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How to cite

EMPERADOR, Devy Maye et al. Systematic review and meta-analysis of antigen rapid diagnostic tests to detect Zaire ebolavirus. In: Diagnostic microbiology and infectious disease, 2024, vol. 111, n° 1, p. 116568. doi: 10.1016/j.diagmicrobio.2024.116568

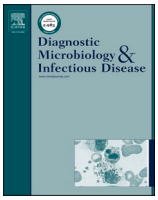
This publication URL: https://archive-ouverte.unige.ch/unige:182789
Publication DOI: 10.1016/j.diagmicrobio.2024.116568

Diagnostic Microbiology & Infectious Disease 111 (2025) 116568

Contents lists available at ScienceDirect

Diagnostic Microbiology & Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio



Systematic review and meta-analysis of antigen rapid diagnostic tests to detect Zaire ebolavirus

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ARTICLE INFO

Keywords:
Ebola
EVD
RDT
Antigen
Diagnostic accuracy
Diagnostic performance

ABSTRACT

We conducted a systematic review and meta-analysis of studies and reports comparing the performance of antigen rapid diagnostic tests (Ag RDT) for diagnosing Ebola disease (EVD). We searched PubMed, EMBASE, and Web of Science for diagnostic studies published between 1976 and 2023, evaluating them with QUADAS-2. Using a bivariate random-effects model, we estimated the pooled sensitivity and specificity of Ag RDTs. Of 64 eligible full studies and reports, 16 met the inclusion criteria. Pooled sensitivity and specificity were 82.1% (95%CI: 75.2 – 88.0) and 97.0% (95%CI: 95.1-98.2), respectively. We conducted subgroup analysis on 4 Ag RDTs, 3 RT-PCR tests, and 4 sample types, showing varied performance. The high specificity and positive predictive value of Ag RDTs support their use to "rule-in" patients with EVD. However, high-sensitivity RDTs suitable for field settings and capable of detecting multiple ebolavirus species are needed.

1. Introduction

Ebola disease (EVD, also known as Ebola virus disease) is a rare but potentially severe and fatal disease caused by viruses in the genus Orthoebolavirus. While four species in the genus have been noted to cause human disease, the most severe disease and the most common cause of outbreaks is consistently associated with the Zaire ebolavirus (*Orthoebolavirus zairense*) [1]. Bats are believed to be the natural host for ebolaviruses, although the specific reservoir species has yet to be determined. Introduction into human populations occurs through close contact with the excreta or other body fluids of bats or other intermediary animal hosts, sometimes followed by human-to-human transmission via direct contact [2]. Initial symptoms usually occur from 2-21 days post-infection and are usually non-specific, such as fever, fatigue, headache, sore throat, and muscle pain. As the disease progresses, nausea, vomiting, and diarrhea usually occur, with hemodynamic instability and hemorrhagic manifestations in severe cases. Survivors of EVD may show sequelae for years after the acute disease. After the first discovery of the Ebola virus in 1976, small EVD outbreaks occurred sporadically in Eastern and Central Africa [3]. However, in recent years, EVD outbreaks have occurred more frequently, with a new outbreak detected at least once yearly and with increasing case counts, highlighting the need for diagnostics for surveillance and early detection and response.

Rapid detection of suspected EVD is key to effective outbreak control, resulting in faster case identification and isolation, and initiation of treatment to improve outcomes. Molecular diagnostics, such as RT-PCR, are considered the gold standard for Ebola virus detection, particularly in the field [4]. However, despite their increasing availability in endemic countries, molecular diagnostics still rely on specialized equipment and trained personnel to safely conduct testing, and most often not available in rural health centers that usually see the first cases of EVD that signal an outbreak.

Recently, rapid diagnostic tests (RDTs) based on the detection of Ebola virus antigens (Ag) have been developed for use in the field [5,6]. Rapid diagnostic tests are generally easier to use, more portable, and cost less than molecular tests, allowing for their use in decentralized settings. Additionally, RDTs typically provide results within minutes, compared to hours or even days for molecular tests, and are particularly important in areas with limited laboratory capacity and supply chains.

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https://doi.org/10.1016/j.diagmicrobio.2024.116568
Received 2 July 2024; Received in revised form 30 September 2024; Accepted 17 October 2024
Available online 20 October 2024

Interim guidelines from the World Health Organization (WHO), released during the 2013-16 EVD epidemic in West Africa, recommended Ag RDTs only in areas with limited laboratory capacity [7]. In addition, the guideline recommended that all RDT results (positive or negative) be confirmed by RT-PCR since RDTs listed for emergency use at that time did not meet the WHO target product profile for sensitivity [8–10]. Since then, a growing number of studies have reported the clinical performance of various Ebola virus Ag RDTs for triaging of suspected cases [11–14], and more recently, for detection in cadavers when the cause of death is unknown but consistent with EVD [15]. Despite this, there remains a need to determine the diagnostic performance of EVD Ag RDTs to support their broader use for individual case diagnosis and surveillance, especially in resource-limited endemic settings. We therefore conducted a systematic review and meta-analysis of studies and reports comparing the performance of Ag RDTs (the "index test") to RT-PCR (the "reference test") for the diagnosis of EVD.

2. Materials and methods

This review is registered under PROSPERO (CRD42023428802). The reporting adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [16]. We conducted a comprehensive search of diagnostic evaluation studies between August 2022 and July 2023 in the PubMed, EMBASE, and Web of Science databases. The initial search terms in PubMed were *(ebola* OR "EVD") AND antigen AND (diagnostic OR test OR assay RDT OR "rapid diagnostic test")*, with more defined terms established for each database (Supplementary Table 1). We also conducted hand searches of the WHO Emergency Use Authorization Listing and the U.S. Food and Drug Administration's Emergency Use Authorization and 510k medical device register for data on Ebola RDTs. We undertook forward and backward searches for studies that met the inclusion criteria to identify additional potential papers.

