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Accuracy of Rapid and Point-of-Care Screening Tests for Hepatitis C

A Systematic Review and Meta-analysis

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Background: 170 million persons worldwide are infected with hepatitis C, many of whom are undiagnosed. Although rapid diagnostic tests (RDTs) and point-of-care tests (POCTs) provide a time- and cost-saving alternative to conventional laboratory tests, their global uptake partly depends on their performance.

Purpose: To meta-analyze the diagnostic accuracy of POCTs and RDTs to screen for hepatitis C.

Data Sources: MEDLINE, EMBASE, BIOSIS, and Web of Science (1992 to 2012) and bibliographies of included articles.

Study Selection: All studies evaluating the diagnostic accuracy of POCTs and RDTs for hepatitis C in adults (aged ≥18 years).

Data Extraction: Two independent reviewers extracted data and critiqued study quality.

Data Synthesis: Of 19 studies reviewed, 18 were meta-analyzed and stratified by specimen type (whole blood, serum, plasma, or oral fluid) or test type (POCT or RDT). Sensitivity was similarly high in POCTs of whole blood (98.9% [95% CI, 94.5% to 99.8%]) and serum or plasma (98.9% [CI, 96.8% to 99.6%]), followed by RDTs of serum or plasma (98.4% [CI, 88.9% to 99.8%]) and POCTs of oral fluid (97.1% [CI, 94.7% to 98.4%]). Specificity was also high in POCTs of whole blood (99.5% [CI, 97.5% to 99.9%]) and serum or plasma (99.7% [CI, 99.3% to 99.9%]), followed by RDTs of serum or plasma (98.6% [CI, 94.9% to 99.6%]) and POCTs of oral fluid (98.2% [CI, 92.2% to 99.6%]).

Limitation: Lack of data prevented sensitivity analyses of specific tests.

Conclusion: Data suggest that POCTs of blood (serum, plasma, or whole blood) have the highest accuracy, followed by RDTs of serum or plasma and POCTs of oral fluids. Given their accuracy, convenience, and quick turnaround time, RDTs and POCTs may be useful in expanding first-line screening for hepatitis C.

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The World Health Organization estimates (1) that 170 million persons worldwide are infected with the hepatitis C virus (HCV). Developing countries in Africa and Asia report the highest prevalence of this virus, which is transmitted predominantly by unscreened blood transfusions, injection drug use, and unsafe therapeutic injections (2). Because HCV and HIV infections share similar routes of transmission, about 40% of HIV-infected persons are co-infected with HCV (3). The prevalence of HIV–HCV co-infection varies from 16% to 33% in injection drug users in North America to 50% in Brazil (2, 4). Morbidity and mortality are also higher in co-infected populations (5–8). Chronic hepatitis C infection is associated with long-term complications, such as liver fibrosis, cirrhosis, and hepatocellular carcinoma (1). Although newer treatments for hepatitis C (such as telaprevir or boceprevir with pegylated interferon and ribavirin) have made viral suppression a possibility, timely screening is critical to the success of these newer treatments (9). In addition to the high burden of co-infection, marginalized at-risk populations face social, structural, and economic barriers, such as limited access to testing (10) and lapses in health insurance (11), which hamper early screening and timely engagement with care. The situation is worse in global low-resource settings, where standardized laboratory tests are expensive and often not covered by public health systems—and thus are rarely performed or offered on-site or in time, leading to suboptimal care and screening.

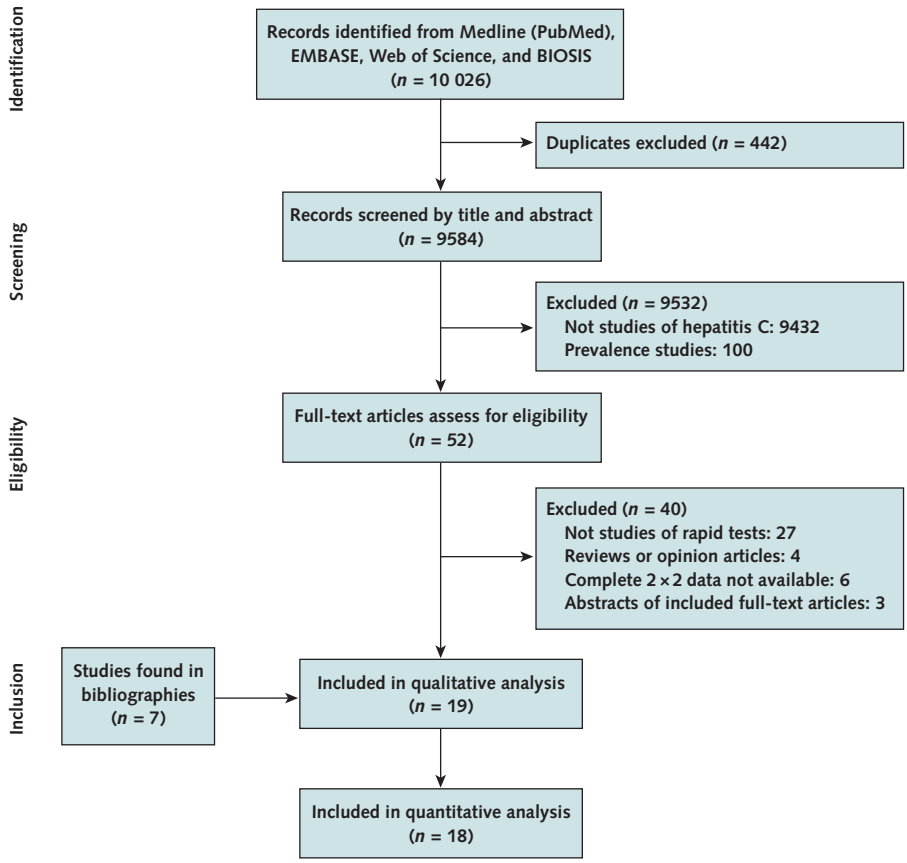
In the United States, the Centers for Disease Control and Prevention (CDC) recommends using an enzyme immunoassay (EIA) and either recombinant immunoblot assay or HCV nucleic acid testing for RNA to diagnose hepatitis C infection (12). Although this algorithm effectively detects active infection, the tests are expensive and have long turnaround times. Convenient, quality-assured, antibody-based rapid diagnostic tests (RDTs) and point-of-care tests (POCTs) could facilitate preliminary screening, although they cannot differentiate between acute and chronic infections. Their rapid turnaround time limits loss to follow-up and facilitates early linkages. Although both diagnostic test types are rapid, RDTs require special equipment, such as centrifuges and refrigerators, whereas POCTs eliminate the need for electricity and are more robust at high temperatures, thus offering additional opportunities to expand screening (13).

