Role and Utility of COVID-19 Laboratory Testing in Low-and Middle-Income Countries: A Systematic Review of Diagnostic Test Accuracy Studies

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Abstract

Background

Accurate and affordable laboratory testing is key for timely diagnosis and appropriate management of COVID-19 patients. As such, robust evidence regarding diagnostic accuracy and costs of available tests would inform policy and practice especially in resource-limited settings. We aimed to determine the diagnostic test accuracy, costs and utility of laboratory test strategies for COVID-19 in LMICs.

Methods

This was a multi-staged protocol-driven systematic review conducted in line with PRISMA guidelines for diagnostic test accuracy studies (PRISMA-DTA). We searched for relevant literature in six databases including: PubMed, Google Scholar, MEDLINE, SCOPUS, Web of Science, and the WHO Global Index Medicus. Studies were screened and coded in pairs. We conducted a structured narrative and quantitative synthesis of the results guided by Fryback and Thornbury framework. The primary outcome was COVID-19 diagnostic test accuracy. The results were reported following the PRISMA-DTA.

Results

Thirteen articles were from studies in China and one from Turkey. All studies included used the Real-time polymerase chain reaction test (RT-PCR) as their reference test. 21.4% (n = 3) of articles were determining the diagnostic accuracy of the PCR test. The remaining studies (n = 11) used other COVID-19 tests as the index tests. It is generally observed that the tests were more specific than sensitive pooled sensitivity and specificity was 87.6%, (95% CI: 82.2% – 93%), 98.1% (95% CI: 96.4%-100%) respectively. The Reverse-transcription loop-mediated isothermal amplification (RT-LAMP) tests had the highest sensitivity as compared to RT-PCR, serological and chemiluminescent immunoassays (CLIA). The specificity and sensitivity of the tests were highest when bronchial lavage samples were used and lowest with the use of serum specimens/sample. No study documented cost of the diagnostic test used.

Conclusion

The evidence on COVID-19 testing in LMICs is summarized in this systematic review. The RT-PCR was used as the reference test in all studies. The diagnostic assays' combined sensitivity and specificity were 87.55% and 98.10%, respectively. In the reviewed literature, no study reported on the cost and cost effectiveness of diagnostic tests. Finally, no studies were carried out on the African continent.

Registration:

This review was registered in PROSPERO No. CRD42020209528. And the protocol published here https://bmjopen.bmj.com/content/11/10/e050296

Background

The coronavirus disease (COVID-19) is a pandemic that resulted into serious and significant morbidity and mortality globally. In order to prevent the spread of the disease, early and accurate diagnosis is critical (1). Therefore, proper clinical management and control of this pandemic necessitates prioritizing rapid laboratory testing of appropriate specimens from patients meeting the suspected case definition for COVID-19 and diagnosis (2).

Currently, the gold standard for the diagnosis of SARS-CoV-2 infection involves detection of viral nucleic acid using nucleic acid amplification tests (NAATs) such as the reverse transcription polymerase chain reaction (RT-PCR)(3). Nucleic acid amplification assays target regions on the SARS-CoV-2 genome particularly the E, RdRP, N and S genes (3). The RT-PCR assay is characterized by rapid detection, high sensitivity, and specificity hence recommended for diagnosis of early COVID-19 infections (4). However, the RT-PCR assay is complex, time-consuming (long turn-around time) and associated with risk of eliciting false-negative and false-positive results because it is easily affected by factors such as collection time, sample type, and nature of sample preservation (1, 5, 6). Each PCR test may cost hundreds of dollars and requires the use of sophisticated equipment, expensive reagents and highly skilled labor (1, 7) all of which constitute a potential barrier to majority of the population. Furthermore, this method is unable to meet the principles of early detection, early isolation, and early treatment hence inauspicious to the prevention and control of the epidemic (5).