Papers were eligible for inclusion if they met the following criteria: (1) reported cross-sectional or case-control studies assessing the performance of Ag RDTs for EVD or reported use of any Ag RDT for EVD, (2) included a study population consisting of individuals that met the case definition of suspected EVD, and (3) reported confirmation of EVD by RT-PCR via manual or automated platforms. Review papers and papers that only described analytical evaluation (i.e. studies using spiked samples to identify analytical parameters of a test), included samples from healthy individuals, described lab-based Ag ELISA or automated ELISA platforms, or used RT-LAMP for confirmation, were excluded.

Retrieved articles were exported to EPPI-Reviewer (Version 4.14.2) and duplicates were removed. One reviewer (DME) completed the eligibility assessment, data extraction, and quality assessment, with second reviewers (IE, CMC) assessing the results. Quality assessments of included papers were based on the Quality Assessment of Diagnostic Accuracy Studies-2 checklist [17]. We assessed four domains (patient selection, index test, reference test, and flow and timing) for risk of bias and the first three domains for applicability using different signaling questions (Supplementary Table 2), and judged papers as "low", "high", or "unclear". Disagreements were discussed and resolved by consensus.

We extracted data to construct standard 2 × 2 tables to calculate sensitivity and specificity, estimating summary sensitivities and specificities with 95% confidence intervals (CI) using a bivariate random-effects model [18] implemented in MetaBayesDTA v.1.5.0 (https://crsu.shinyapps.io/MetaBayesDTA/) [19–21] and in R studio (version 2023.12.0+369) using the meta package [22]. When there was only one study per test, we reported individual sensitivities and specificities with 95% CI using the binomial exact method. We assessed heterogeneity by visual inspection of the forest plots of the sensitivity and specificity, along with the shape of the summary receiver operating characteristic curves.

We conducted subgroup analysis on the following groups: 1) index test manufacturer, 2) sample type (serum only, plasma only, whole and capillary blood, and oral fluid), and 3) reference test used. For subgroups based on sample type, index test, or reference test used, parameters reported in three studies or more were made a separate category, while those used in fewer than three studies were combined into a common category of "other".

3. Results

The searches resulted in 777 studies for screening after removing 185 duplicates (Fig. 1). Of 64 identified eligible full-text studies and reports, 16 met the inclusion criteria (Table 1) [11–15,23–33]. The remaining were excluded because they were commentary reports, reviews that provided limited results from clinical samples (e.g. described test development or analytical studies), included different populations to calculate performance, described test development, or evaluated an ELISA-based diagnostic.

3.1. Study characteristics

Table 1 describes the key characteristics of the included studies. The included studies had cross-sectional, case-control, or a mixture of both designs and were published in English and French between 2015 and 2023. The studies included specimens from the Democratic Republic of the Congo [13–15,27], Guinea [25,26,30], Liberia [23,28], and Sierra Leone [11,12,24,29,31–33]. One study reported results from both Sierra Leone and West Africa [29]. The included studies evaluated 13 RDTs, including three iterations of the DPP Ebola tests and 5 RT-PCR reference tests. Specimens were from patients suspected to have EVD, patients hospitalized in Ebola Treatment Centers with RT-PCR-confirmed EVD, deceased individuals, or as part of ongoing outbreak surveillance. All studies tested blood or blood components, including whole or capillary blood, plasma, and serum, while three studies tested oral swab specimens from cadavers [15,28,30]. Seven studies clearly stated testing on fresh samples [12–15,25,30,31], with the remaining studies stating testing on stored samples. Few studies reported participant demographics; of those who provided the information, the mean age range of the participants was 27 – 39 years, with women making up between 42 – 55% of the study population [12,14,24,26].

3.2. Quality assessment

The results of the quality assessment are shown in Fig. 2. Two assessments were conducted for one manuscript as two different study designs were described [12]. There was a higher risk of bias and applicability in the patient selection domain due mainly to the inclusion of case-control studies [14,24,26,27,29,32,33] and limited clinical description of included samples [12,14,25,26,29,32,33], respectively.

3.3. Meta-analysis

Thirty-nine data points resulting in 23,843 tests performed were included for meta-analysis. The average disease prevalence in the pooled analysis was 35%. The bivariate-effect model showed a pooled sensitivity and specificity of Ag RDTs to detect EVD of 82.1% (95%CI: 75.2 – 88.0) and 97.0% (95%CI: 95.1-98.2), respectively (Table 2). Although sensitivity estimates ranged widely between studies (20 – 100%, Supplementary Figure 1), the specificity estimate range was much narrower (80 - 100%, Fig. 3, Supplementary Figure 2).

3.4. Sub-group analysis

3.4.1. Index and reference tests

We included four Ag RDTs for the subgroup analysis with a sufficient number of studies – ReEBOV Antigen RDT (Coregenix/Zalgen Labs), OraQuick Ebola RDT (Orasure Technologies), QuickNavi Ebola RDT (Denka Seiken), and EBOLA Ag K-SeT (Coris; Table 2). For ReEBOV