Several POCTs are in use, including the OraQuick HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, Pennsylvania), Anti-HCV Ab rapid test (Tema Ricerca, Bologna, Italy), SM-HCV Rapid Test (SERO-Med Labor Spezialitaten, Pollenfeld, Germany), Dual Path Platform test (Chembio Diagnostic Systems, Medford, New York), Multiplo Rapid HIV/HCV Antibody Test (MedMira, Halifax, Nova Scotia, Canada), SD Bioline

See also:

Web-Only
CME quiz (preview on page I-30)

Figure. **Study flow diagram.**



HCV (Standard Diagnostics, Yongin, Korea), Bioeasy HCV Test (Bioeasy Diagnóstica, Belo Horizonte, Minas Gerais, Brazil), Hexagon HCV (Human Diagnostics Worldwide, Wiesbaden, Germany), and Genedia HCV Rapid LF (Green Cross Medical Science, Yongin, Korea). The RDTs on the market include the Diagnos HCV Bi-Dot (J. Mitra, New Delhi, India), HCV Tri-Dot (J. Mitra), Advanced Quality One Step HCV Test (Bionike, San Francisco, California), SeroCard HCV (Trinity Biotech, Bray, Ireland), and HCV Spot (MP Biomedicals, Santa Ana, California).

In 2010, the U.S. Food and Drug Administration approved the OraQuick HCV Rapid Antibody Test and granted a waiver from the Clinical Laboratory Improvements Amendments of 1988 to allow its use in nontraditional settings. This offered the potential to increase HCV screening into hitherto untapped domains.

Given the high absolute burden of HIV–HCV co-infection in marginalized populations (such as injection drug users) in North America and Europe, the high prevalence of HCV mono-infection in Africa and Asia (2), and the high costs of conventional serologic tests, introducing and integrating HCV RDTs and POCTs into mandated HIV programs may lead to cost savings and expedited first-line screening of at-risk populations. Global public health agencies are interested in knowing the diagnostic performance of these tests but, to our knowledge, this evidence has not been synthesized. To address this knowledge gap, we reviewed evidence on the diagnostic performance of globally available RDTs and POCTs to screen for hepatitis C.

Methods

We reviewed the diagnostic accuracy variables (sensitivity, specificity, likelihood ratios [LRs], and diagnostic odds ratios [DORs]) of available RDTs and POCTs that screen for hepatitis C in oral fluid, whole blood, serum, or plasma specimens. We evaluated studies conducted worldwide in adults (aged ≥18 years), regardless of their risk profile, in all study settings (laboratory- or field-based) and all study designs (cross-sectional studies and case–control or serum panel assessments). We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in reporting the synthesis.

Data Sources and Searches

We searched MEDLINE (via PubMed), EMBASE (via Ovid), BIOSIS, and Web of Science from 1992 to

Table 1. **Characteristics of Reviewed Studies**

Study, Year (Reference)	Location	Sample Size, *n*	Risk Level	Study Design	Reference Standard	Specimen
Poovorawan et al, 1994 (31)	Singapore	192	Mixed	Cross-sectional	ELISA	Serum
Mvere et al, 1996 (29)	Zimbabwe	206	Mixed	Cross-sectional	EIA	Serum
Montebugnoli et al, 1999 (32)	Italy	100	NA	Case–control	ELISA and RIBA	Whole blood
Kaur et al, 2000 (28)	India	2754	Mixed	Cross-sectional	EIA	Serum
Yuen et al, 2001 (30)	China	195	NA	Case–control	EIA	Serum
WHO, 2001 (23)	Asia, Africa, Latin America, and Europe	257	NA	Case–control	ELISA, RIBA, and PCR	Serum
WHO, 2001 (24)	Asia, Africa, Latin America, and Europe	257	NA	Case–control	ELISA, RIBA, and PCR	Serum
WHO, 2002 (25)	Asia, Africa, Latin America, and Europe	257	NA	Case–control	ELISA, RIBA, and PCR	Serum
Hui et al, 2002 (7)	Hong Kong	197	High	Cross-sectional	EIA	Whole blood
Daniel et al, 2005 (27)	India	2590	Mixed	Cross-sectional	EIA	Serum
Njouom et al, 2006 (26)	Cameroon	161	NA	Case–control	EIA	Plasma
Torane and Shastri, 2008 (18)†	India	60	NA	Case–control	ELISA	Whole blood
Nyirenda et al, 2008 (5)	Malawi	193	High	Cross-sectional	ELISA, CLIA, and line immunoassay	Serum
Ivantes et al, 2010 (6)	Brazil	71	Mixed	Cross-sectional	CLIA	Whole blood
Lee et al, 2010 (21)	United States	571	Mixed	Cross-sectional	EIA and RIBA	Oral fluid Whole blood Finger-stick blood Plasma Serum
Lee et al, 2011 (22)	United States	2180	High	Cross-sectional	EIA, RIBA, and PCR	Oral fluid
		2178	High	Cross-sectional	EIA, RIBA, and PCR	Whole blood
		2176	High	Cross-sectional	EIA, RIBA, and PCR	Finger-stick blood
		2178	High	Cross-sectional	EIA, RIBA, and PCR	Plasma
		2180	High	Cross-sectional	EIA, RIBA, and PCR	Serum
Smith et al, 2011 (19)	United States	1081	High	Cross-sectional	CLIA and RIBA	Serum
Smith et al, 2011 (20)	New York	197	High	Cross-sectional	MEIA and RIBA	Oral fluid
	New York	285	High	Cross-sectional	MEIA and RIBA	Oral fluid
	Denver	279	High	Cross-sectional	EIA and RIBA	Oral fluid
	Denver	385	High	Cross-sectional	EIA and RIBA	Whole blood
	Dallas	432	High	Cross-sectional	CLIA	Whole blood
	Seattle	265	High	Cross-sectional	MEIA and RIBA	Oral fluid
	Seattle	265	High	Cross-sectional	MEIA and RIBA	Whole blood
Drobnik et al, 2011 (11)	New York	482	High	Cross-sectional	EIA and RIBA	Oral fluid

