CI 93-96%)**

Table 11: Example calculations for N. meningitidis serogroup A using the CERMES duplex dipstick ICT under laboratory conditions with an *assumed disease prevalence of 20%*.

		PCR (local)		
		NmW present	*NmW absent*	
CERMES ICT	*Positive*	TP **194(190-196)**	FP **40(32-56)**	
	Negative	FN **6(4-10)**	TN **760(744-768)**	
Prevalence: **20 %**		**200**	**800**	**1000**

BinaxNOW ICT for S.pneumoniae

Laboratory conditions (no field studies found)

Three studies assessed the diagnostic accuracy of the BinaxNOW ICT under laboratory conditions, with a total of 1151 participants. All three papers used CSF culture as a reference standard; two paper added nested in-country PCR for discordant results (Moisi et al 2003, Samra et al 2003).

Table 12: Diagnostic accuracy of BinaxNOW ICT under laboratory conditions for S. pneumoniae

	Paper	**Participants**	**S. pneumoniae**
Sensitivity	Moisi et al 2003	209	99% (95% CI 92%-100%)
	Saha et al 2005	450	100% (95% CI 96%-100%)
	Samra et al 2003	492	95% (95% CI 77%-100%)
		1151	**Pooled sensitivity: 99% (96-100%)**
Specificity	Moisi et al 2003	209	99% (95% CI 96%-100%)
	Saha et al 2005	450	90% (95% CI 87%-93%)
	Samra et al 2003	492	100% (95% CI 99%-100%)
		1151	**Pooled: 96% (95-97%)**

Table 13: Example calculations for S. pneumoniae using the BinaxNOW ICT under laboratory conditions with an *assumed disease prevalence of 20%*.

		CSF culture (local)		
		S Pn present	*S Pn absent*	
Binax NOW	*Positive*	TP **198 (192-200)**	FP **32 (24-40)**	
	Negative	FN **2 (0-8)**	TN **768 (760-776)**	
Prevalence: **20 %**		**200**	**800**	**1000**

LATEX AGGLUTINATION TESTS

Pastorex meningitis latex agglutination kit

LABORATORY CONDITIONS

Three papers assessed the diagnostic accuracy of the Pastorex LAT for serogroup A under laboratory conditions. Two of these papers also assessed the diagnostic accuracy of Pastorex for Nm W (Djibo et al 2006, Ouedraogo et al 2012). Two of these papers used local PCR alone as a reference standard (Djibo et al 2006, Ouedraogo et al 2012[3]). One (Borel at al 2006) used local CSF culture and PCR.

Results for serogroup A are shown in Table 14; results for serogroup W are shown in Table 15.

Due to only three papers being found and the different reference standard used for each, results have not been pooled and thus true and false positives and negatives for a theoretical population of 1000 have not been calculated.

Table 14: Diagnostic accuracy of Pastorex LAT under laboratory conditions for N. meningitidis serogroup A

	Paper	Participants	N. meningitidis serogroup A
Sensitivity	Borel et al 2006	484	88% (95% CI 84%-91%)
	Djibo et al 2006	602	87% (95% CI 81%-91%)
	Ouedraogo et al 2012	438	100% (95% CI 81%-100%)
Specificity	Borel et al 2006	484	93% (95% CI 87%-96%)
	Djibo et al 2006	602	96% (95% CI 93%-98%)
	Ouedraogo et al 2012	438	99% (95% CI 97%-100%)

[3] Ouedraogo el al (2012) used local PCR for all patients with culture for a subgroup; reported PCR results are used in this analysis

Table 15: Diagnostic accuracy of Pastorex LAT under laboratory conditions for N. meningitidis serogroup W or Y (NB: Pastorex cannot distinguish between serogroup W&Y)			
	Paper	**Participants**	**N. meningitidis serogroup W or Y**
Sensitivity	Djibo et al 2006 Ouedraogo et al 2012	599 438	85% (95% CI 78%-89%) 100% (95% CI 94%-100%)
Specificity	Djibo et al 2006 Ouedraogo et al 2012	599 438	99% (95% CI 97%-99%) 99% (95% CI 96%-99%)

FIELD CONDITIONS

One paper assessed the diagnostic accuracy of the Pastorex LAT for serogroup A under field conditions (Rose and Gerstl 2009). This paper used local CSF culture and PCR as a reference standard.

Due to only one paper being found, results have not been pooled. The true and false positives and negatives for a theoretical population of 1000 have been calculated based on this single paper.

