



Systematic review

The diagnostic accuracy of rapid diagnostic tests for Ebola virus disease: a systematic review

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ABSTRACT

Background: Ebola virus disease (EVD) is a dangerous condition that can cause an epidemic. Several rapid diagnostic tests (RDTs) have been developed to diagnose EVD. These RDTs promise to be quicker and easier to use than the current reference standard diagnostic test, PCR.

Objectives: To assess the diagnostic accuracy of RDTs for EVD.

Methods: A systematic review of diagnostic accuracy studies.

Data sources: The following bibliographic databases were searched from inception to present: MEDLINE (Ovid), Embase, Global Health, Cochrane Central Register of Controlled Trials, WHO Global Index Medicus database, Web of Science, PROSPERO register of Systematic Reviews, and Clinical Trials.Gov.

Study eligibility criteria: Diagnostic accuracy studies.

Participants: Patients presenting to the Ebola treatment units with symptoms of EVD.

Interventions: RDTs; reference standard, RT-PCR.

Assessment of risk of bias: Quality Assessment of Diagnostic Accuracy Studies-2 tool.

Methods of data synthesis: Summary estimates of diagnostic accuracy study were produced for each device type. Subgroup analyses were performed for RDT type and specimen material. A sensitivity analysis was performed to assess the effect of trial design and bias.

Results: We included 15 diagnostic accuracy studies. The summary estimate of sensitivity for lateral flow assays was 86.1% (95% CI, 86–86.2%), with specificity of 97% (95% CI, 96.1–97.9%). The summary estimate for rapid PCR devices was sensitivity of 96.2% (95% CI, 95.3–97.9%), with a specificity of 96.8% (95% CI, 95.3–97.9%). Pre-specified subgroup analyses demonstrated that RDTs were effective on a range of specimen material. Overall, the risk of bias throughout the included studies was low, but it was high in patient selection and uncertain in the flow and timing domains.

Conclusions: RDTs possess both high sensitivity and specificity compared with RT-PCR among symptomatic patients presenting to the Ebola treatment units. Our findings support the use of RDTs as a 'rule in' test to expedite treatment and vaccination. **Andrew B. Dagens, Clin Microbiol Infect 2023;29:171**

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Introduction

Ebola virus disease (EVD) is a viral haemorrhagic fever that can lead to severe illness and death. Diagnosing EVD clinically is difficult because the early symptoms are non-specific and are similar to other endemic diseases such as dengue, typhoid, and Lassa fever [1].

The reference standard of EVD diagnosis is RT-PCR [2]. Ebola virus RNA is detectable in the serum by RT-PCR within 3 days of symptom onset [3]. The experience of the West African epidemic suggests that with adequate laboratory facilities, diagnosis can be confirmed within 2–6 hours [1].

Unfortunately, access to RT-PCR is limited in West Africa due to the lack of staffing and laboratory facilities [1]. Rapid diagnostic tests (RDTs) may be a useful alternative. There are two classes of RDTs for EVD—lateral flow assays (LFAs) and PCR-based technologies. LFAs use immunochromatography to detect target antigens. LFAs give rapid results and are easy to use and require no laboratory infrastructure.

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LFAs were used in the 2014–2016 West African epidemic to support triage decisions [8], identifying high-risk patients pending definitive PCR results. An alternative approach is to simplify and automate RT-PCR. ‘Rapid PCR’ devices use a self-contained, cartridge system to identify the EBOV nucleoprotein and glycoprotein gene targets. Unlike LFAs, the device produces a cycle threshold (Ct) value and is semi-quantitative. Rapid PCR devices promise to be as accurate as traditional RT-PCR and simpler to operate.

The ideal RDT would be cheap, quick, highly accurate, and safe, requiring little expertise to perform and interpret the results. The aim of this systematic review was to assess the diagnostic accuracy of RDTs for EVD among patients presenting to the Ebola treatment units (ETUs) with symptoms suggestive of EVD.

Methods

This systematic review was produced following the methods of the Cochrane Collaboration [10] using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria [11]. It was prospectively registered in the PROSPERO database (CRD 42021244645). There was no patient or public involvement in this study.

Data sources and searches

We searched the following databases from inception to the search date (2 May 2021): MEDLINE, Embase, Global Health, Cochrane Register of Controlled Trials, WHO Global Index Medicus, Web of Science, PROSPERO, and Clinical Trials.Gov. Reference lists of the included studies were checked for additional references. The full search strategy is provided in [Appendix 1](#).

To ensure applicability to clinical practice, we included only diagnostic accuracy studies of RDTs. We excluded case series, animal, laboratory, or mortuary studies and review articles. We excluded studies where there was a manipulation of samples (such

as ‘spiked’ studies). There were no exclusions for country of origin, date of publication, or language of publication.

Inclusion criteria

We included diagnostic accuracy studies conducted on live patients of any age or sex with confirmed or suspected EVD. We included studies from hospitals and dedicated ETUs (often rudimentary facilities used during the West African epidemic for the treatment of patients with EVD) but not asymptomatic screening programmes.

To be included, the diagnostic accuracy study had to report sufficient detail to extract or calculate the number of true positives, false positives, false negatives, and true negatives (i.e. sufficient data to construct a 2×2 table).

Data extraction and quality assessment

We used the systematic review software system Rayyan (Rayyan Systems Inc. 2020) for the screening of studies identified by the literature search. Two reviewers independently screened the studies for inclusion against the pre-defined inclusion and exclusion criteria in the protocol. Disagreement on eligibility was managed by discussion with a third reviewer.

Our primary outcome was diagnostic accuracy; we constructed a 2×2 table from each study. To explore potential sources of heterogeneity between studies, data for three covariates were also extracted.