Besides the NAATs, immunoassays have been developed as supplemental tools for rapid detection of antibodies (IgM and IgG) against COVID-19 or SARS-CoV-2 antigens (using rapid antigen tests) in biological samples like nasopharyngeal secretions (1, 8–11). The serological immunoassays detect antibodies to SARS-CoV-2 and these may include the enzyme-linked immunosorbent assays (ELISAs), chemiluminescent immunoassays (CLIAs) and lateral flow immunoassays (LFIAs) (2, 12). Serological tests are indirect measures of the infection and have proven to be useful in confirming past COVID-19 infections (2, 8). They therefore aid in investigating an ongoing outbreak, retrospective assessment of the attack rate or extent of an outbreak (2). Rapid antigen tests such as lateral flow immunoassays that detect the presence of SARS-CoV-2 viral proteins (antigens) in respiratory tract specimens are also currently used in diagnosis of COVID (3, 13). They are based on immunochromatography, which employs antibodies spotted onto nitrocellulose membranes that interact with specific antigens from the patient sample (1). Immunoassays are less costly, more accessible to patients and have a short turnaround time compared to the RT-PCR assays (1, 2). Therefore, they are very important for real-time patient management and infection control decisions. However, they are likely to suffer from poor sensitivity in early infection mostly due to the low infectious burden or sampling variability (8). Existing evidence also highlights inconsistencies in the diagnostic accuracy of these assays. More so, most of the evidence on diagnostic accuracy is largely from developed countries, where the Covid-19 curves

are flattening. Low- and middle- income settings are now the epi-center of the pandemic, yet, evidence for diagnostic accuracy for existing tests is largely lacking. This review addresses this knowledge gap on diagnostic accuracy for available assays to further strengthen the role of testing in the COVID-19 response in these settings.

Rationale

A recent systematic review and meta-analysis of the diagnostic accuracy studies from China, Denmark, Italy, Japan, Spain, Sweden, United Kingdom, United States & Germany, reported a pooled sensitivity of ELISA measuring IgG or IgM was 84.3%, 66.0% for lateral flow immunoassays (LFIAs) and 97.8% for the chemiluminescent immunoassays (CLIAs), (14). In the same study, the pooled specificities ranged from 96.6–99.7%, (14). In a similar meta-analysis of studies from North and South America, Europe, and China, the average sensitivity for rapid antigen tests was 56.2% and average specificity 99.5% (15). In this study, the average sensitivity of rapid immunoassays was 95.2% and specificity of 98.9 (15). Basing on the findings from these review studies, the diagnostic accuracy of these assays varies substantially and remains questionable. Also, these reviews may not be used to depict the diagnostic accuracy of the assays in low- and middle-income countries (LMICs), that this review explores. Hence the need for evidence from studies from LMICs to inform context specific policy and practice.

Review Question

The specific review question is “What is the effectiveness of laboratory testing strategy for COVID-19 in hospitals and community populations in LMICs?”, that is guided by the following elements of PICOST (Table 1).

Table 1
The PICOST model for the review question

PICOST element	Description
Population/Setting	Adults (18 years and above) in low- and middle – income countries (LMIC) settings as defined by the World Bank
Intervention/ Exposure	New index laboratory test; peripheral laboratory testing strategy or mass testing (pooling)
Comparator	Reference tests for COVID-19 (gold standard) and the current standard of testing strategy (centralized and individualized)
Outcome	Types of tests available; diagnostic test accuracy (sensitivity, specificity, predictive values); costs and cost–effectiveness of tests; relative risk of testing a strategy
Study designs	Diagnostic accuracy studies of observational designs (cross sectional, case control and cohort studies), and diagnostic strategy studies of experimental designs or randomized trials on COVID-19 laboratory testing
Timing of outcome assessment	72 hours turn–around–time (TAT) from testing specimen

Methods

This evidence synthesis was protocol driven. This protocol was registered in PROPSERO (https://www.crd.york.ac.uk/prospero/) registration number CRD42020209528 and was published in a peer reviewed journal (https://bmjopen.bmj.com/content/11/10/e050296) after further development following PRISMA-DTA statement (16). This review therefore seeks to generate evidence-based recommendations that support, effectiveness of testing strategies and the utility of testing in control and management of COVID-19 in LMICs using the Fryback and Thornbury model (17) which proposed a comprehensive assessment of efficacy of a diagnostic technique at six levels. This involves determining the technical quality (does the test measure what it purports to measure), diagnostic accuracy (sensitivity and specificity of test), diagnostic thinking efficacy (does the test help clinicians come to a diagnosis), therapeutic efficacy (does it aid in planning treatment), do patients benefit from use of the test and its societal efficacy (cost–benefit and cost-effectiveness) (18).