Table 16: Diagnostic accuracy of Pastorex LAT under laboratory conditions for N. meningitidis serogroup A			
	Paper	**Participants**	**N. meningitidis serogroup A**
Sensitivity	Rose and Gerstl 2009	143	65% (95% CI 53%-75%)
Specificity	Rose and Gerstl 2009	143	84% (95% CI 72%-92%)

Table 17: Example calculations for N. meningitidis serogroup A using the Pastorex LAT under field conditions with an *assumed disease prevalence of 20%*.

		Local PCR and culture		
		NmA present	*NmA absent*	
RDT	*Positive*	TP **130 (106-150)**	FP **128 (64-224)**	
	Negative	FN **70 (50-94)**	TN **672 (576-736)**	
Prevalence: **20 %**		**200**	**800**	**1000**

BD Directigen meningitis latex agglutination kit

LABORATORY CONDITIONS

Three papers assessed the diagnostic accuracy of the BD Directigen meningitis LAT kit. One of these was unpublished field data from an outbreak of N. meningitidis serogroup W in the Gambia. The remaining papers assessed the diagnostic accuracy of the kit for N. meningitidis, S. pneumoniae and H. influenzae. N. meningitidis serogroups were not reported. Source populations were heterogeneous. All three papers used local CSF culture as a reference standard.

Due to heterogeneity of field and lab setting, as well as population, results have not been pooled and thus true and false positives and negatives for a theoretical population of 1000 have not been calculated. Results have been displayed overleaf in landscape format (Table 18) for ease of reading.

Table 18: Diagnostic accuracy of BD DIrectigen meningitis LAT						
	Paper	**Participants**	**N. meningitidis serogroup W**	**N. meningitidis serogroup unspecified**	**S. pneumoniae**	**H. influenzae**
Sensitivity	Hossein et al (unpublished)	63	100% (95%CI 93-100%)	n/a	n/a	n/a
	Cuevas et al 1989	91	n/a	100% (95%CI 48-100%)	88% (95%CI 69-97%)	88% (95%CI 47-100%)
	Hoban et al		n/a	33% (95%CI 01-91%)	100% (95%CI 54-100%)	78% (95%CI 56-93%)
Specificity	Hossein et al (unpublished)	63	40% (95%CI 12-74%)	n/a	n/a	n/a
	Cuevas et al 1989	91	n/a	99% (95%CI 94-100%)	100% (95%CI 95-100%)	96% (95%CI 90-99%)
	Hoban et al		n/a	100% (95%CI 93-100%)	96% (95%CI 87-100%)	100% (95% 90-100%)

4. Methodological quality of included studies

The overall methodological quality is summarised in Figures 2-3.

Risk of bias

Approximately 30% of studies had a low risk of introducing bias through selection of patients. The majority of the remaining studies were unclear, in most cases because they did not describe a sampling method. Just under 10% of studies were deemed to be at high risk of bias, in most cases due to exclusion criteria employed.

Under 20% of studies had a low risk of bias being introduced through the conduct or interpretation of the index test (RDT). The remainder were unclear about the conduct of the RDT or did not report, for example, on who performed the RDT, on blinding of the operator to the reference standard results or training of the operator.

Around 40% reported an acceptable reference standard, whilst the remainder were unclear about, for example, who performed the reference standard or blinding of reference standard operators to the index test (RDT) result. Reference standard risk of bias was judged to be high if not all participants had the same reference standard test in a way which could systematically affect results. In total, 73% reported blinding of the reference test operator to the index test (RDT) result.

35% of studies gave detail of the time interval between index tests and reference standards. All papers used the same CSF sample for index and reference tests.

Overall, there was a low risk of patient flow introducing bias in 50% of included studies, with concerns about just over 25%. An overview of these figures is shown at figure 2. For detail by paper, see figure 3.

Figure 2: Risk of bias judgement and applicability, by domain of QUADAS-2 assessment