1. Prevalence: Although theoretically sensitivity and specificity should be unaffected by prevalence, measures of diagnostic accuracy do vary across populations with different disease prevalence. Prevalence here acts as a proxy for other changes that influence the value of a test, e.g. community awareness of a disease leading to early presentation.

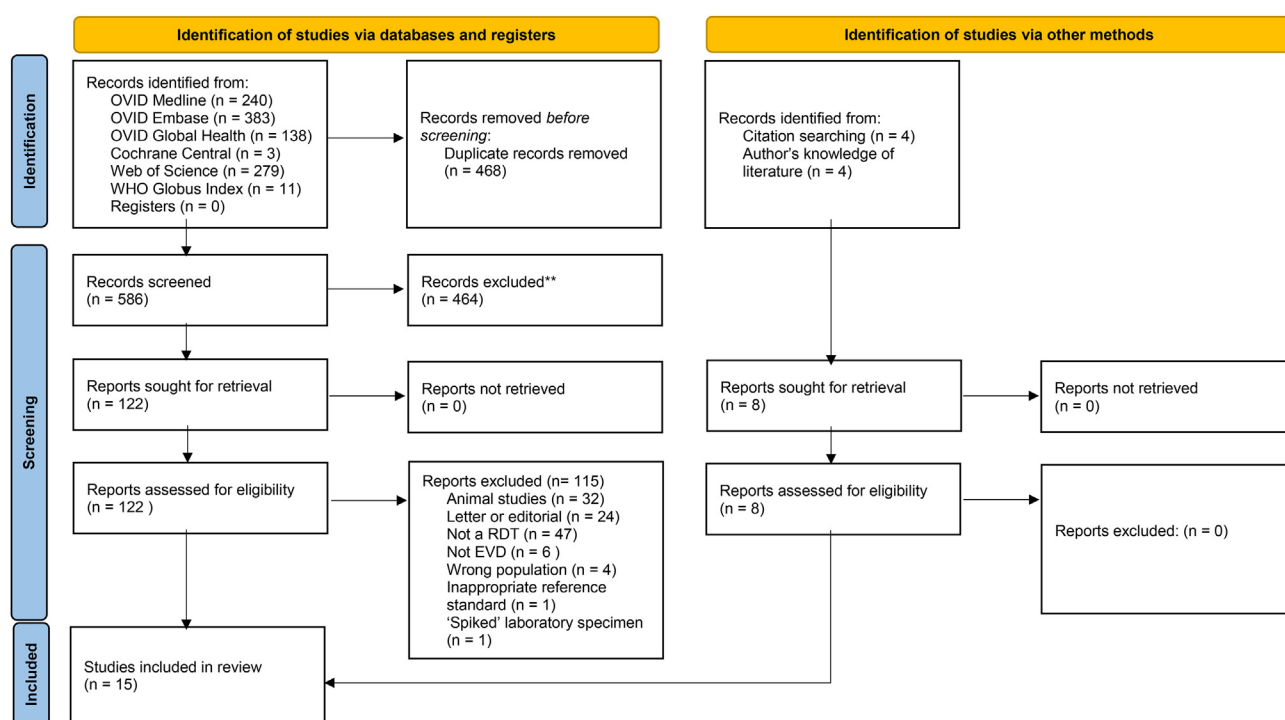


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of included studies. A ‘spiked’ sample is prepared by adding a known analyte; unlike a diagnostic specimen, the quality and quantity of the analytes can be controlled.

Table 1
Characteristics of included studies

Study	Setting	Time period ^a	Participants	Prevalence	Age (y)	Female (%)	Case definition and clinical data.
PCR-based tests							
Gay-Andrieu et al. [23]	Guinea 2015	2015	156	30%	Mean, 36	NS	WHO case definition. Children were excluded.
Semper et al. [19]	Sierra Leone	2014–2015	218	10%	mean, 25; range, 1–96	43%	Residual samples taken from specimens sent to a field laboratory in Sierra Leone. Only the Sierra Leone data were incorporated.
Weller et al. [21]	Sierra Leone and United Kingdom	NS	44	43%	NS	NS	
van Vuren et al. [20]	Sierra Leone	2014–2015	281	43%	NS	NS	Suspected EVD cases to the field Ebola molecular laboratory in Freetown, Sierra Leone. No clinical details provided.
Yang et al. [17]	Sierra Leone	2014	375	72%	mean, 33; range, 1–105	41%	Patients presenting to an ETU in Sierra Leone meeting that hospital's case definition.
Lateral flow immunoassays							
Boisen et al. [18]	Sierra Leone	2014–2015	176	65%	NS	NS	WHO case definition of EVD.
Broadhurst et al. [9]	Sierra Leone	2015	106	26%	mean, 27.6; range, 1–91	55%	WHO case definition, excluded all those who were haemodynamically unstable or unable to consent. Mean symptom duration of 4 days.
Colavita et al. [26]	Sierra Leone	2014–2015	210	50%	median, 32; range, 15–49	50%	Patients presenting to the ETU with fever, vomiting or diarrhoea.
Couturier et al. [25]	Guinea	NS	140	15%	NS	NS	Case-control study, used known positive specimens from the West African outbreak in Guinea.
Gallais et al. [22]	Guinea	2015	144	40%	NS	NS	WHO case definition. Children were excluded.
Moran et al. [7]	Guinea	2014	205	53%	mean, 39; range, 3–90	45%	Stored specimens collected at a Guinea ETU. No clinical data.
Phan et al. [6]	Liberia	2016	290	15%	NS	NS	Suspected EVD based on clinical symptoms presenting to a Liberian ETU.
VanSteelandt et al. [5]	Guinea	2015	37	19%	NS	NS	The eligibility criteria for live patients to receive an RDT varied over place in time (i.e. matching the suspect case definition for EVD, having a febrile illness, having fever plus three other EVD symptoms).
Walker et al. [16]	Sierra Leone	2015	138	10%	median, 32; range, 24–47	31%	Screened using a national case definition for EVD.
Wonderley et al. [4]	Sierra Leone	2014–2016	444	48%	NS	NS	Patients admitted to an ETU and stored specimens from a range of viraemia levels.