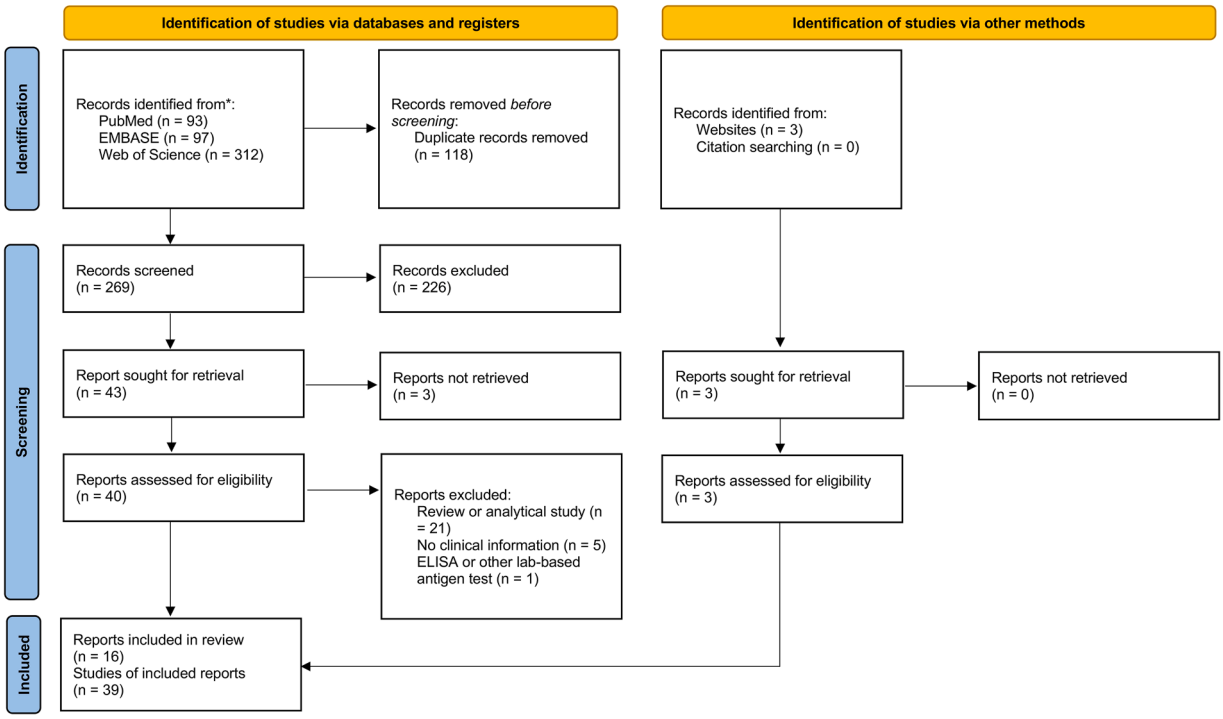

Fig. 1. PRISMA flow diagram of studies.

Antigen RDT, we included three studies [11,12,32] representing 1,479 samples from seven data points. Pooled sensitivity and specificity were 90.1% (95%CI: 82.5-94.8) and 90.1% (95%CI: 84.3-94.2), respectively. Six studies that evaluated the OraQuick Ebola RDT [14,15,27,29,30,33] were included, representing 6,423 samples from nine data points, with a pooled sensitivity of 75.1% (95%CI: 60.7-84.9) and a pooled specificity of 98.9% (97.6-99.5). Three studies [13,14,27], representing 9,376 samples, were included that assessed the QuickNavi Ebola RDT, finding a pooled sensitivity and specificity of 74.0% (95%CI: 50.5-87.0) and 98.8% (95%CI: 94.5-99.6), respectively. Finally, we included three studies [14,24,27], representing 1,955 samples, that evaluated the EBOLA Ag K-SeT, resulting in a pooled sensitivity and specificity of 54.3% (95%CI: 27.4-80.2) and 97.1% (95%CI: 91.5-98.5), respectively.

We had sufficient studies to conduct subgroup analysis on three RT-PCR reference tests –RealStar Ebola RT-PCR (Altona diagnostics), Xpert Ebola (Cepheid), and Trombley assay. We included four studies [12,24,31,32], representing 2,026 samples from eight data points for the Altona test, resulting in a pooled sensitivity and specificity of 90.6% (95%CI: 84.6-94.6) and 93.7% (89.6-96.7), respectively. Four studies were included for the Trombley test [11,12,26,32], representing 2,361 samples from ten data points. Pooled sensitivity using the Trombley test was 81.6% (95%CI: 75.4-86.6), and pooled specificity was 92.1% (95%CI: 88.8-95.0). Lastly, five studies for the Xpert Ebola test [13–15,27,33] were included, representing 14,928 samples from 11 data points, resulting in a pooled sensitivity of 61.9% (95%CI: 48.0-74.6) and pooled specificity of 98.7% (95%CI: 97.8-99.2).

3.4.2. Sample type

Six studies were included for plasma, representing 3,543 samples from 14 data points [11,12,23,24,28,32], showing a pooled sensitivity and specificity of 85.0% (95%CI: 79.6-89.4) and 93.2% (95%CI: 89.3-95.8), respectively. For the three studies that tested serum, representing 971 samples from five data points [11,25,26], we found a pooled sensitivity of 84.0% (95%CI: 74.4-90.2) and a pooled specificity of 92.5% (95%CI: 84.7-96.3). We included nine studies that tested capillary or whole blood, representing 18,426 samples from 16 data points [11,13,14,25,27,29–31,33]. Although pooled sensitivity for capillary and whole blood was 68.5% (95%CI: 57.4-78.4), lower than the other sample types, the 95% confidence intervals overlapped with the other sample types. Pooled specificity for capillary and whole blood was similar to other sample types (98.2% [95%CI: 97.1-98.9]). Lastly, four studies that tested oral fluid [15,28,29,33], representing 903 samples from four data points, resulted in a higher pooled sensitivity than other sample types (94.0% [95%CI: 86.5-97.7]), although confidence intervals overlapped. Pooled specificity for oral fluid was 98.2% (95%CI: 95.1-99.3), like the other sample types.