CLIA = chemiluminescent immunoassay; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; MEIA = microparticle enzyme immunoassay; NA = not applicable; PCR = polymerase chain reaction; RIBA = recombinant immunoblot assay; WHO = World Health Organization.
* **Table 2** lists manufacturer information for all tests.
† This study was excluded from the meta-analysis.

2012. The last search was conducted on 1 March 2012. An example MEDLINE search string (restricted to humans only): ("Hepatitis C"[MeSH] OR "Hepatitis C Antibodies"[MeSH] OR "Hepatitis C Antigens"[MeSH] OR "HCV") AND ("Point-of-Care"[MeSH] OR "rapid test" OR "rapid assay"). We used similar search strings for the other 3 databases. We also searched bibliographies of included articles for studies missed by the original search.

Study Selection

We included studies conducted in adults, both abstracts and full-text articles, if they provided enough raw data to recreate the 2×2 diagnostic tables. We did not exclude articles on the basis of study location, language of publication, or study design. However, we excluded studies on prevalence or the accuracy of laboratory-based tests, those missing relevant information on the index test (such as type [RDT or POCT] or manufacturer), manufacturer reports, and package inserts. We did not include manufacturer reports because they provide inadequate details on study conduct; have overt conflicts of interest; often provide accuracy estimations without CIs; and exclude important methodological details on study design, patient populations, and samples. The **Figure** shows a flow chart of the search.

Two reviewers independently conducted the searches and screened articles for eligibility. After initial identifica-

Table 1—Continued

Test*	Sensitivity (95% CI), %	Specificity (95% CI), %
HCV Spot	97.6 (87.4–99.9)	92.6 (87.3–96.3)
HCV Spot	90.9 (58.7–99.8)	97.9 (94.8–99.4)
Anti-HCV Ab Rapid test	100 (92.9–100)	98 (89.4–99.9)
Diagnos HCV Bi-Dot	87.5 (71–96.5)	100 (99.9–100)
SM-HCV Rapid Test	98 (93–99.8)	100 (96.2–100)
Advanced Quality One Step HCV Test	97.1 (89.8–99.6)	96.3 (92.5–98.5)
SeroCard HCV	98.5 (92.1–100)	100 (98.1–100)
HCV Tri-Dot	100 (94.7–100)	91.5 (86.6–95.1)
HCV Spot	100 (94.7–100)	93.7 (89.2–96.7)
HCV Tri-Dot, 4th Generation	100 (94.7–100)	98.9 (96.2–99.9)
Genedia HCV Rapid LF	98.5 (92.1–100)	98.4 (95.4–99.7)
SD Bioline HCV	96.9 (89.5–99.6)	100 (98.1–100)
SM-HCV Rapid Test	83.5 (75.2–89.9)	100 (95.9–100)
HCV Tri-Dot	99.3 (95.5–100)	99.0 (98.5–99.4)
Hexagon HCV	87.7 (80.3–93.1)	93.6 (82.5–98.7)
HCV Spot	0 (0–11.6)	100 (88.4–100)
HCV Spot	22.2 (2.8–60)	96.4 (92.7–98.5)
Bioeasy HCV Test	100 (88.4–100)	92.7 (80.1–98.5)
OraQuick HCV Rapid Antibody Test	99.2 (95.5–100)	100 (99.2–100)
OraQuick HCV Rapid Antibody Test	100 (97.0–100)	100 (99.2–100)
OraQuick HCV Rapid Antibody Test	100 (97.0–100)	100 (99.2–100)
OraQuick HCV Rapid Antibody Test	100 (97–100)	99.8 (98.8–100)
OraQuick HCV Rapid Antibody Test	100 (97–100)	99.8 (98.8–100)
OraQuick HCV Rapid Antibody Test	98.1 (96.9–99.0)	99.6 (99.2–99.9)
OraQuick HCV Rapid Antibody Test	99.7 (99.9–100)	99.9 (99.5–100)
OraQuick HCV Rapid Antibody Test	99.7 (99–100)	99.9 (99.6–100)
OraQuick HCV Rapid Antibody Test	99.9 (99.3–100)	99.9 (99.5–100)
OraQuick HCV Rapid Antibody Test	99.9 (99.3–100)	99.9 (99.6–100)
Dual Path Platform test	97.8 (96.1–98.7)	99.8 (99–100)
Multiplo Rapid HIV/HCV Antibody Test	88.3 (85.3–90.7)	99.8 (99–100)
OraQuick HCV Rapid Antibody Test	99.3 (98.1–99.7)	99.5 (98.4–99.8)
Dual Path Platform test	91.2 (85.6–94.8)	81.6 (68.6–90)
OraQuick HCV Rapid Antibody Test	94.7 (90.8–97)	92.1 (83.8–96.3)
Dual Path Platform test	92.2 (87.5–95.2)	97.7 (92–99.4)
	94 (90.6–96.2)	97.1 (91.8–99)
Multiplo Rapid HIV/HCV Antibody Test	78.9 (74.6–82.7)	83.3 (71–91.5)
OraQuick HCV Rapid Antibody Test	92.2 (87.5–95.2)	97.2 (90.9–99.3)
	97.4 (94.1–98.9)	98.6 (92.9–99.8)
OraQuick HCV Rapid Antibody Test	93.9 (87.1–97.7)	99.5 (98.1–99.9)