EVD, Ebola virus disease; ETU, Ebola treatment unit; NS, not specified; RDT, rapid diagnostic test.

^a The period during which specimens were collected.

Table 2
Included studies, index, and reference tests

Study	Study design	Specimen	Index test	Reference standard
PCR-based tests				
Gay-Andrieu et al. [23]	Prospective diagnostic accuracy study	Whole blood, buccal swabs	Biofire® PCR	RT-PCR Altona assay
Semper et al. [19]	Prospective diagnostic accuracy study	Whole blood	Cepheid GeneXpert®	RT-PCR Trombley
Weller et al. [21]	Retrospective laboratory study	Plasma	Biofire FieldAssay E-threat	RT-PCR TaqMan
van Vuren et al. [20]	Prospective diagnostic accuracy study	Whole blood	Cepheid GeneXpert®	RT-PCR TaqMan
Yang et al. [17]	Prospective diagnostic accuracy study	Whole blood, buccal swabs, and whole blood and buccal swabs	EBOV RPA assay®	RT-PCR EZ1 Taqman assay
Lateral flow immunoassays				
Boisen et al. [18]	Prospective diagnostic accuracy study	Whole blood Plasma	ReEBOV® RDT	RT-PCR Altona
Broadhurst et al. [9]	Prospective diagnostic accuracy study, both point of care and laboratory samples	Whole blood	ReEBOV® POC ReEBOV® laboratory	RT-PCR Altona RT-PCR Trombley
Colavita et al. [26]	Retrospective laboratory study	Plasma	EBOLA Ag K-SeT	RT-PCR Altona
Couturier et al. [25]	Case-control study	Plasma	Ebola sGP Detection Kit®	RT-PCR Altona
Gallais et al. [22]	Prospective diagnostic accuracy study	Whole blood, plasma	eZYScreen®	RT-PCR Altona
Moran et al. [7]	Retrospectively laboratory study, stored specimens	Plasma	Dual Path Platform (Chembio, Medford, USA) technology	RT-PCR Altona
Phan et al. [6]	Prospective diagnostic accuracy study	Buccal swab, plasma, and plasma and buccal swab	NMRC LFA	RT-PCR Quiagen
VanSteelandt et al. [5]	Prospective diagnostic accuracy study	Whole blood	OraQuick	PCR at several sites. Assays not described
Walker et al. [16]	Prospective diagnostic accuracy study	Whole blood	DSTL RDT	TRT-PCR Altona
Wonderly et al. [4]	Retrospective case-control study of stored specimens	Plasma	DEDIATEST OneStep Ebola REBOV SD Ebola Zaire Ag	RT-PCR Altona RT-PCR Trombley

LFA, lateral flow assay; RDT, rapid diagnostic test.

2. Ct threshold: To approximate the severity of the disease within each patient cohort.
3. Specimen type including whole blood, plasma, and buccal swabs.

The risk of bias in each study was explored using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. We assessed transparency and reporting using the Standards for Reporting Diagnostic accuracy studies toolkit [12].

Statistical analysis

Data for diagnostic accuracy from each study were extracted to construct 2×2 tables. Where data were reported for multiple Ct thresholds, we conducted a 2×2 table for each threshold. We produced paired forest plots of sensitivity and specificity in each study with corresponding 95% CIs using the REVMAN software. Two subgroup analyses were specified a priori: LFAs and rapid PCR devices. To produce a pooled estimate of diagnostic accuracy for each subgroup, we fashioned summary receiver operating curves.

The summary receiver operating curves and paired forest plots were constructed using the MetaDTA tool [15]. We used the highest reported Ct in studies reporting multiple Ct thresholds to ensure that all threshold values were clinically relevant.

In the sensitivity analyses, we explored the risk of bias by excluding those studies that possessed a 'high' risk of bias in more than one QUADAS-2 domain and those studies conducted using a retrospective study design. Retrospectively performed diagnostic accuracy studies are at an increased risk of bias [13]. A funnel plot was not produced to assess the possibility of publication bias. Publication bias in diagnostic accuracy studies is poorly understood, and the value of funnel plots is uncertain [14].

Results

Study characteristics

We identified 1054 titles for screening (Fig. 1), and 15 studies were eligible for inclusion. Where studies reported on more than one test, we extracted data for each test and sample type. As such,

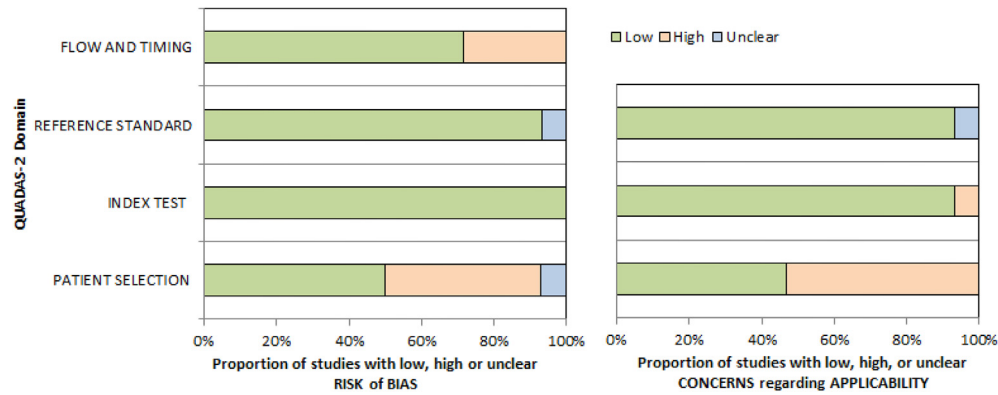


Fig. 2. Quality Assessment of Diagnostic Accuracy Studies-2. (a) Risk of bias, and (b) concerns regarding applicability.