Eligibility & Selection of Studies

We included studies if they were published in peer reviewed journals from January 2020 to date; were about polymerase chain reaction (PCR) assay tests for COVID-19; rapid point of care diagnostic tests; studies conducted on adults (18 years and above) in LMIC settings; were observational designs (cross sectional, case control and cohort studies), systematic reviews and randomized controlled trials on COVID-19 laboratory testing.

We excluded studies about index COVID-19 tests without a reference standard; clinical COVID-19 diagnosis alone without verification with any laboratory test; predictive or prognostic or diagnostic modeling studies on COVID-19 testing; manufacturers brochures on COVID-19 testing; studies in children < 18 years as they were an unlikely source of transmission or COVID-19 laboratory tests not recommended by the World Health Organization (WHO).

Data Sources

We performed article search was in the following databases; PubMed, Google Scholar, MEDLINE, SCOPUS, Web of Science and the WHO Global Index Medicus. Additional targeted searches were conducted in websites of organizations championing COVID-19 management for grey literature including but not limited to manufacturers of COVID-19 laboratory tests, centers for disease control and prevention (CDC) in Africa, China, Europe and the USA; World Health Organization (WHO); specialized research institutions in Africa such as the Uganda Virus Research Institute (UVRI) and Kenya Medical Research Institute

(KEMRI); and departments of health such as the Ministry of Health Uganda, South Africa (southern Africa), Nigeria (west Africa), Rwanda and Kenya (eastern Africa). A list of key experts in diagnosis and testing was developed and contacted to get more information on this subject matter.

Electronic Search Strategy

The electronic search strategy was developed by our information science specialist (AKK). This search strategy was piloted in PubMed, to test for precision of appropriate articles retrieved. We identified additional relevant articles by manually searching reference lists of selected articles, consulting experts in this field and searching targeted libraries and websites such as Cochrane Collaboration Library and COVID-19 Evidence Network to support Decision-making (COVID-END).

Search Terms

We used the following key terms to conduct initial searchers electronically: COVID-19, 2019-nCOV, novel corona virus disease, 'Wuhan pneumonia', and 'severe acute respiratory syndrome' related corona virus-2, SARS-CoV-2, corona virus disease-19. We expanded these terms using Mesh options in PubMed to identify the tests; testing, tests, diagnosis, diagnostics, COVID-19 'point of care tests', Wuhan corona virus tests, laboratory test, corona virus tests and corona virus testing. The search was limited to low-middle income countries and the search terms were combined using Boolean operators (AND, OR, NOT) in appropriate electronic search engines (19). The search string from PubMed was adapted to the syntax of other targeted databases for this review (Additional file 1).

Data Management, Screening & Selection

EndNote software vX9 (Camelot UK Bidco Ltd /Clarivate Analytics 70 St. Mary Axe, London, United Kingdom) was used for the initial management of references for the search results. The retrieved articles were exported to Endnote and duplicates were removed. The studies were then screened in duplicate following *a priori* criteria for eligibility. The screening was performed in Excel spreadsheet version 2019 *(Microsoft Corporation, Redmond, Washington, Seattle)* independently by two review team pairs (KOO, EK, LN or EN), any disagreements between the reviewers was resolved by consensus and further disagreements referred to a senior reviewer (EAO or OM).

Data Abstraction & Coding

The data abstraction form was developed in Excel spreadsheet. The coding process was performed independently by four research team members (KOO, EK, LN, EN) whose results were reconciled, and disagreements were resolved through discussion and later independent senior reviewers (EAO, OM) validated their results for quality control and assurance to ensure completeness and correctness. The following data was extracted from the articles; author, year of publication, author affiliation, study designs, funding source and other PICOST items in a table format as shown in Table 1. The outcome data items were types of tests available; diagnostic test accuracy (sensitivity, specificity, predictive values); costs and cost–effectiveness of tests; relative risk of testing strategy.