tion of all studies and deletion of duplicates, we did a preliminary screening of 10 026 articles based on title and abstract. Of these, 52 were considered for full-text review, of which 12 were included in the study. A hand-search of the bibliographies of included articles yielded 7 more articles, for a total of 19 eligible studies.

Data Extraction and Quality Assessment

Two reviewers independently abstracted data using a prepiloted form and critiqued the quality of the studies, with a third reviewer contacted in case of disagreement. We consulted authors when the 2×2 tables were missing data or the study method was unclear.

We extracted data on the characteristics of the study population, including sampling strategies (purposive or consecutive random sampling), risk for hepatitis C as defined by the authors, sample size, inclusion and exclusion criteria, specimen tested (oral fluid, whole blood, serum, or plasma), whether the test was an RDT or a POCT, reference standard, funding sources, and any reported conflicts of interest. We also extracted raw data—numbers of true-positive, true-negative, false-positive, and false-negative results—and items necessary to assess study quality.

Tests that were easy to use (such as those with no need for sample processing), were robust at higher temperatures, and had a long shelf life (>6 months) were considered POCTs. We defined RDTs as those requiring sample processing and refrigerators for storage. Both RDTs and POCTs had to be performed in less than 30 minutes.

We classified reference standards as perfect or imperfect on the basis of CDC recommendations; EIA and recombinant immunoblot assay or EIA and nucleic acid testing were classified as perfect, whereas all other algorithms (such as EIA alone) were classified as imperfect.

We assessed the methodological and reporting quality of studies by using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool (14) and the STARD (Standards for the Reporting of Diagnostic Accuracy Studies) checklists (15), giving equal weight to all items. The QUADAS-2 checklist assessed potential bias in studies with respect to patient selection, index test, reference test, and patient flow (14). In assessing the quality of studies, we also focused on reference standards used and any reported conflict of interest.

Data Synthesis and Analysis

We did all statistical analyses in Intercooled Stata, version 9 (StataCorp, College Station, Texas).

For our meta-analysis of estimates of accuracy, we used the bivariate model, which assumes that the measures of sensitivity and specificity from a study are negatively correlated and that the logit transformations of sensitivity and specificity have a bivariate normal distribution (16). We calculated the sensitivity, specificity, positive LR, negative LR, and DOR. The **Appendix** (available at www.annals.org) defines the diagnostic accuracy measures used in this study. The LRs of a test inform the pretest probability of disease and provide a posttest probability. A positive LR higher than 5 and a negative LR less than 0.2 provide strong diagnostic evidence (17).

Before meta-analysis, we stratified studies into 4 subgroups based on the specimen tested and whether the test was a POCT or an RDT. Because data were insufficient for all tests and all of the tests under investigation were antibody-based, we stratified evidence into 4 subgroups on the same basis: POCTs of serum or plasma, POCTs of whole blood or finger-stick blood, RDTs of serum or plasma, and POCTs of oral fluid.

Role of Funding Source

Our study was funded by the Canadian Institutes of Health Research. The funding source had no role in the conception, design, or conduct of the review. The investi-

gators independently designed, executed, and conducted the review and wrote the manuscript.

RESULTS

Characteristics of Studies

Table 1 (18–32) shows the study characteristics. A total of 19 studies were reviewed, of which only 18 could be meta-analyzed. One study (18), which reported a sensitivity of 0% and specificity of 100% with no reasonable explanations, was excluded from the quantitative analysis.

The 18 pooled studies contributed 38 data points (**Appendix Table 1**, available at www.annals.org). Some studies contributed additional data points by comparing the accuracy of 2 or more tests (19, 20), reporting data from multiple study sites (20), or reporting the accuracy of a test in more than 1 type of specimen (20–22).

Of the 19 total studies, 11 (58%) were conducted in developing settings (5, 6, 18, 23–30). Sample sizes ranged from 60 to 2754 persons. **Table 2** lists the index test characteristics.

Study Quality

The quality of study reporting ranged from poor to good (STARD scores from 8 to 20 of 25) (**Table 3**). Twelve studies (63%) (5–7, 11, 19–22, 27–29, 31) were cross-sectional, and the remainder were case–control studies (assessed by the QUADAS-2 checklist). Only 3 studies (16%) (7, 29, 32) reported blinding of test readers, whereas 1 explicitly reported lack of blinding (22). Nine studies (47%) (11, 19–25, 32) used a CDC-recommended reference standard (EIA and recombinant immunoblot assay), whereas the remaining 10 studies used only 1 test (EIA, microenzyme immunoassay, or chemiluminescent immunoassay) as the reference standard. All of the research groups administered the same reference test to all patients, thus avoiding partial or differential verification bias.