Lateral Flow Tests

Study	TP	FP	FN	TN	Specimen type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Phan 1	8	9	1	219	Buccal	0.89 [0.52, 1.00]	0.96 [0.93, 0.98]		
Boisen 1	72	2	44	58	Plasma	0.62 [0.53, 0.71]	0.97 [0.88, 1.00]		
Colavita	93	2	12	103	Plasma	0.89 [0.81, 0.94]	0.98 [0.93, 1.00]		
Courturier	18	0	3	119	Plasma	0.86 [0.64, 0.97]	1.00 [0.97, 1.00]		
Gallois 1	41	0	14	89	Plasma	0.75 [0.61, 0.85]	1.00 [0.96, 1.00]		
Moran	84	8	25	88	Plasma	0.77 [0.68, 0.85]	0.92 [0.84, 0.96]		
Phan 2	41	8	5	236	Plasma	0.89 [0.76, 0.96]	0.97 [0.94, 0.99]		
Wonderly DEDATEST	108	24	46	147	Plasma	0.70 [0.62, 0.77]	0.86 [0.80, 0.91]		
Wonderly One Step	138	26	16	144	Plasma	0.90 [0.84, 0.94]	0.85 [0.78, 0.90]		
Wonderly REBOV	133	29	23	142	Plasma	0.85 [0.79, 0.90]	0.83 [0.77, 0.88]		
Wonderly SD Ebola Zaire Ag	110	1	46	170	Plasma	0.71 [0.63, 0.78]	0.99 [0.97, 1.00]		
Boisen 2	123	6	7	66	Whole blood	0.95 [0.89, 0.98]	0.92 [0.83, 0.97]		
Broadhurst 1	28	6	0	71	Whole blood	1.00 [0.88, 1.00]	0.92 [0.84, 0.97]		
Broadhurst 2	45	18	0	214	Whole blood	1.00 [0.92, 1.00]	0.92 [0.88, 0.95]		
Gallois 2	49	1	17	87	Whole blood	0.74 [0.62, 0.84]	0.99 [0.94, 1.00]		
Van Steelandt	5	8	2	22	Whole blood	0.71 [0.29, 0.96]	0.73 [0.54, 0.88]		
Walker	15	9	0	107	Whole blood	1.00 [0.78, 1.00]	0.92 [0.86, 0.96]		

PCR Tests

Study	TP	FP	FN	TN	Specimen type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yang 1	264	3	7	101	Buccal	0.97 [0.95, 0.99]	0.97 [0.92, 0.99]		
Semper 1	22	8	0	181	Buccal	1.00 [0.85, 1.00]	0.96 [0.92, 0.98]		
Weller	21	4	4	31	Plasma	0.84 [0.64, 0.95]	0.89 [0.73, 0.97]		
Semper 2	22	8	0	181	Whole blood	1.00 [0.85, 1.00]	0.96 [0.92, 0.98]		
Vuren	107	2	15	157	Whole blood	0.88 [0.81, 0.93]	0.99 [0.96, 1.00]		
Yang 2	51	1	1	34	Whole blood	0.98 [0.90, 1.00]	0.97 [0.85, 1.00]		
Gay-Andrieu	45	0	2	87	Whole blood	0.96 [0.85, 0.99]	1.00 [0.96, 1.00]		
Yang 3	213	2	6	67	Whole blood + Buccal	0.97 [0.94, 0.99]	0.97 [0.90, 1.00]		

Fig. 3. Paired plots of rapid diagnostic test sensitivity grouped by test type and specimen material. Where a study included more than one index test, they were numbered e.g. Phan 1, Boisen 2.

although 15 studies were included, there were 25 comparisons in our analysis. Ten studies used a lateral flow–based device as their index test (3540 patients), whereas five studies used a PCR-based index test (1647 patients). Population characteristics for each included study are described in Table 1; the details of study design are described in Table 2.

The demographic characteristics of participants were rarely well described. However, in those seven studies that provided sufficient information [7,9,16,17,19,23,26], the mean age of the participants ranged from 27 to 32 years, and most patients were male (range, 48–68%). There was little detail available on the disease severity. Studies were performed at different stages of the epidemic; therefore, disease prevalence varied between studies, ranging from 10% to 72%. The pooled prevalence of EVD was 28%.

Those studies using PCR technology as their index test did not consistently pre-specify or justify the PCR Ct used. The studies also used a range of Ct ‘cut-offs’ for the reference test, with the highest being 45 and the lowest 33. Similarly, no studies have accurately reported the timing of the reference test in relation to clinical data. For example, none of the studies detailed at which stage of the disease process the index test or the reference test was taken.

All included studies used RT-PCR as their reference standard, but the specific assay used varied. Seven studies have used only the Altona assay [7,16,18,22,23,25,26], and one study has only used the Trombley assay [19]. Two studies compared Trombley and Altona assays [4,9], whereas the remaining four studies used assays that are less commonly used in clinical practice.

Table 3
Specimen material used in the included studies, contribution to final analysis

Total studies	15
Lateral flow device as the index test	10 [5–8,10,19,21,25,28,29]
PCR technology as the index test	5 [20,22–24,26]
Lateral flow devices as the index test	17
Whole blood sample as the specimen material	6 [6,7,10,19,21,25]
Plasma as the specimen material	10 [5,7,8,21,25,28,29]; Wonderly et al. [4] explored four LFAs in the same study
Buccal swab as the specimen material	1 [7]
PCR-based device as the index test	8
Buccal swab as the specimen material	2 [20,22]
Plasma as the specimen material	1 [7]
Whole blood sample as the specimen material	4 [20,22,23,26]
Whole blood sample + buccal swab as the specimen material	1 [20]
Contribution to the final analysis	25 items
Lateral flow tests	17
PCR-based tests	8

Often a publication would test more than one device on more than one type of specimen. As such, there are 25 data points contributing to the final analysis from 15 studies.