4. Discussion

Compared to RT-PCR, the overall pooled sensitivity and specificity for Ag RDTs were 82.1% and 97.0%, respectively, falling short of the desired test performance of >95% sensitivity and >98% specificity described in the WHO's target product profile (TPP) document for EVD diagnostics [8].

Despite not meeting the WHO's target product profile benchmarks, the high specificity and positive predictive value (94%) of Ag RDTs support their use as a "rule-in" device, meaning that, in the context of patients presenting for care who test positive by Ag RDT, the healthcare provider can be confident that the patient has EVD. In addition, a positive Ag RDT can be used to inform safe burial practices, reducing the risk of spread from suboptimal infection prevention control practices.

Our results indicate that presently available Ag RDTs would miss approximately 18% of EVD cases. These false-negative diagnostic results could have particularly dire consequences for EVD, given its contagiousness and high mortality. Patients who test negative may be treated with fewer precautions compared to those who test positive, increasing the risk of infection to healthcare workers and other patients. False-negative individuals may also be excluded in contact tracing, potentially leading to enhanced transmission. Therefore, Ag RDTs should not be used as "rule-out" tests, with negative results requiring confirmatory PCR testing.

Our pooled sensitivity estimate was lower than two previously published systematic reviews (82.1% vs 86%) [34,35], although the trend remains the same. Despite the availability of previous systematic

Table 1
Description of included studies

Author, year of publication	Study location	Year of samples	Study design	Study demographics	Sample type tested	Index test (Developer)	Reference test (Developer)	Sample size	Clinical sensitivity (95% CI)	Clinical specificity (95% CI)	Disease prevalence	Funding source
Boisen et al, 2016 [11]	Sierra Leone	2014-2015	Cross-sectional	Not available	Serum	ReBOV Antigen RDT (Coregenix/ Zalgen Labs)	Trombley	196	94.6 (89.2-98.7)	80.5 (70.3-88.4)	0.61	Not available
			Cross-sectional	Not available	Plasma	ReBOV Antigen RDT (Coregenix/ Zalgen Labs)	Trombley	212	85.7 (76.4-92.4)	97.3 (92.4-99.4)	0.43	
Broadhurst et al, 2015 [12]	Sierra Leone	2015	Cross-sectional	Mean age: 27.6 (SD: 15.8), Median age: 27.0 (IQR 16.8-36.5); 54.7% female	Capillary blood	ReBOV Antigen RDT (Coregenix/ Zalgen Labs)	RealStar Ebola (Altona)	106	100 (87.7-100)	92.2 (83.8-97.1)	0.27	Gift from foundation; tests donated by Coregenix
			Cross-sectional	Not available	Whole blood	ReBOV Antigen RDT (Coregenix/ Zalgen Labs)	RealStar Ebola (Altona)	277	100 (92.1-100)	92.2 (88.0-95.3)	0.16	
			Case-control	Not available	Plasma	ReBOV Antigen RDT (Coregenix/ Zalgen Labs)	Trombley	35	85	100	-	
Chembio, 2019 [23]	Liberia	Not specified	Cross-sectional	not available	Plasma	DPP Ebola (Chembio)	Ebola virus VP40 Real-time RT-PCR assay (US CDC)	30	85.0 (64.0-94.8)	90.0 (59.6-98.2)	0.67	Not available
Colavita et al, 2017 [24]	Sierra Leone	2014-2015	Cross-sectional	Median age: 32 (IQR 17-36); 42% female	Plasma	EBOLA Ag K-SeT (Coris)	RealStar Ebola (Altona)	210	88.6 (82.5-94.7)	98.1 (95.5-100.7)	0.50	Not available
Gallais et al, 2017 [25]	Guinea	2015	Cross-sectional	Not available	Serum	Ebola eZYSCREEN (CEA)	RealStar Ebola (Altona) + Weidmann protocol	144	74.5	100	-	Not available
			Cross-sectional	Not available	Whole blood	Ebola eZYSCREEN (CEA)	RealStar Ebola (Altona) + Weidmann protocol	137	65.3	98.9	-	
Makiala et al, 2019 [13]	Democratic Republic of Congo	2018-2019	Cross-sectional	Not available	Whole blood	QuickNavi (Denka Seiken)	Xpert Ebola (Cepheid)	928	85.0 (75.3-92.0)	99.8 (99.2-100)	0.09	Not available
Moran et al, 2020 [26]	Guinea	2014-2015	Cross-sectional	Mean age: 39 (range 3-90); 45% female	Serum	DPP Fever (Chembio)	Trombley	205	89.9 (82.3-94.6)	90.6 (82.5-95.4)	0.53	Not available
			Cross-sectional	Mean age: 39 (range 3-90); 45% female	Serum	DPP Ebola (Chembio)	Trombley	205	77.06 (67.8-84.3)	91.7 (83.8-96.1)	0.53	
			Cross-sectional	Mean age: 39 (range 3-90); 45% female	Serum	DPP Ebola-malaria (Chembio)	Trombley	205	77.98 (68.8-85.1)	95.8 (89.1-98.7)	0.53	
Mukadi-Bamuleka et al, 2022 [15]	Democratic Republic of Congo	2019-2020	Cross-sectional	Not available	Oral swab	OraQuick Ebola RDT (Orasure)	Xpert Ebola (Cepheid)	196	85.7	99.6	0.04	Not available
Mukadi-Bamuleka et al, 2022 [14]	Democratic Republic of Congo	2018-2019	Cross-sectional	Not available	Whole blood	QuickNavi (Denka Seiken)	Xpert Ebola (Cepheid)	7548	87.4 (63.6-96.8)	99.6 (99.3-99.8)	0.08	Not available
			Cross-sectional	Not available	Whole blood	OraQuick Ebola RDT (Orasure)	Xpert Ebola (Cepheid)	1571	57.4 (38.8-75.8)	98.3 (97.5-99.0)	0.06	
			Cross-sectional	Not available	Venous blood	EBOLA Ag K-SeT (Coris)	Xpert Ebola (Cepheid)	845	38.9 (23.0-63.6)	97.4 (85.3-99.6)	0.06	
Mukadi-Bamuleka et al, 2023 [27]	Democratic Republic of Congo	2018-2021	Case-control	Not available	Whole blood	EBOLA Ag K-SeT (Coris)	Xpert Ebola (Cepheid)	900	25.0 (22.3–27.9)	95.9 (94.2–97.1)	-	Institute of Tropical Medicine Antwerp, EDCTP, DGD Belgium
			Case-control	Not available	Whole blood	OraQuick Ebola RDT (Orasure)	Xpert Ebola (Cepheid)	900	61.6 (57.0–65.9)	98.1 (96.2–99.1)	-	