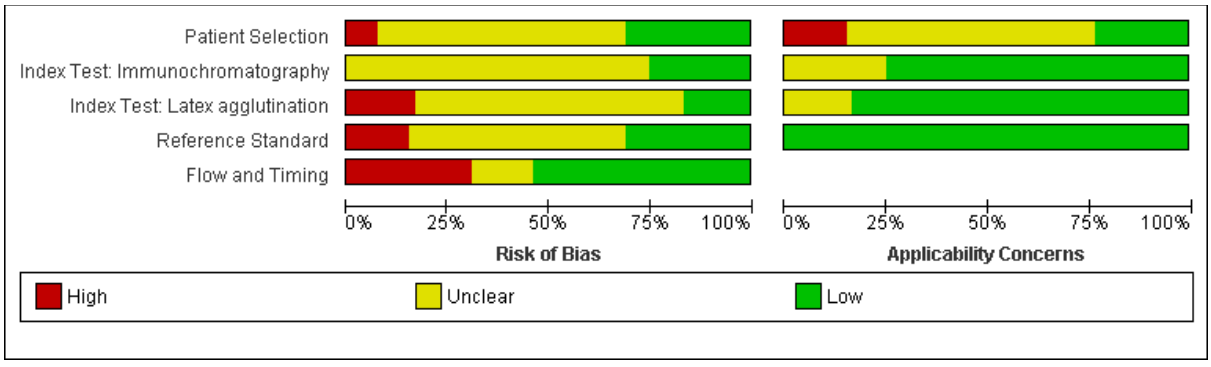
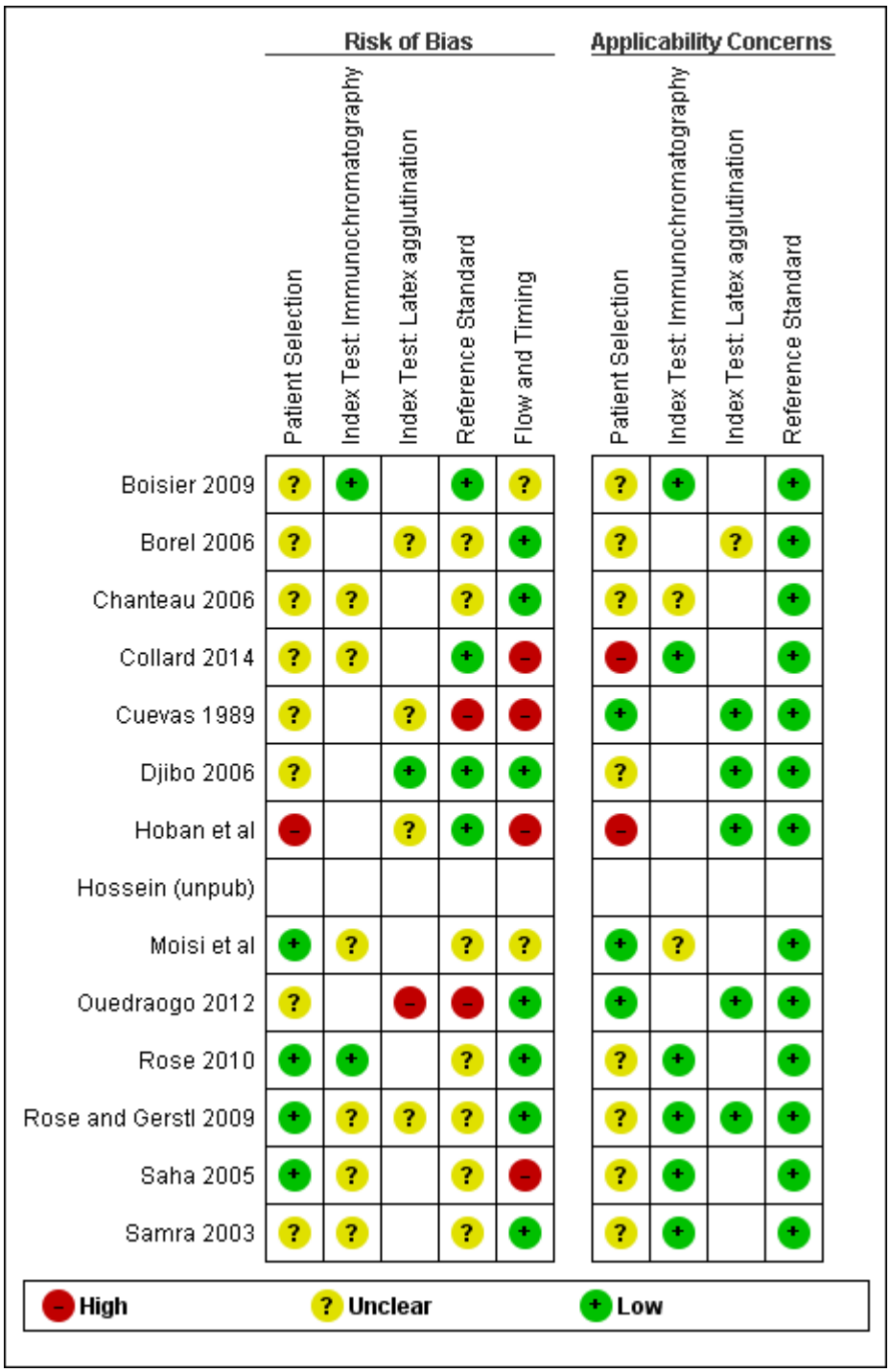


Figure 3: Overview of results of assessment of study quality, using the quality criteria of diagnostic accuracy studies derived from QUADAS-2.