Risk of bias assessment

The risk of bias was assessed using the QUADAS-2 tool. A detailed description is provided in [Appendix 1](#) and summarized in [Fig. 2](#). Globally, the risk of bias was low but with concerns in the domain of patient selection ([Fig. 2a](#)). Studies would often omit the details of their study population (see [Appendix 1](#) STARD reporting standards) or the selection criteria would be poorly described, leading to an uncertain risk of bias in these domains. There was an uncertain risk of bias in the flow and timing domain (four studies rated as uncertain risk of bias). Frequently, these studies were

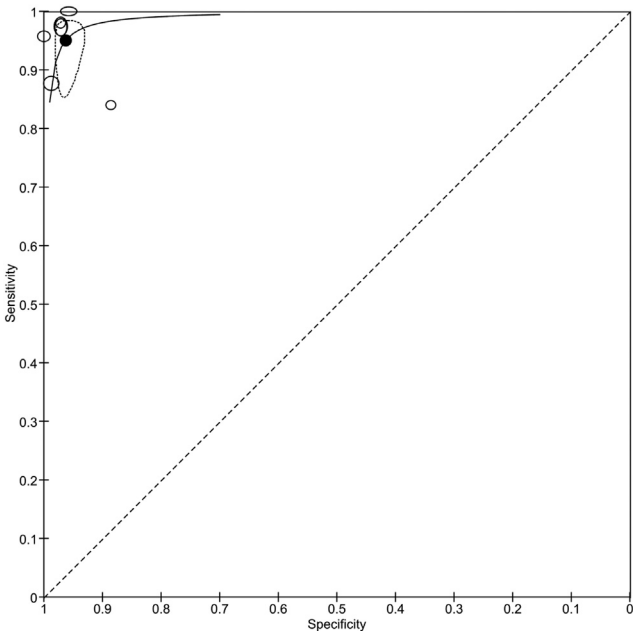


Fig. 5. Hierarchical Summary Receiver Operating Characteristic of PCR-based tests: each circle represents a study weighted by study size. The black circle is the sample estimate with overlaid 95% prediction region.

performed retrospectively, with a significant time delay between the index and reference test. The proportion of studies with concerns regarding applicability was globally low but with concerns in the domain of patient selection ([Fig. 2b](#)).

Synthesis of results

The sensitivity of lateral flow tests ranged from 62% (95% CI, 53–71%) [18] to 100% (95% CI, 97–100%) [25] ([Fig. 3](#)). For PCR tests,

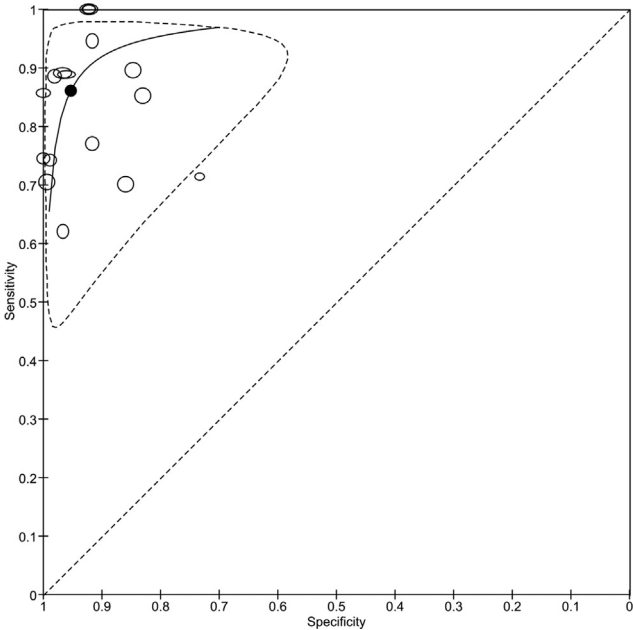


Fig. 4. Hierarchical summary receiver operating curve of diagnostic accuracy of lateral flow rapid diagnostic tests for Ebola virus disease with summary estimate and 95% confidence region. Each study is represented by a circle; larger circles indicate a larger sample size.

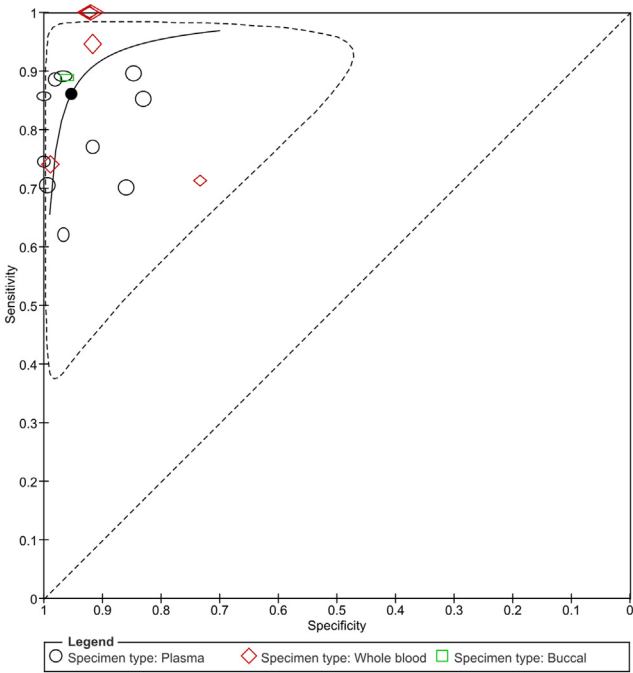


Fig. 6. Hierarchical Summary Receiver Operating Characteristic with specimen material labelled. The type of specimen material used did not appear to influence the accuracy of lateral flow tests.