(*continued on next page*)

Table 1 (*continued*)

			Case-control	Not available	Whole blood	QuickNavi (Denka Seiken)	Xpert Ebola (Cepheid)	900	56.8 (53.6–60.0)	97.5 (96.2–98.4)	-	
			Case-control	Not available	Whole blood	Ebola Zaire Ag RDT (SD Biosensor)	Xpert Ebola (Cepheid)	900	21.6 (18.1-25.7)	99.1 (97.4-99.7)	-	
Phan et al, 2016 [28]	Liberia	2014-2015	Cross-sectional	Not available	Plasma	Ebola LFI (NMRC)	EZ1/EZ2 rRT-PCR	290	87.8 (75.3-94.3)	97.5 (94.7-98.9)	0.17	Not available
			Cross-sectional	Not available	Oral swab	Ebola LFI (NMRC)	EZ1/EZ2 rRT-PCR	237	88.9 (56.5-98.0)	96.1 (92.7-97.9)	0.04	
US FDA - Orasure, 2020 [29]	Sierra Leone	2014-2015	Case-control	Not available	Whole blood	OraQuick Ebola RDT (Orasure)	Ebola virus VP40 Real-time RT-PCR assay (US CDC)	75	84.0 (63.9-95.5)	98.0 (89.4-100)	-	Not available
	West Africa	2014-2015	Case-control	Not available	Oral swab	OraQuick Ebola RDT (Orasure)	Not mentioned	228	97.1 (85.5-99.5)	100 (98.1-100)	-	
VanSteelandt et al, 2017 [30]	Guinea	2015-2016	Cross-sectional	Not available	Whole blood	OraQuick Ebola RDT (Orasure)	Not mentioned	37	38.5	91.7	-	Not available
			Cross-sectional	Not available	Whole blood	OraQuick Ebola RDT (Orasure)	Not mentioned	3099	16.7	100	-	
Walker et al, 2015 [31]	Sierra Leone	2015	Cross-sectional	Not available	Capillary blood	EVD RDT (DSTL)	RealStar Ebola (Altona)	131	100 (78.2-100)	92.0 (85.8-96.4)	0.12	Wellcome trust; tests donated by United Kingdom Defense Science and Technology Laboratory
WHO - Orasure, 2020 [33]	Sierra Leone	Not specified	Case-control	Not available	Oral fluid	OraQuick Ebola RDT (Orasure)	Xpert Ebola (Cepheid)	244	94.12 (83.8-98.8)	100 (98.1-100)	-	Not available
Wonderly et al, 2019 [32]	Sierra Leone	2015	Cross-sectional	Not available	Plasma	Ebola Zaire Ag RDT (SD Biosensor)	RealStar Ebola (Altona)	327	84.5 (77.1-90.3)	99.0 (96.4–99.9)	-	Not available
			Cross-sectional	Not available	Plasma	ReBOV RDT (Coregenix/ Zalgen Labs)	RealStar Ebola (Altona)	327	93.2 (87.5–96.8)	80.3 (74.1–88.6)	-	
			Cross-sectional	Not available	Plasma	One step Ebola test (Intec)	RealStar Ebola (Altona)	324	98.4 (94.4–99.8)	80.2 (74.0–85.5)	-	
			Cross-sectional	Not available	Plasma	DEDIATEST EBOLA (Senova)	RealStar Ebola (Altona)	325	79.5 (71.–86.2)	84.3 (78.5–89.1)	-	
			Cross-sectional	Not available	Plasma	Ebola Zaire Ag RDT (SD Biosensor)	Trombley	327	70.5 (62.7–77.5)	99.4 (96.8–100)	-	
			Cross-sectional	Not available	Plasma	ReBOV RDT (Coregenix/ Zalgen Labs)	Trombley	327	85.3 (78.7–90.4)	83.0 (76.6–88.3)	-	
			Cross-sectional	Not available	Plasma	One step Ebola test (Intec)	Trombley	324	89.6 (83.7–93.9)	84.7 (78.4–89.8)	-	
			Cross-sectional	Not available	Plasma	DEDIATEST EBOLA (Senova)	Trombley	325	70.1 (62.2–77.2)	86.0 (79.8–90.8)	-	