Outcomes

The primary outcome is the diagnostic test accuracy (sensitivity and specificity) of COVID-19 laboratory test methods in LMICs. The secondary outcomes were the types of COVID-19 tests that are available in low- and middle-income countries; effect (relative risk) of the diagnostic testing strategy; cost and cost-effectiveness (incremental cost effectiveness ratio) of the various COVID-19 testing algorithms.

Framework for Review Synthesis

We used the Fryback and Thornbury framework (17) to establish diagnostic test efficacy focusing on three levels. These were the "technical efficacy", "diagnostic accuracy efficacy" and "societal efficacy". This six-tiered model is a continuum for diagnostic test efficacy and was used to assess the effectiveness of laboratory testing strategy for COVID-19 among hospital and community populations in LMICs. The other three levels including; "diagnostic thinking efficacy", "therapeutic efficacy" and "patient outcome efficacy" were less applicable in this review.

Briefly, the three levels of our interest were: (a) technical efficacy, which is concerned with physical parameters describing the technical quality of a diagnostic test derived under optimal laboratory conditions and are prerequisites for consideration of efficacy at all subsequent levels. These included the following; turnaround time, type of the sample and diagnostic test algorithm i.e., single test or series of tests; (b) diagnostic accuracy efficacy is characterized by the yield of abnormal or normal diagnoses in a case series. Diagnostic test accuracy was measured as a percentage of the correct diagnoses in the case series, positive and negative predictive values and sensitivity and specificity of a given COVID-19 laboratory diagnostic test; (c) societal efficacy went beyond the individual risk and benefit of a given COVID-19 test and denoted the cost borne by a society as whole for the diagnostic test to be acceptable for use regardless of the efficacy of the test on individual patient application at any other level.

Risk of Bias Assessment

Four reviewers (EN, KOO, LN, EK) independently evaluated the methodological quality of studies using the quality assessment of diagnostic accuracy studies approach (QUADAS-2 tool) (20). Bias was assessed by making judgments (high, low and unclear) on individual elements from five domains (selection bias,

attrition bias, performance bias, reporting bias, detection bias and other biases i.e., conflict of interest). Any disagreements were resolved through discussion and involvement of a senior reviewer (MO or EO).

Assessment of Heterogeneity

To assess the level of statistical heterogeneity in the articles, I^2 statistic was used(22). The I^2 statistic would indicate percentage (%) heterogeneity that can be attributed to between-study variance. Interpretation: I^2 = 25% (low), I^2 = 50% (moderate), I^2 = 75% (high). Sub-group analysis was done on articles with low and moderate heterogeneity.

Data Synthesis

The synthesis was in form of summary of findings tables, simple graphs and forest plots as applicable using a STATA v16. The Fryback and Thornbury framework was used to guide this synthesis (21). First, a structured narrative synthesis of the results was conducted. This was used to describe the types of data available including tests and the study designs. Secondly, the quantitative synthesis was outcome based considering the primary outcome; diagnostic test accuracy of COVID-19 laboratory tests and secondary outcomes: costs & type of tests. We used mixed effects model the Duckworth–Lewis–Stern method (DLS) to compute the overall target score for the accuracy. Reporting of these findings was in line with the PRISMA-DTA statement (16).