Four studies (21%) (11, 21, 30, 32) reported a financial relationship with or received funding from industry, 6 (32%) (5, 7, 18, 22, 26, 27) omitted disclosure of conflicts of interest, 1 (28) explicitly declared no conflict of interest, 3 (23–25) were independent evaluations from the World Health Organization, and 5 (6, 19, 20, 29, 31) reported receiving tests in kind from manufacturers but no conflict of interest.

Results Pooled by Subgroup

Table 1 reports estimates of sensitivity and specificity from each study. **Appendix Table 1** reports the raw data. **Table 4** lists pooled estimates for each subgroup.

POCTs of Serum or Plasma

Tests investigated in this subgroup were Genedia HCV Rapid LF, SD Bioline HCV, Hexagon HCV, OraQuick HCV Rapid Antibody Test, Dual Path Platform test, Multiplo Rapid HIV/HCV Antibody Test, and SM-HCV Rapid Test. Among 11 data points, the pooled sensitivity was 98.9% (95% CI, 96.8% to 99.6%) and the pooled specificity was 99.7% (CI, 99.3% to 99.9%). The positive LR (342.7 [CI, 140.5 to 836.4]), negative LR (0.01 [CI, 0.004 to 0.03]), and DOR (33 800.4 [CI, 5862.3 to 194 885.2]) were similar to those for POCTs of whole blood or finger-stick blood.

POCTs of Whole Blood or Finger-Stick Blood

Tests in this subgroup were Anti-HCV Ab rapid test, Bioeasy HCV Test, SM-HCV Rapid Test, Dual Path Platform test, Multiplo Rapid HIV/HCV Antibody Test, and OraQuick HCV Rapid Antibody Test. Among 10 data points, the pooled sensitivity was 98.9% (CI, 94.5% to 99.8%) and the pooled specificity was 99.5% (CI, 97.5% to 99.9%). The positive LR was 208.7 (CI, 38.3 to 1136.6), the negative LR was 0.01 (CI, 0.002 to 0.06), and the DOR was 19 438.6 (CI, 858.4 to 440 169.7).

RDTs of Serum or Plasma

Tests in this subgroup were Advanced Quality One Step HCV Test, SeroCard HCV, Diagnos HCV Bi-Dot, HCV Tri-Dot, and HCV Spot. Among 10 data points, the pooled sensitivity was 98.4% (CI, 88.9% to 99.8%) and the pooled specificity was 98.6% (CI, 94.9% to 99.6%). This subgroup had a high DOR (4135.2 [CI, 517.5 to 330 421.1]) and positive LR (68.4 [CI, 19.1 to 246.2]), and a low negative LR (0.02 [CI, 0.002 to 0.12]).

POCTs of Oral Fluid

Tests in this subgroup were OraQuick HCV Rapid Antibody Test and Dual Path Platform test. Among 7 data points, the pooled sensitivity was 97.1% (CI, 94.7% to 98.4%) and the pooled specificity was 98.2% (CI, 92.2% to 99.6%). The positive LR (54.8 [CI, 11.9 to 251.4]), negative LR (0.03 [CI, 0.01 to 0.06]), and DOR (1870.9 [CI, 263.9 to 13 263.6]), indicated high accuracy for oral specimens.

DISCUSSION

Our meta-analysis suggests that POCTs of blood (serum, plasma, or whole blood) have the highest accuracy, followed by RDTs of serum or plasma and then by POCTs of oral fluids. However, all subgroups showed high positive LRs, low negative LRs, and high DORs; the best LRs and DORs were reported for POCTs of serum and plasma, followed by those of whole blood, RDTs of serum and plasma, and POCTs of oral fluids. When sensitivity and specificity are similar, interpretation of the LR and DOR of the test influences conclusive changes from pretest to posttest probability of hepatitis C infection (17). Given the convenience of POCTs and their rapid turnaround time, these results show great potential for expanded first-line screening for hepatitis C infection and demonstrate the utility of blood-based singleton POCTs and of multiplex

Table 2. **Test Specifications**

Test (Reference)	Manufacturer	Time to Result, *min*	Antigen Used	Specimen Required for Testing	Volume Required for Testing	Storage Temperature, ° *C*	Shelf Life, *mo*	Test Type
OraQuick HCV Rapid Antibody Test (19)	OraSure Technologies, Bethlehem, Pennsylvania	20–40	Core, NS3, NS4	Oral fluid, whole blood, serum, plasma	1 drop	2–30	NA	POCT
Dual Path Platform test (19)	Chembio Diagnostic Systems, Medford, New York	15–30	Core, NS3, NS4, NS5	Oral fluid, whole blood, serum, plasma	NA	NA	24	POCT
Multiplo Rapid HIV/HCV Antibody Test (19)	MedMira, Halifax, Nova Scotia, Canada	3	Core, NS3	Whole blood, serum, plasma	1 drop	2–30	NA	POCT
SD Bioline HCV (25)	Standard Diagnostics, Yongin, Korea	5–20	Core, NS3, NS4, NS5	Whole blood, serum, plasma	10–20 μL	2–30	18	POCT
Hexagon HCV (26)	Human Diagnostics Worldwide, Wiesbaden, Germany	5–20	Core, NS3, NS4, NS5	Whole blood, serum, plasma	NA	15–30	NA	POCT
Genedia HCV Rapid LF (24)	Green Cross Medical Science, Yongin, Korea	20–30	Core, NS3, NS4, NS5	Whole blood, serum, plasma	10–20 μL	2–30	18	POCT
Anti-HCV Ab rapid test (32)	Tema Ricerca, Bologna, Italy	3	NA	Whole blood	1 drop	NA	NA	POCT
SM-HCV Rapid Test (30)	SERO-Med Labor Spezialitaten, Pollenfeld, Germany	3	Core, NS3, NS4	Whole blood, serum	30–40 μL	2–8; after opening, should be stored at <30	NA	POCT
Bioeasy HCV Test (6)	Bioeasy Diagnóstica, Belo Horizonte, Minas Gerais, Brazil	10	Core, NS3, NS4, NS5	Whole blood, serum, plasma	10 μL	2–30	NA	POCT
Advanced Quality One Step HCV Test (23)	Bionike, San Francisco, California	6	NA	Serum, plasma	4 μL	2–30	18	RDT
SeroCard HCV (23)	Trinity Biotech, Bray, Ireland	19		Serum, plasma, whole blood	80 μL	2–8	16	RDT
Diagnos HCV Bi-Dot (23)	J. Mitra, New Delhi, India	3	Core, NS3, NS4, NS5	Serum, plasma	NA	2–8	15	RDT
HCV Tri-Dot (23)	J. Mitra, New Delhi, India	5	Core, NS3, NS4, NS5	Serum, plasma	45 μL	2–8	12	RDT
HCV Spot (23)	MP Biomedicals, Santa Ana, California	10	NA	Serum, plasma	45 μL	2–25	6–8	RDT