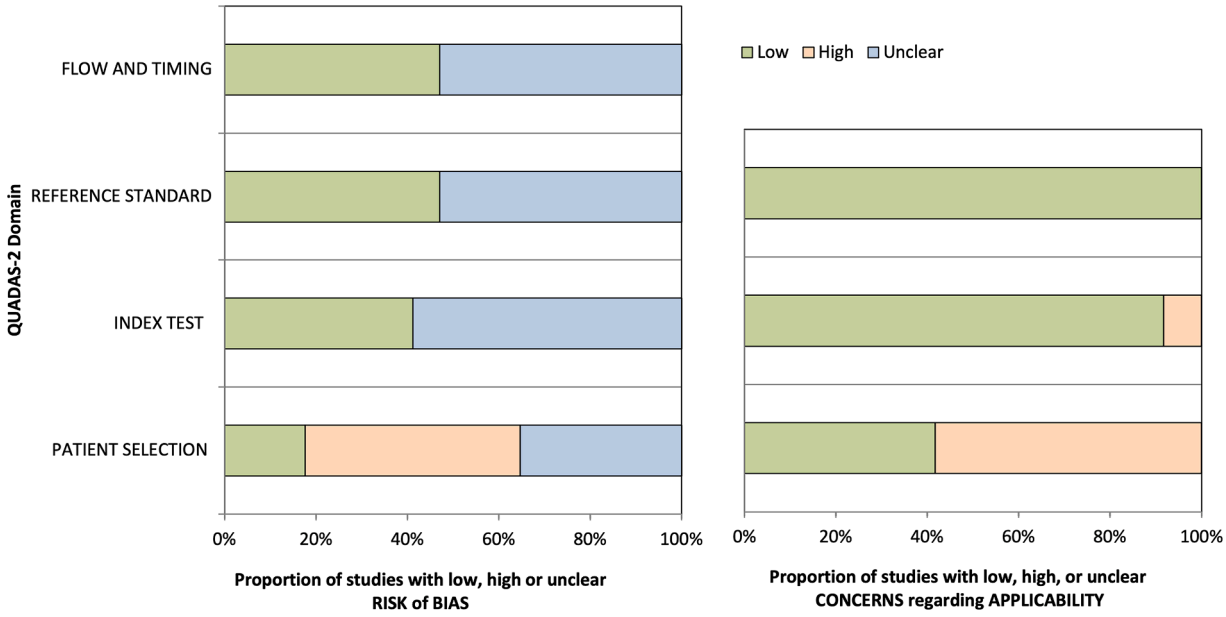

Fig. 2. Quality assessment of included studies using the QUADAS-2 tool.

Table 2
Meta-analysis of antigen-based rapid tests for Ebola virus disease.

Group and study	# data points (# of studies)	Sample size	Result (95% CI) Pooled sensitivity, %	Pooled specificity, %	Positive likelihood ratio	Negative likelihood ratio	Diagnostic OR
All studies [11–15,23–33]	39 (16)	23,843	82.1%* (75.2-88.0)	97.0%** (95.1-98.2)	27.5 (17.1-43.8)	0.19 (0.13-0.26)	149 (83-270)
Index test							
ReEBOV Antigen RDT [11,12,32]	7 (3)	1,479	90.1% (82.5-94.8)	90.1% (84.3-94.2)	9.1 (5.7-15.5)	0.11 (0.06-0.19)	84 (36-192)
OraQuick Ebola RDT [14,15,27, 29,30,33]	9 (5)	6,423	75.1% (60.7-84.9)	98.9% (97.6-99.5)	69.3 (30.7-153.1)	0.25 (0.15-0.40)	278 (101-773)
QuickNavi Ebola RDT [13,14,27]	3 (3)	9,376	74.0% (50.5-87.0)	98.8% (94.5-99.6)	61.8 (12.3-175.6)	0.26 (0.13-0.51)	238 (30-983)
EBOLA Ag K-SeT [14,24,27]	3 (3)	1,955	54.3% (27.4-80.2)	97.1% (91.5-98.5)	18.5 (5.4-40.1)	0.47 (0.21-0.76)	40 (8-167)
Other [23,25–28,31,32]	19 (8)	6,389	80.8% (73.8-86.6)	94.8% (92.0-96.6)	15.6 (10.0-23.9)	0.20 (0.14-0.28)	77 (45-138)
Reference test							
RealStar Ebola RT-PCR [12,24,31, 32]	8 (4)	2,026	90.6% (84.6-94.6)	93.7% (89.6-96.7)	14.4 (8.8-26.2)	0.10 (0.06-0.17)	145 (67-309)
Trombley [11,12,26,32]	10 (4)	2,361	81.6% (75.4-86.6)	92.1% (88.8-95.0)	10.3 (6.8-16.3)	020 (0.15-0.27)	53 (29-94)
Xpert Ebola [13–15,27,33]	11 (5)	14,928	61.9% (48.0-74.6)	98.7% (97.8-99.2)	46.4 (25.4-79.4)	0.39 (0.26-0.53)	122 (51-277)
Other [23,28–30,33]	10 (6)	4,352	79.5% (65.4-88.0)	98.3% (95.7-99.3)	46.8 (17.7-118.4)	0.21 (0.12-0.35)	221 (72-678)
Sample type							
Plasma [11,12,23,24,28,32]	14 (6)	3,543	85.0% (79.6-89.4)	93.2% (89.3-95.8)	12.5 (7.9-20.2)	0.16 (0.11-0.20)	78 (42-142)
Serum [11,25,26]	5 (3)	971	84.0% (74.4-90.2)	92.5% (84.7-96.3)	12.8 (6.5-25.1)	0.17 (0.11-0.27)	66 (25-154)
Capillary or whole blood [11,13, 14,25,27,29–31,33]	16 (9)	18,426	68.5% (57.4-78.4)	98.2% (97.1-98.9)	38.9 (23.1-64.8)	0.32 (0.22-0.43)	122 (63-237)
Oral fluid** [15,28,29,33]	4 (4)	903	94.0% (86.5-97.7)	98.2% (95.1-99.3)	52.4 (19.0-133.6)	0.06 (0.02-0.14)	854 (215-3527)
Sensitivity analysis							
Cross-sectional only [11–15, 23–28,30,31]	19 (11)	16,772	85.4% (74.9-91.6)	96.9% (94.0-98.4)	27.7 (14.3-52.7)	0.15 (0.09-0.26)	187 (83-381)

CI: Confidence interval, OR: odds ratio. *$\tau^2 = 1.749$, $I^2 = 96.3\%$, $p<0.001$ **$\tau^2 = 2.372$, $I^2 = 93.7\%$, $p<0.001$.

reviews on Ebola RDTs, our review included more recent research conducted in the Democratic Republic of the Congo. Additional data from Central and East Africa, where most EVD outbreaks have occurred, assists in generalizing these results to high-risk countries and allows us to conduct further subgroup analyses.