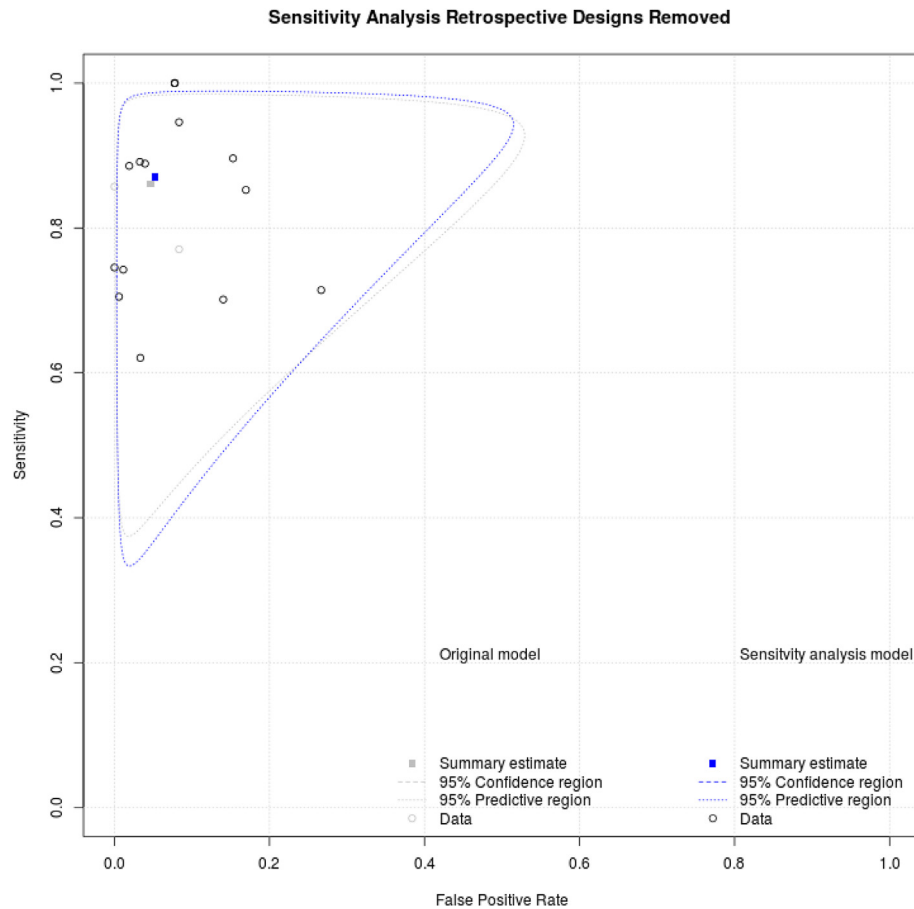


Fig. 7. Sensitivity analysis for lateral flow devices, with retrospective study designs removed; the summary estimate is barely changed.

there was less variation in sensitivity, ranging from 88% (95% CI, 81–93%) [21] to 100%. Similarly, all RDT types were highly specific for EVD. Seven studies found that RDTs, whether LFAs [6,9,16] or PCR devices [17,19,20,23], were 100% specific for EVD (Table 3).

Subgroup and sensitivity analyses

Lateral flow devices

Fig. 4 displays the results from ten individual studies exploring the diagnostic accuracy of 17 lateral flow RDTs for the diagnosis of EVD.

Overall, lateral flow tests demonstrated a summary estimate of sensitivity of 86% (95% CI, 86–86.2%), with a specificity of 97% (95% CI, 96.1–97.9%). However, there was a wide variation in the individual study results, leading to a wide prediction region.

The variation within these results can be partly attributed to the study design. The lowest reported sensitivity was 62% (95% CI, 53–71%) [18], targeting the ReEBOV antigen using whole blood specimens at the point of care. The same study reported a higher sensitivity when the samples were tested in a laboratory setting, suggesting that where a test takes place is an important factor for consideration when implementing testing. However, the studies reporting both the highest and lowest sensitivity were conducted under similar conditions. Across all studies, the specificity of the lateral flow devices for EVD varied between 73% and 100%. The two studies that reported a sensitivity of 100% [9,16] tested whole blood samples from patients at the point of care or in a nearby laboratory.

PCR-based devices

The combined estimates for RDTs using rapid PCR technology are presented in Fig. 5.

Rapid PCR RDTs demonstrated high sensitivity (summary estimate 96.2%; 95% CI, 92.4–98.1%) and specificity (summary estimate 96.8%; 95% CI, 95.3–97.9%), compared with conventional PCR.

The distribution of results was much less varied among PCR tests. The lowest reported sensitivity was by Weller et al. [21], who reported a sensitivity of 84% (95% CI, 64–95%) in a combined population of patients from Sierra Leone and the United Kingdom. The investigators suggest that the low sensitivity in their sample (nine discrepant results) was from patients with an abnormally low viral load. The specificity of the PCR RDTs was also high, approaching 100% in some cases.

The included studies used different specimen materials. The type of specimen material did not affect the overall diagnostic accuracy of either type of test (Fig. 6). We did not further assess heterogeneity by producing summary estimates of diagnostic accuracy by specimen material because it was not possible to distinguish the effect of the LFA device versus the effect of the specimen type.

Sensitivity analysis was performed to assess the effect of the retrospective design on the summary estimate for both lateral flow (Fig. 7) and rapid PCR index tests (Fig. 8). In neither case was the summary estimate significantly changed.