Table 2. Summary of the main findings from the included studies

Article	*Country*	*Design*	*Details of test*	*Sample size*	*Matrix used*	*Manufacturer Ss& Sp*	*Positive PCR*	*Positive POC*	*Negative PCR*	*Negativ POC*
Lin, C, 2020	China	Cross-sectional	RT-PCR (Cepheid Gene xpert)	52	Sputum and throat swabs	Ss=95 Sp=100	Sputum 40, Throat swabs 23	NR	Sputum 12, Throat swabs 29	NR
Sarıgul,2020	Turkey	Cross-sectional	Two RT-PCR kits; i.e the Bio-Speddy kit and Diagnovital	96	Oropharyngeal /nasopharyngeal swab	Bio-Speddy Ss=98, Sp=100	68	NR	28	NR
Jiang, M, 2020	China	Cross-sectional	Rapid RT-LAMP assay	260	sputum, swabs and tears		NR	NR	NR	NR
Liu, R, 2020	China	Cross-sectional	Direct chemiluminescence technique	133	Blood Serum		91	IgM=105, IgG=129	42	IgM=28 IgG=4
Liu, X, 2020	China	Cross-sectional	Quantum dot immunofluorescent IgG and IgM kits	32	Blood serum	Ss=90 Sp=99	NR	IgM=20	NR	IgM=12
Li, Y, 2020	China	Cross-sectional	Real time RT-PCR	610	Pharyngeal swab		241		369	
Li, Z, 2020	China	Cross-sectional	IgG-IgM combined antibody test lateral flow immune assay	525	Whole blood, serum, plasma	NR	397	352	128	116
Yan, C, 2020	China	cross-sectional	A Loop lamp RNA amplification kit (Eiken Chemical Co., Ltd., Tokyo, Japan	130	swabs and bronchoalveolar lavage fluid	Ss=90 Sp=100	58	58	72	72
Xiang, F, 2020	China	Case-control	ELISA (IgG & IgM)	169	serum, nasopharyngeal and/or oropharyngeal swab		NR	IgM=72 IgG=75	NR	IgM=78 IgG=75
Lu, R et al, 2020	China	cross-sectional	real-time fluorescent and visual RT-LAMP assays	56	throat swabs		34	34	18	18
Jin, Y, 2020	China	Case-control	chemiluminescence immunoassay (CLIA)	76	Serum		NR	IgG=27, IgM=13	NR	IgG=3 IgM=3
Lou, B, 2020	China	Case-control	enzyme-linked immunosorbent assays), colloidal-gold lateral-flow immunoassays (CLFIA) and chemiluminescence microparticle immunoassays	380	plasma and sputum		NR	IgG=27, IgM=13, CLFIA IgM=69, IgA=77, ELISA IgM=74, IgG=71, IgA=78 LFIA IgM=71, IgG=69, IgAb=78 combined IgM=75, IgG=75, IgAb=79	NR	IgG=3 IgM=3 CLFIA IgM=29 IgA=29 ELISA IgM=30 IgG=10 IgAb=3 LFIA IgM=20 IgG=20 IgAb= 199 combin IgM=20 IgG=99, IgAb= 197

Chen, L, 2020	China	Cross-sectional	chemiluminescence immunoassay analyzer (Shenzhen Yahuilong Biotechnology Co. Ltd.)	103	nasopharyngeal swab;		NR	(63)85.9%	NR	2
Qian, C, 2020	China	Case-control	IgM & IgG chemiluminescence immunoassay (CLIA)	2113	serum	Ss=75 Sp=100	NR	NR	NR	NR
Weihua Yang, 2020	China	RCT	Loopamp reverse transcription nucleic acid amplification kit (Eiken China Co., Ltd., Shanghai, China)	208	Throat swabs	Ss=100%	17	17	191	191
Lui Wanbing 2020	China	Case control	rS-based ELISA kit (Hotgen, Beijing, China) and rN-based ELISA kit (Lizhu, Zhuhai, China) for IgM detection, ELISA plates	314	Serum	NR	214	rS-based ELISA kit: IgM=165 IgG=159 IgM and or IgG=176 rN-based ELISA kit: IgM=150; IgG=146; IgM and or IgG=172	NR	NR

Results

Study Identification and Selection

A total of 3,672 citations were yielded after searching various databases i.e google scholar, Medline-OVID, PubMed, and the following additional sources; US-CDC, WHO COVID-19, Africa-CDC, UVRI, Ministry of health (MOH)-Uganda, National Institute of Health (NIH), COVID-END and New Zealand guides ((Fig. 1)

After adjusting for duplicates, 3,099 citations remained. Of these, 2,378 articles were excluded after reviewing the titles and abstracts as they did not meet a priori inclusion criteria. A total of 721 full text articles were screened in detail using pre-determined inclusion criteria. Out of these, 54 articles were included for data abstraction and an additional 10 articles were included from reference searching. Upon data extraction we excluded 46 articles since they didn't have relevant outcomes. Of the articles included for coding, 16 articles met the eligibility criteria and were included in the review as shown in (Fig. 1) below.