When assessing the best-performing sample type, we found that the use of capillary or whole blood has a lower pooled sensitivity (68.5% [95%CI: 57.4-78.4) compared to other sample types. In contrast, Muzembo *et al.* found the highest pooled sensitivity (99% [95%CI: 67-100]) to be from testing whole and capillary blood [34]. Although

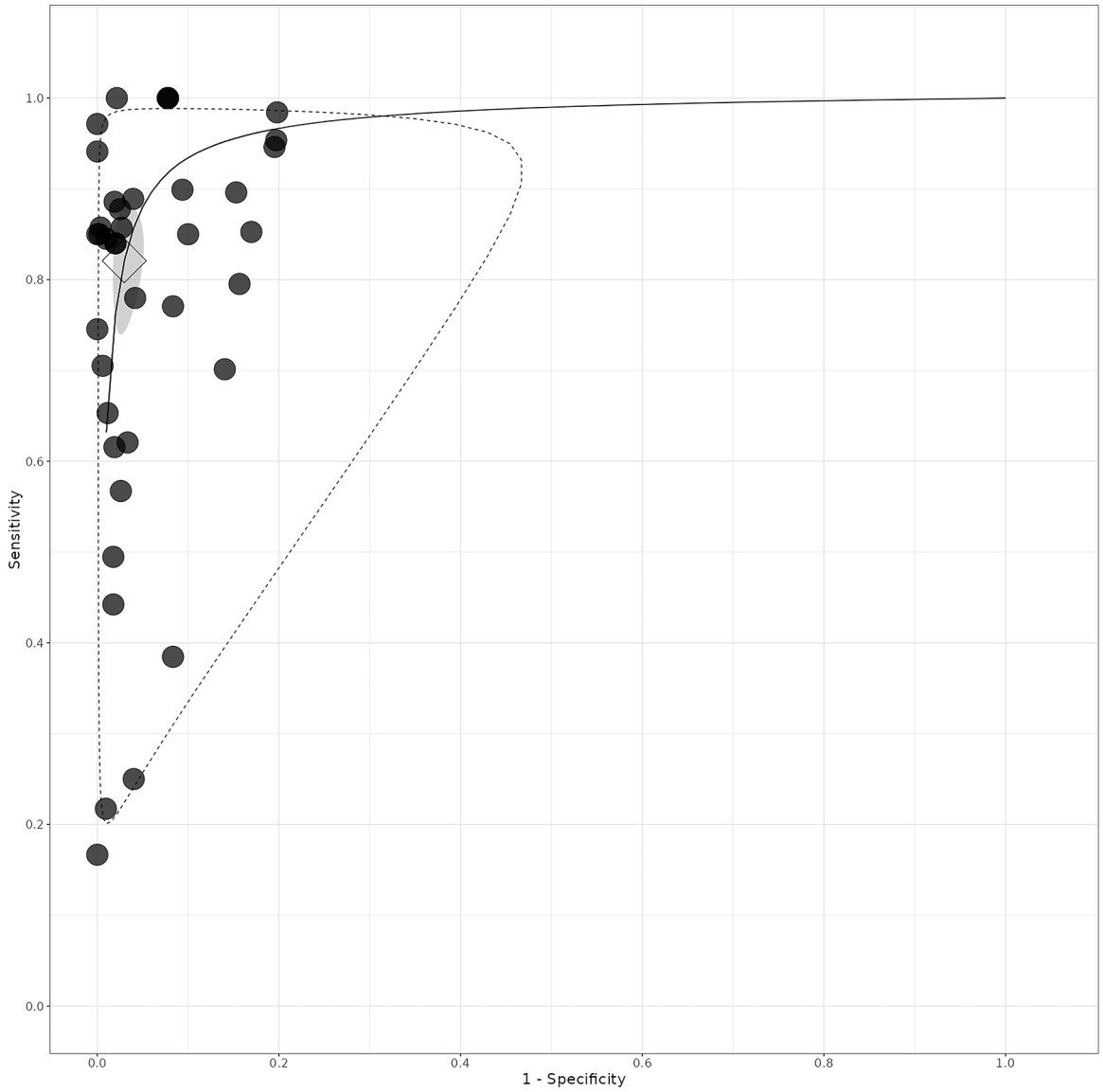

Fig. 3. SROC curve of pooled performance of Ebola RDTs compared to RT-PCR.
Caption under figure: The dotted line represents the 95% prediction region from the bivariate model; the greyed-out area represents the 95% credible region from the bivariate model.

confidence intervals overlap, including newer studies resulted in an increased sample size and most likely explains our lower estimate. Additionally, whole blood samples are at risk of hemolysis with long-term storage, which could increase the number of false negatives as hemolyzed blood would prevent absorption of the RDT strip. This may be the case for the studies we included, which specified the use of stored samples in the evaluation, although the total number of studies is low [27].

Interestingly, we observed higher pooled performance using oral fluid compared to blood. Two studies that used Ag RDTs on cadavers were included in the meta-analysis [15,28], which may explain the higher performance of oral fluid as viremia, and presumably, virus shedding into oral fluid, is higher in non-EVD survivors versus EVD survivors [36–38]. A previous studies showed the detection of ebolavirus RNA in paired blood and oral fluid [39]. However, since only four studies were included in the meta-analysis, additional research is needed on using oral fluid to detect viral antigens, including samples from symptomatic patients, to confirm this observation.