NA = not available; POCT = point-of-care test; RDT = rapid diagnostic test.

POCTs designed to provide integrated HIV and HCV screening of at-risk populations.

The high positive and low negative LRs found in each subgroup, especially those that tested serum, plasma, and whole blood, also imply that RDTs and POCTs can meaningfully inform the posttest probability of infection. The pooled accuracies of these tests have implications for their use in clinical and nonclinical outreach settings. For example, POCTs of oral fluids showed a slightly higher false-negative rate than POCTs of whole blood or finger-stick blood, which could be due to the lower concentration of antibodies or the weaker binding in oral fluid than in blood samples (33). The false-negative rate is of particular concern in high-risk groups, in which a high rate is more likely to lead to an undetected infection. In such scenarios, timely confirmatory testing could resolve a preliminary screening result. However, the convenience and rapid turnaround time of oral fluid–based POCTs, their ease of use, and patient preference for noninvasive sample collection may compensate for their slightly lower sensitivity. In sum, these tests could be safely integrated into expanded screening initiatives as first-line screening tests by using downstream blood-based algorithms to detect infections missed by oral fluid tests.

The POCTs that showed promise in individual studies were the Anti-HCV Ab rapid test, SM-HCV Rapid Test, OraQuick HCV Rapid Antibody Test, and Dual Path Platform test. The RDT HCV Tri-Dot also had high accuracy (**Table 1**).

Our meta-analysis is subject to the detection, spectrum, and sampling biases of the original studies. Of the 6 included case–control studies, only 3 (7, 29, 32) explicitly mentioned blinded reading of index test results, suggesting possible detection bias in the remaining studies. This could artificially inflate sensitivity and specificity estimates of the index test. The use of a case–control design also entails an extreme comparison of index tests in healthy and sick persons, suggesting possible spectrum bias.

Our results should be interpreted with some cautions. First, reference standards were found to influence the accuracy of POCTs (19, 20). When the CDC-recommended ideal reference standard was used, sensitivity and specificity were higher than when an imperfect EIA reference standard was used (20). Only 9 of the included studies (11,

Table 3. **QUADAS-2 Assessments and STARD Scores**

Study, Year (Reference)	Risk of Bias				Applicability Concerns			STARD Score*	Comments
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard		
Poovorawan et al, 1994 (31)	Low	Unclear	High	Low	Low	Low	Low	12	–
Mvere et al, 1996 (29)	Low	Low	High	Low	Low	Low	Low	11	–
Montebugnoli et al, 1999 (32)	High	Low	Low	Low	Low	Low	Low	12	–
Kaur et al, 2000 (28)	Low	Unclear	High	Low	Low	Low	Low	11	–
Yuen et al, 2001 (30)	High	High	Low	Low	Low	Low	Low	11	–
WHO, 2001 (23)	High	Unclear	Low	Low	Low	Low	Low	NA	Draft report, so STARD assessment was not possible
WHO, 2001 (24)	High	Unclear	Low	Low	Low	Low	Low	NA	Draft report, so STARD assessment was not possible
WHO, 2002 (25)	High	Unclear	Low	Low	Low	Low	Low	NA	Draft report, so STARD assessment was not possible
Hui et al, 2002 (7)	Low	Low	High	Low	Low	Low	Low	17	–
Daniel et al, 2005 (27)	Low	Unclear	Low	Low	Low	Low	Low	10	–
Njouom et al, 2006 (26)	High	High	High	Low	Low	Low	Low	10	–
Nyirenda et al, 2008 (5)	Low	Low	High	Low	Low	Low	Low	15	–
Torane and Shastri, 2008 (18)	NA	NA	NA	NA	NA	NA	NA	NA	Letter to the Editor; insufficient study details provided
Ivantes et al, 2010 (6)	Low	Low	High	Low	Low	Low	Low	15	–
Lee et al, 2010 (21)	High	Unclear	Low	Low	Low	Low	Low	8	Financial relationship reported with OraSure Technologies (Bethlehem, Pennsylvania)
Drobnik et al, 2011 (11)	Low	Low	Low	Unclear	Low	Low	Low	13	–
Lee et al, 2011 (22)	Low	High	Low	Low	Low	Low	Low	20	–
Smith et al, 2011 (19)	Low	Unclear	Low	Low	Low	Low	Low	19	–
Smith et al, 2011 (20)	Low	Unclear	Low	Low	Low	Low	Low	17	–

NA = not available; QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2; STARD = Standards for the Reporting of Diagnostic Accuracy Studies; WHO = World Health Organization.
* Of 25 total items.