5. SHELF LIFE, COSTS AND TEST PRACTICALITIES

Table 19 (below) summarises the practical aspects (shelf life, storage conditions, exclusions, cost and manufacturer) for each RDT considered in this review.

Table 19: Characteristics of rapid diagnostic tests reviewed in this study

Factor	CERMES ICT	BinaxNOW	Pastorex	BD Directigen Meningitis
Shelf life	ACW component: Heat stable at up to 25C for up to 2 years Y component: Heat stable at up to 25C for up to 8 months	Shelf life one year	Unopened shelf life not clear Shelf life once opened (pack of 25 tests) one month	Unopened: One year (refrigerated) Shelf life of reagent bottles once opened not clear
Storage conditions	Does not need to be refrigerated Store at up to 25C	Store at 2-30C	Store at 2-8C Cold chain required Do not freeze	Keep refrigerated. Do not freeze
Notable exclusions	Does not detect serogroup X	Only detects S. pneumoniae	Does not distinguish between W&Y Does not detect serogroup X	Does not detect serogroup X
Cost	See PICO 2 Recommendation framework			
Manufacturer	CERMES	Alere	BioRAD	BD

6. SUMMARY AND RECOMMENDATIONS

SUMMARY

- There is limited evidence for the effectiveness of RDTs for N.meningitidis
- Two main groups of RDTs were identified; Latex Agglutination Tests (LATs) and Immunochromographic Tests (ICTs)
- One ICT for N.*meningitidis* and one ICT for S.*pneumoniae* were identified
- No ICTs for multiple organisms were identified
- LATs require storage conditions which may not be practical in field conditions in sub-Saharan Africa
- No RDTs that can detect and characterise N. meningitidis serogroup X were found
- There was considerable heterogeneity in reference test use between identified studies; some studies highlight the variability in the accepted reference standards of CSF culture and PCR, particularly when compared with results from WHO Collaborating Centre laboratories
- Existing evidence suggests accuracy varies between laboratory and field settings
- The quality of the available evidence is not high

RECOMMENDATIONS

- There is a need for more studies in the field setting of all RDTs
- The development of heat-stable RDTs which detect a range of organisms is a priority

Papers included in this review

Boisier, P., Elhaj Mahamane, A., Amadou Hamidou, A., Sidikou, F., Djibo, S., Nato, F. & Chanteau, S. 2009. Field evaluation of rapid diagnostic tests for meningococcal meningitis in Niger. *Tropical Medicine and International Health,* 14(1):111-117.

Borel, T., Rose, A., Guillerm, M., Sidikou, F., Gerstl, S. & Djibo, A. 2006. High sensitivity and specificity of the Pastorex latex agglutination test for Neisseria meningitidis serogroup A during a clinical trial in Niger. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 100(10):964-969.

Chanteau, S., Dartevelle, S., Mahamane, A.E., Djibo, S., Boisier, P. & Nato, F. 2006. New rapid diagnostic tests for Neisseria meningitidis serogroups A, W135, C, and Y. *PLoS medicine,* 3(9).

Collard, J.-M., Wang, X., Mahamane, A.E., Idia, I., Issaka, B., Ousseni, M., Mayer, L.W., Nato, F. & Moulia-Pelat, J.-P. 2014. A five-year field assessment of rapid diagnostic tests for meningococcal meningitis in Niger by using the combination of conventional and real-time PCR assays as a gold standard. *Trans R Soc Trop Med Hyg,* 108(1):6-12.

Cuevas LE, Hart CA, Mughogho G. Latex particle agglutination tests as an adjunct to the diagnosis of bacterial meningitis: a study from Malawi. *Annals of Tropical Medicine and Parasitology* Aug 1989;83(4):375-379

Djibo, S., Njanpop Lafourcade, B.M., Boisier, P., Moussa, A., Kobo, G., Sidikou, F., Hien, A., Bieboure, G., Aguilera, J.F., Parent du Chatelet, I., Gessner, B.D. & Chanteau, S. 2006. Evaluation of the Pastorex meningitis kit for the rapid identification of Neisseria meningitidis serogroups A and W135. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 100(6):573-578.

Hoban, D.J., Witwicki, E. & Hammond, G.W. 1985. Bacterial antigen detection in cerebrospinal fluid of patients with meningitis. *Diagnostic Microbiology & Infectious Disease,* 3(5):373-379.