A sensitivity analysis was also performed to assess the effect of studies with a high risk of bias upon review. With the removal of

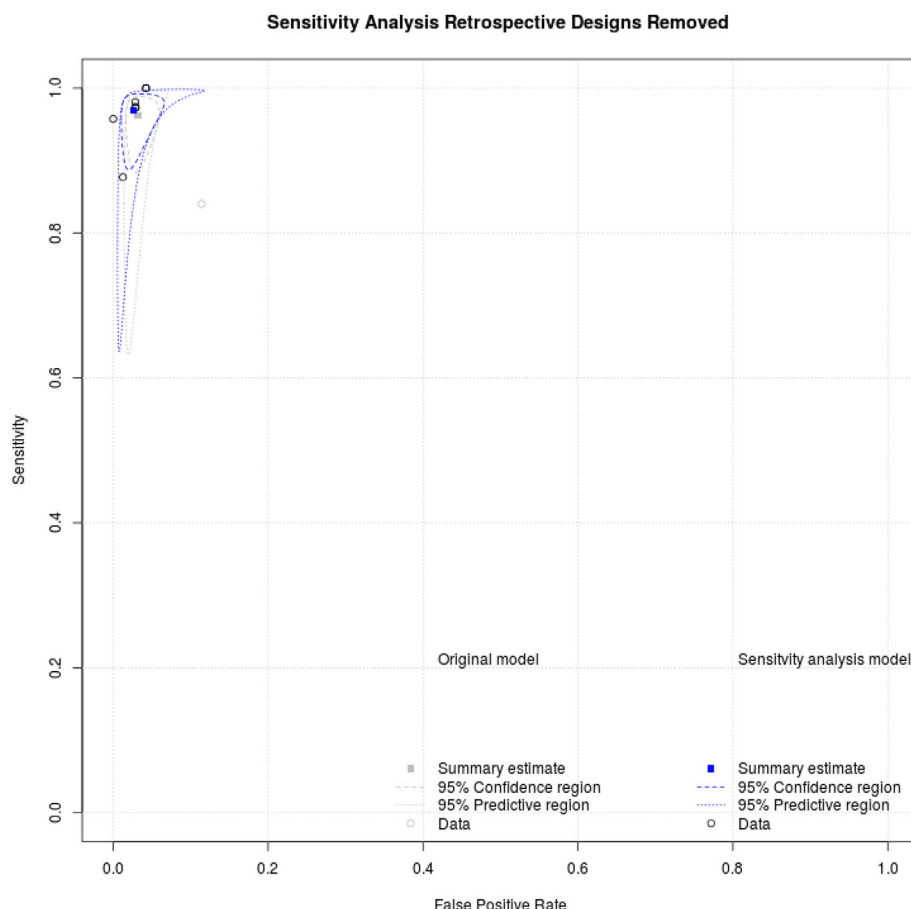


Fig. 8. Sensitivity analysis for rapid PCR devices, with retrospective study designs removed.

high risk of bias studies, there was a small increase in the overall sensitivity from 96.2% to 97%, whereas the specificity reduced from 96.8% to 85.6%. Removing those studies with a high risk of bias increased the size of the prediction region.

Discussion

In patients presenting with suspected EVD, all forms of RDT demonstrated high levels of sensitivity and specificity compared with the 'reference standard' for diagnosis, PCR. This systematic review combined data from 5178 individual patients tested for EVD using an RDT with subgroup analysis demonstrating essential differences between types of RDT (lateral flow and PCR tests).

LFAs

The first LFAs for EVD received WHO emergency use authorization in March 2015. WHO strongly advises that PCR remains the definitive tool for EVD diagnosis and recommends a specific, limited role for LFAs where PCR is not available. This is primarily to reduce the nosocomial transmission by triage pending a PCR test result.

Broadly, the findings from this review are consistent with the guidance of the WHO. Our summary estimate of sensitivity (86.1%; 95% CI, 86–86.2%) is consistent with the initial WHO estimate, but our estimate of specificity was quite high: 95.3% (95% CI, 95.2–95.4%). However, we found a significant variation between the type of lateral flow device used and whether fresh blood or banked plasma was used.

The very high specificity of lateral flow (Table 4) assays demonstrated in our review supports their role as a 'rule in' device. In the context of a patient presenting to an ETU with a positive lateral flow assay, the attending physician can have a high degree of confidence that their patient has EVD.

However, the devices are insufficient themselves to 'rule out' disease. In a hypothetical cohort with a prevalence of 28% (the average across the included studies), the negative predictive value of a LFA test would be 94%, which is insufficiently high to eliminate the risk of false negatives in a large cohort. Given the repercussions of a false negative diagnosis, we support the strategy of following LFA with laboratory PCR testing for all patients.

However, a negative result is sufficiently reassuring that patients with no other clinical signs may be triaged as 'low risk', pending definitive PCR diagnosis. In future, it would be helpful if modelling studies determine the minimum threshold for an acceptable sensitivity to prevent disease spread, providing a 'benchmark' sensitivity for device development.

Rapid PCR

Currently, there is no WHO (or other normative body) guidance on using rapid PCR devices for EVD. Our review found that rapid PCR devices had a high sensitivity 96.2% (95% CI, 92.4–98.1%) and a specificity of 96.8% (95% CI, 95.3–97.9%), compared with laboratory-based PCR. Within a hypothetical cohort of 1000 patients with an EVD prevalence of 28%, rapid PCR would possess very high Negative Predictive Value (NPV) (98%) and Positive Predictive