19–25, 32) used the CDC-recommended reference standard to ascertain true disease status. Misclassification by reference standards is known to influence the measured sensitivity and specificity of index tests (34). Accuracy estimates from studies that used imperfect reference standards to ascertain true disease status may have been artificially inflated or lowered because of misclassification by the reference standard. A standardization of reference standards is needed for future diagnostic accuracy studies.

Second, important factors to consider when interpreting the test results are co-infection status (for example, with HIV or hepatitis B), immune response, and their influence on diagnostic accuracy. In a CDC study (19), HIV seropositivity was found to have a statistically significant influence on the rate of false-positive results, with an adjusted odds ratio of 11 (CI, 2.53 to 48.17) reported for the Dual Path Platform test and an adjusted odds ratio of 3.95 (CI, 1.53 to 10.24) reported for the Multiplo Rapid HIV/HCV Antibody Test. This illustrates that both HIV co-infection and initiation of HIV treatment could influence the immune response, thus altering test accuracy. However, only 2 CDC-based implementation studies considered this issue (19, 20).

Because of the limited data on this issue, future implementation research studies stratified by co-infection (such as with HIV, hepatitis B, or syphilis) are needed to resolve the issue of accuracy in the presence of co-infection. The influence of co-infection (naive or treated) on diagnostic accuracy will be especially relevant as multiplex POCT as-

Table 4. **Results of Meta-analysis, by Specimen Subgroup**

Subgroup	Pooled Sensitivity (95% CI), %	Pooled Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)	DOR (95% CI)
Oral fluid POCTs	97.1 (94.7–98.4)	98.2 (92.2–99.6)	54.8 (11.9–251.4)	0.03 (0.01–0.06)	1870.9 (263.9–13 263.6)
Whole blood and finger-stick POCTs	98.9 (94.5–99.8)	99.5 (97.5–99.9)	208.7 (38.3–1136.6)	0.01 (0.002–0.06)	19 438.6 (858.4–440 169.7)
Serum and plasma POCTs	98.9 (96.8–99.6)	99.7 (99.3–99.9)	342.7 (140.5–836.4)	0.01 (0.004–0.03)	33 800.4 (5862.3–194 885.2)
Serum and plasma RDTs	98.4 (88.9–99.8)	98.6 (94.9–99.6)	68.4 (19.1–246.2)	0.02 (0.002–0.12)	4135.2 (517.5–33 042.1)

DOR = diagnostic odds ratio; LR = likelihood ratio; POCT = point-of-care test; RDT = rapid diagnostic test.

says that integrate tests for HIV, hepatitis B, and HCV are or will be marketed for point-of-care use and as integrated HIV–sexually transmitted illness screening becomes the global standard of care in the near future.

Third, the effect of HCV genotype (genotypes 1 to 6) on diagnostic accuracy is worth further consideration. Genotype explorations were mentioned in a few studies as a potential influence on diagnostic accuracy, but their effect is unknown.

Fourth, at least 4 studies (11, 21, 30, 32) reported receiving industry funding. When comparisons were possible, these studies reported more optimistic estimates of accuracy than did independently funded studies. Although the enforcement of stricter quality standards and the use of particular study designs (such as case–control), select study populations, and the best reference standards may have played a role, these findings need to be independently replicated by non–industry-funded studies.

Fifth, the index tests included in this meta-analysis detected antibodies to HCV and therefore could not detect infection within about 3 months or differentiate between acute and chronic infections (1). If clinical suspicion of a positive POCT or RDT result is high, further testing would be required. In the case of a possible false-negative result, further screening with another RDT or conventional laboratory-based tests could be considered, depending on available resources. For cases with a preliminary positive result, polymerase chain reaction testing is necessary to identify active infection, as is assessment of liver enzyme levels (35). More research is needed to determine how to effectively link screening with further linkages and follow-up, especially in hard-to-reach populations and low-resource settings.

Finally, evidence on POCTs will be of greater use to policymakers and guideline developers if outcomes beyond accuracy are documented. These include patient-centered outcomes and operational research outcomes, such as acceptability, preference, feasibility, impact, uptake, time to initiation of confirmatory testing, referrals, and treatment linkages. Accuracy was the sole focus in these studies, so pertinent downstream issues remain unexplored. Similarly, future research on the cost-effectiveness of RDTs or POCTs in different settings, populations, and contexts is warranted to make informed decisions on these tests and on testing strategies.

To our knowledge, this is the first systematic review to synthesize global evidence on POCTs and RDTs that screen for hepatitis C. We used QUADAS-2 and STARD to assess quality and followed PRISMA guidelines in reporting results. Despite our wide search strategy, we could have missed studies in this rapidly growing field and our review may also be subject to publication bias. Although sensitivity analyses that focused on the accuracy of individual tests would have been useful, they could not be done because of a lack of adequate data by test types and the presence of zero cells that precluded pooling of data. The scarcity of studies and data on some tests may also imply that they are not in use anymore.

Both RDTs and POCTs offer many advantages: a fast turnaround time (27, 34), low psychological stress, declaration of results at the point of care with the potential for affecting clinical management, early detection of undiagnosed cases of hepatitis C (21), relatively easier identification of infection by paramedics or other health professionals (27, 30, 32), and high intra- and interobserver agreement or concordance (19). These advantages could be optimized by integrating them into usual care pathways in outpatient clinics, emergency departments, and public health clinics, as has been done with point-of-care HIV screening assays. Given the lack of global evidence, this review comes closer to independently assessing the role of RDTs and POCTs for widespread use in the field by synthesizing all available data on their accuracy and provides further evidence of the benefit of RDTs and POCTs for other developed countries, such as Canada and the United Kingdom, where their use is not yet approved.