Hossein et al (unpublished data)

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7. GRADE PROFILES

CERMES ICT under field conditions for N. meningitidis serogroup W

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients pre-test probability of 20%	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with)	2 Studies 1717 Patients	observational studies	serious [1]	serious [2]	not serious	not serious [3]	not serious[4]	184 (176 to 188) [5]	LOW
False negatives (patients incorrectly classified as not having)								16 (12 to 24) [5]	
True negatives (patients without)	2 Studies 1717 Patients	observational studies	serious [1]	serious [2]	not serious	not serious [3]	not serious [4]	760 (744 to 768) [6]	LOW
False positives (patients incorrectly classified as having)								40 (32 to 56)[6]	

1. High risk of bias regarding patient flow in one study.
2. High concern regarding patient selection.
3. Sensitivity and specificity of two studies were pooled separately (see text for explanation). Small CIs.
4. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
5. Based on pooled sensitivity of 92% (95%CI 88-94%)
6. Based on pooled specificity of 95% (95%CI 93-96%)

CERMES ICT under laboratory conditions for N. meningitidis serogroup W

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients pre-test probability of 20%	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with)	3 Studies 1751 Patients	observational studies	serious [1]	serious [2]	not serious	not serious [3]	not serious[4]	194 (190 to 196) [5]	LOW
False negatives (patients incorrectly classified as not having)								6 (4 to 10) [5]	
True negatives (patients without)	3 Studies 1751 Patients	observational studies	serious [1]	serious [2]	not serious	not serious [3]	not serious [4]	760 (744 to 768) [6]	LOW
False positives (patients incorrectly classified as having)								40 (32 to 56)[6]	

1. High risk of bias regarding patient flow in one study.
2. High concern regarding patient selection.
3. Sensitivity and specificity of three studies were pooled separately (see text for explanation). Small CIs.
4. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
5. Based on pooled sensitivity of 97% (95%CI 95-98%)
6. Based on pooled specificity of 95% (95%CI 93-96%)

Pastorex LAT under laboratory conditions for N. meningitidis serogroup W or Y[1]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients pre-test probability of 20%	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with)	2 studies 1037 Patients	observational studies	not serious	not serious	not serious	not serious	not serious	170 (156 to 178) [3]	LOW
False negatives (patients incorrectly classified as not having)								30 (22 to 44) [3]	
True negatives (patients without)	2 studies 1037 Patients	observational studies	not serious	not serious	not serious	not serious	not serious [2]	792 (776 to 792) [4]	LOW
False positives (patients incorrectly classified as having)								8 (8 to 24)[4]	

1. Pastorex cannot differentiate between Nm W&Y
2. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
3. Based on lowest reported sensitivity of 85% (95%CI 78-89%)
4. Based on lowest reported specificity of 99% (95%CI 97-99%)

BD Directigen meningitis LAT under laboratory conditions for N. meningitidis serogroup W

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients pre-test probability of 20%	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with)	1 study 63 Patients	observational study	Unable to assess[1]	Unable to assess	Unable to assess	Unable to assess	Unable to assess	200 (186-200)[2]	VERY LOW
False negatives (patients incorrectly classified as not having)								0 (0 to 14)[2]	
True negatives (patients without)	1 study 63 Patients	observational study	Unable to assess	Unable to assess	Unable to assess	Unable to assess	Unable to assess	320 (96 to 592) [3]	VERY LOW
False positives (patients incorrectly classified as having)								480 (208 to 704)[3]	

1. Only results of this study were available to reviewers so methodological quality cannot be assessed
2. Based on reported sensitivity of 100% (95%CI 93-100%)
3. Based on reported specificity of 40% (95%CI 12-74%)

BinaxNOW under laboratory conditions for S. pneumoniae (no field studies found)

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients pre-test probability of 20%	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with)	3 Studies 1151 Patients	observational studies	serious [1]	not serious	not serious	not serious [3]	not serious[4]	198 (192 to 200) [5]	LOW
False negatives (patients incorrectly classified as not having)								2 (0 to 8) [5]	
True negatives (patients without)	3 Studies 1151 Patients	observational studies	serious [1]	not serious	not serious	not serious [3]	not serious[4]	768 (760 to 776) [6]	LOW
False positives (patients incorrectly classified as having)								32 (24 to 40)[6]	

1. High risk of bias regarding patient flow in one study.
2. Unclear risk of bias regarding index test in all studies.
3. Sensitivity and specificity of three studies were pooled separately (see text for explanation). Small CIs.
4. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
5. Based on pooled sensitivity of 99% (95%CI 96-100%)
6. Based on pooled specificity of 96% (95%CI 95-97%)