Table 4

Summary of findings

Population	Patients with symptoms consistent with EVD. All ages all sexes				
Prior testing	Nil				
Settings	Presenting to the Ebola treatment units				
Index test	Rapid diagnostic tests				
Reference test	RT-PCR				
Studies	Diagnostic accuracy studies				
Test/subgroup	Summary accuracy (95% CI)	Number of participants	Prevalence	Implications	Comments
Lateral flow assays	Sensitivity: 86.1% (86–86.2%) Specificity: 95.3% (95.2–95.4%)	3540	28%	In a population of 1000 with a prevalence of 28%, 280 will have EVD. Of these, 39 will be labelled as 'low risk' for EVD and mixed with low-risk patients pending PCR. Of the 720 patients without EVD, 34 will test positive and be placed in the high-risk area, exposing to patients with EVD unnecessarily.	Moderate risk of spectrum bias because of poor reporting of the enrolled population.
Rapid PCR	Sensitivity: 96.2% (92.4–98.1%) Specificity: 96.8% (95.3–97.9%)	1647	28%	In a population of 1000 with a prevalence of 28%, 280 will have EVD. Of these, 11 will incorrectly test negative and mix with the low-risk patients pending PCR. Of the 720 patients without EVD, 23 will test falsely positive and be unnecessarily exposed to patients with EVD.	Moderate risk of spectrum bias because of poor reporting of the enrolled population.

EVD, Ebola virus disease.

Value (PPV) (92%). Using rapid PCR would lead to 28 fewer false negative diagnoses than LFA. However, rapid PCR would still miss 11 cases of EVD.

The variation in sensitivity among rapid PCR devices was less marked than amongst LFAs. The least sensitive test was still 89% sensitive. The envisaged goal of rapid PCR devices is to replace traditional PCR in definitively 'ruling out' EVD without the need for complex equipment. Our review would support this strategy, but further research to inform practice, such as a randomized trial, would be beneficial. The logistical hurdles in providing rapid molecular diagnostics are not the focus of this review. However, we noted that many of the rapid PCR devices were trialled in 'field laboratories' established by the Western NGOs [19], overseas governments [17] or other sources of overseas aid [20] as humanitarian contributions to the emergency response. It is uncertain whether rapid PCR diagnostics are truly sustainable in resource-poor settings without the contingency funding of these external organizations. One important practical advance is that these tests appeared effective on buccal specimens, which are safer to obtain than blood draws and might offer an opportunity for self-collection of samples if these results are validated in further studies.

The role of RDTs in the changing clinical management of EVD

The clinical management of suspected EVD has changed dramatically in the last decade. There was no effective therapeutic intervention available during the 2014–2016 West African

epidemic, and patients could be offered only supportive care. A range of effective drug interventions [28,29] and vaccines [30,31] are now available.

Expedition diagnosis is key to the efficacy of these treatments. The PALM II trial of EVD treatments demonstrated an 11% increase in the odds of 28-day mortality for every day that symptoms persisted before receiving a treatment [28]. This trial was conducted in urban centres, where there was good access to laboratory RT-PCR testing. An equally important development has been the provision of vaccines in a 'ring strategy' to the contacts of patients with EVD [32]. This strategy also relies upon the prompt confirmation of EVD for judicious, rapid contact tracing. The vaccine may provide a window of protection to restrict virus replication while adaptive immunity becomes established, and RDTs may prove to be invaluable in supporting this strategy. The strength of a positive LFA as a 'rule in' device, combined with the safety of Ebola therapeutics, might suggest that a positive lateral flow test is sufficiently specific to support commencing treatment. Certainly, rapid PCR tests appear sensitive and specific enough to be used alone in commencing treatment. Such a strategy should be trialled in future efficacy studies.

Strengths and limitations

To our knowledge, this is the only systematic review published on EVD RDTs and represents the best available summary estimate of their diagnostic accuracy. This review complies with best practices for the conduct of reviews of diagnostic accuracy studies.

There were several limitations to this review. Our search strategy balanced an attempt to be exhaustive without needless interrogation of the many narrative articles on EVD. We explored the effect of broadening our search to include full text terms and identified a further 377 975 returns. We judged that this was unmanageable, with a likely low yield of additional data.

The limitations of the published literature should also be noted. Overall, the risk of bias throughout the included studies was low, but with several studies at high risk of bias in the domain of patient selection. As such, the quality of evidence is mixed, allowing us to make only qualified recommendations [27]. Our protocol envisaged an analysis correlating the viral load with diagnostic accuracy. However, we were unable to conduct this analysis as Ct thresholds were rarely reported. A minority of studies have explored the use of buccal samples for diagnosis. The role of buccal specimens in EVD diagnosis is yet to be established, and these results must be interpreted carefully.

Finally, many of the included studies used ‘banked’ specimens that were tested several years after the outbreak in West Africa. It was impossible to differentiate the potential effect of sample degradation upon diagnostic accuracy, and this should be acknowledged as a potential confounder. However, our finding that those studies conducted at the point of care were broadly similar to the larger cohort would seem reassuring.

Conclusions

This review provides moderate support for the strategy of using LFAs as a ‘triage’ test for EVD in symptomatic patients. LFAs are both sensitive and specific for EVD diagnosis in the context of patients presenting to the ETUs with symptoms consistent with EVD, pending final PCR testing. In field laboratory conditions, rapid PCR-based devices are sensitive and specific for EVD. The concordance is sufficiently high that rapid PCR may be a suitable replacement for definitive PCR in those areas where access to laboratories is very limited, although this requires confirmation in a diagnostic randomized controlled trial. Our data suggest that both types of RDTs show sufficiently adequate performance, suggesting that a positive test could be used to initiate the early treatment of symptomatic patients and vaccination of their contacts.

Author contributions

D.D. led this project, wrote the protocol, extracted the data, and produced the manuscript. L.S. and A.R. contributed to the writing of the final manuscript, contributing their interpretation of the data in a clinical context. A.P. supervised the project, providing guidance throughout all stages of its development.

Transparency declaration

A.P. holds grant funding from the National Institute for Health Research School for Primary Care Research. The other authors declare that they have no conflicts of interest. There was no external funding for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2022.09.014>.

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