We found POCTs of blood (serum, plasma, or whole blood), RDTs of serum or plasma, and POCTs of oral fluid to be accurate and suitable for screening initiatives. In light of their accuracy and the urgent need to increase hepatitis C screening in marginalized and at-risk populations and in endemic HCV settings, these tests could play a substantial role in expanded global screening initiatives, which would eventually impact the control of HCV infection at the population level.

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Appendix: Definitions of Relevant Accuracy Estimates

Sensitivity refers to the proportion of people with disease who have a positive test result (36):

$$\text{Sensitivity} = \frac{TP}{(TP + FN)}$$

Specificity refers to the proportion of people without disease who have a negative test result (36):

$$\text{Specificity} = \frac{TN}{(TN + FP)}$$

The *positive LR* is the ratio of the likelihood of a positive test result when the disease is present to the likelihood when it is absent (37):

$$+\text{LR} = \left(\frac{TP}{(TP + FN)}\right) \Big/ \left(1 - \frac{TN}{(TN + FP)}\right)$$

$$= \frac{Sensitivity}{(1 - Specificity)}$$

This tells us how much more often a positive test result occurs in those with the condition than in those without.

The *negative LR* is the ratio of the likelihood of a positive test result when the disease is absent to the likelihood when it is present (37):

$$-\text{LR} = \left(1 - \frac{TP}{(TP + FN)}\right) \Big/ \left(\frac{TN}{(TN + FP)}\right)$$

$$= \frac{(1 - Sensitivity)}{Specificity}$$

This tells us how much more often a negative test result occurs in those with the condition than in those without.

The *diagnostic odds ratio* (DOR) is the ratio of the odds of a positive result when the disease is present to the odds of a positive result when the disease is absent (38):

$$\text{DOR} = \frac{TP}{FP} \Big/ \frac{FN}{TN} = \frac{+LR}{-LR}$$

Appendix Table 2 defines true- and false-positive and true- and false-negative results.

Appendix Table 1. Raw Data From Studies Included in the Meta-analysis

Study	Index Test*	Sample Tested	Results, *n*			
			True Positive	False Positive	False Negative	True Negative
Poovorawan et al, 1994 (31)	HCV Spot	Serum	41	11	1	139
Mvere et al, 1996 (29)	HCV Spot	Serum	10	4	1	191
Montebugnoli et al, 1999 (32)	Anti-HCV Ab rapid test	Whole blood	50	1	0	49
Kaur et al, 2000 (28)	Diagnos HCV Bi-Dot	Serum	28	0	4	2719
Yuen et al, 2001 (30)	SM-HCV Rapid Test	Serum	98	0	2	95
WHO, 2001 (23)	Advanced Quality One Step HCV Test	Serum	66	7	2	182
	SeroCard HCV	Serum	67	0	1	189
	HCV Tri-Dot	Serum	68	16	0	173
	HCV Spot	Serum	68	12	0	177
WHO, 2001 (24)	HCV Tri-Dot, 4th Generation	Serum	68	2	0	189
	Genedia HCV Rapid LF	Serum	67	3	1	186
WHO, 2002 (25)	SD Bioline HCV	Serum	64	0	2	189
Hui et al, 2002 (7)	SM-HCV	Whole blood	91	0	18	88
Daniel et al, 2005 (27)	HCV Tri-Dot	Serum	138	24	1	2427
Njouom et al, 2006 (26)	Hexagon HCV	Plasma	100	3	14	44
Nyirenda et al, 2008 (5)	HCV Spot	Serum	2	7	7	186
Ivantes et al, 2010 (6)	Bioeasy HCV Test	Whole blood	30	3	0	38
Lee et al, 2010 (21)	OraQuick HCV Rapid Antibody Test	Oral fluid	121	0	1	449
		Whole blood	122	0	0	450
		Finger-stick blood	122	0	0	450
		Serum	122	1	0	449
		Plasma	122	1	0	449
Lee et al, 2011 (22)	OraQuick HCV Rapid Antibody Test	Oral fluid	739	5	14	1418
		Whole blood	753	2	2	1421
		Finger-stick blood	752	1	2	1421
		Serum	756	1	1	1422
		Plasma	755	2	1	1420
Smith et al, 2011 (19)	Dual Path Platform test	Serum	525	1	12	543
	Multiplo Rapid HIV/HCV Antibody Test	Serum	474	1	63	543
	OraQuick HCV Rapid Antibody Test	Serum	533	3	4	541
Smith et al, 2011 (20)						
New York	Dual Path Platform test	Oral fluid	135	9	13	40
	OraQuick HCV Rapid Antibody Test	Oral fluid	198	6	11	70
Denver	Dual Path Platform test	Oral fluid	177	2	15	85
		Whole blood	265	3	17	100
Dallas	Multiplo Rapid HIV/HCV Antibody Test	Whole blood	303	8	81	40
Seattle	OraQuick HCV Rapid Antibody Test	Oral fluid	177	2	15	70
		Whole blood	188	1	5	71
Drobnik et al, 2011 (11)	OraQuick HCV Rapid Antibody Test	Oral fluid	92	2	6	382

WHO = World Health Organization.
* **Table 2** lists manufacturer information for all tests.

Appendix Table 2. Test Result Interpretation

Index Test Result	Reference Test Result	
	Positive	Negative
Positive	True positive	False positive
Negative	False negative	True negative