We had sufficient data to assess 4 Ag RDTs. Of the 4 tests, only the OraQuick Ebola RDT was granted approval in the United States by the Food and Drug Administration (US FDA) through its De Novo review pathway [40] and listed under WHO emergency use authorization [33]. The claimed clinical sensitivity of the test was 84.0% in whole blood and 97.1% in oral fluid, higher than the pooled performance found in this study. The claimed clinical specificity was comparable to our study. Notably, the ReEBOV Ebola RDT test showed the highest pooled estimates of clinical sensitivity and specificity (90.1% and 90.1%, respectively) in our study. This test previously had US FDA and WHO emergency use authorizations, although was subsequently removed from both listings at the developer's request [41–44].

Interestingly, we found Ag RDT sensitivity to be lowest when the Xpert EBOV test was used as the reference standard. The Xpert EBOV test has US FDA and WHO EUA listing for detecting EBOV using blood and oral fluid specimens [44,45]. Previous reviews showed pooled clinical sensitivity of the Xpert EBOV test between 96 – 98% compared to RT-PCR kits [35,46]. Additionally, analytical evaluations demonstrated a lower limit of detection compared of the Xpert Ebola test to the Altona RealStar Ebola RT-PCR kit [46], suggesting better sensitivity compared to RT-PCR kits. The higher sensitivity of the Xpert EBOV tests may have resulted in underestimates of the performance of Ag RDTs, including the

QuickNavi Ebola RDT.

Although not included in our analysis, others have reported the additional role of viral load affecting the performance of Ag RDTs, where lower Ct values, indicative of higher viral loads, showed improved Ag RDT sensitivity [32,35]. Additionally, EBOV antigen targets used in the assays may have affected performance. Most tests included in our study that reported their target analyte detected viral antigen 40 (VP40), with one test (SD Bioline) reporting the detection of VP40, glycoprotein (GP), and nucleoprotein (NP), and another test (QuickNavi) reporting the detection of NP. Both EBOV GP and VP40 have been identified as relevant diagnostic markers [47,48], with soluble GP (sGP) being highly expressed in EVD [49,50]. New developments using sGP resulted in improved EBOV detection [51,52]; further development using GP or sGP for Ag RDTs should be considered.

Our study had some limitations. Firstly, we could only identify publications evaluating the performance of Zaire ebolavirus, highlighting the need for additional research on the performance of Ag RDTs for other ebolavirus species. Secondly, our inclusion of case-control studies may have affected pooled test performance. However, when we conducted a sensitivity analysis using cross-sectional studies only (Table 2), we found a slightly higher pooled test sensitivity and similar pooled specificity, suggesting that including case-control studies did not significantly affect the final meta-analysis. Additionally, including studies using stored samples may underestimate test performance, particularly for serum and whole blood, as hemolytic samples can interfere with RDT readouts [53,54]. Furthermore, we were unable to analyze performance based on symptoms or key demographics such as gender and age, as most studies included in the review did not report on these categories. Assessing performance based on symptoms is important as viral kinetics during various stages of disease may play a role in the optimal use of Ag RDT [36,55].

Our study has several strengths. First, we included clinical performance results in reports from regulatory bodies such as the WHO and US FDA, which are not usually published in scientific journals. Results from these regulatory bodies were critical in understanding the performance of COVID-19 diagnostics [56,57] given the need to supply validation and evaluation data for regulatory review, and should be considered key databases for systematic reviews of diagnostic test performance. Lastly, the inclusion of recent results from Central Africa increased the generalizability of our findings to the region.

5. Conclusion

In conclusion, currently available Ag RDTs for detecting Zaire ebolavirus do not meet the recommended performance requirements described by the WHO TPP. However, given their rapid turnaround time, available Ag RDTs may still be useful in the field, especially during a known outbreak. Although negative results may require retesting, particularly among individuals with a high suspicion of EVD, a positive Ag RDT result can significantly reduce the time needed for isolation, treatment, and safe burial. While capillary and whole blood samples are easier to collect in the field, caution is needed to ensure appropriate sample collection, transport, and storage to maintain sample quality before testing. Further assessment using oral fluid, especially among symptomatic individuals, would be beneficial in determining its usability. Despite the utility of screening tests for outbreak containment, our findings suggest that better-performing RDTs suitable for field settings are needed. Given the outbreak of Sudan virus disease (SVD) caused by Sudan ebolavirus in Uganda in 2022-2023 [58,59], the availability of new generation RDTs capable of detecting multiple ebolavirus species would be ideal. New tests introduced to the market should undergo additional field testing to ensure performance; therefore, it is crucial to integrate diagnostic evaluation studies into early outbreak response for EVD.

Glossary

Ag RDT – Antigen rapid diagnostic test
EVD – Ebola virus disease
EBOV – Ebola virus, Zaire
RT-PCR – reverse-transcriptase polymerase chain reaction
TPP – target product profile

Funding

DME, CKC, and DGB work at FIND and receive grants from the UK government (FCDO), the German government (BMZ), and the Canadian government.

CRediT authorship contribution statement

Devy M. Emperador: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cassandra Kelly-Cirino:** Writing – review & editing, Validation, Supervision, Methodology. **Daniel G. Bausch:** Writing – original draft, Validation, Supervision, Methodology. **Isabella Eckerle:** Writing – review & editing, Validation, Supervision, Methodology.

Declaration of competing interest

That there is no conflict of interest for this paper

Acknowledgments

The authors would like to thank Emmanuel Agogo and the Pandemic Threats team at FIND for their support of this review.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diagmicrobio.2024.116568.

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