Characteristics of Included Studies

Out of the 16 articles included in the final full text review, fifteen (15) articles were from studies in China and one (1) from Turkey. No studies regarding this review were obtained from Africa. All studies included in this review were published in 2020. The reported study designs include five (5) case controls, one (1) randomized Trial and ten (10) cross-sectional studies (Table 2).

Half, 50.0% (8/16) of included articles reported on the severity of disease of the study participants. No study reported on the cost of the test used. The turnaround time of the diagnostic tests was reported by 37.5% (6/16) of the studies. 56.3% (9/16) studies reported on the sensitivity of the point of care tests used and 50% (8/16) had information on the diagnostic test specificity (Table 2).

Characteristics of Excluded Studies

Out of the 3,672 records identified through the various search strategies, 15.6% (573/3672) duplicates were removed. Of the remaining 3099 records, 76.7% (2378/3099) studies were excluded on title and abstract. This is because they did not meet the inclusion criteria of the review i.e., 7.15% (n = 170) were

published before 2019, 77.54% (n = 1844) did not have COVID-19 testing as the intervention, 3.36% (n = 80) had populations that were not from a LMIC setting, 6.06% (n = 144) were letters and commentaries and 5.89% (n = 140) studies were not done on humans (Fig. 1).

The remaining 721 articles were assessed for eligibility on full text and 92.5% (n = 667) of these were excluded. Of the excluded articles, 06 articles were not in English, 62 articles were excluded on study design, 540 articles had no relevant outcomes, 58 articles excluded because setting was not LMIC and 01 was a duplicate (Fig. 1). Other 48 articles were excluded at coding for not having the relevant outcome.

Risk of Bias Included Studies

The QUADAS tool has 14 items and assesses the following domains of quality; whether the spectrum is representative of patients who will receive the test in practice; the selection criteria was clearly described, reference standard and index test are short enough to sure that the condition of interest did not change between the two tests, the whole sample or random sample received verification using a reference standard of diagnosis, patients received the same reference standards, reference standard was independent of the index test, description of the execution index test and the reference standard in detail, independent interpretation of the reference standard results, and the availability of the same clinical data at the point of interpretation as would be available when the test is used in practice, reporting of both uninterpretable and intermediate results and explanation of withdrawals. From the possible score of 14, the mean score was 10.4, the highest 14 and lowest 7. Five studies scored below the average score of 7 (Table 3). The attributes of the studies which had low scores include selection criteria, this was not described in ten (n = 10) of the included studies. The uninterpretable/ intermediate test results were not reported in ten (n = 10) of the studies and withdrawals from studies were not presented in six (n = 6) of the included studies

Table 3. Assessment of Diagnostic Accuracy Studies

Study	QUADAS scores	Risk of bias
Chenyao Lin, et al., 2020	12	low
Figen Sarıgul et al., 2020	11	low
Lui Wanbing et al., 2020	11	low
Minghua Jiang et al, 2020	12	low
Xiang et al., 2020	12	low
Xuemei Liu et al., 2020	12	low
Weihua Yang, 2020	12	low
Yan C et al., 2020	12	low
Rui Liu et al., 2020	13	low
Zhengtu Li et al., 2020	14	low
Yafang Li et al., 2020	10	high
Renfei Lu et al., 2020	8	high
Yujiao Jin et al., 2020	7	high
Bin Lou et al., 2020	9	high
Chen, Lan et al., 2020	7	high
Chungen Qian et al., 2020	7	high

Heterogeneity

We found some moderate heterogeneity, which was highest in the studies that focused on serological tests, (I^2 = 82.89, P < 0.001), with (25) reporting the lowest sensitivity of 48%, see Figs. 2 and 3. In terms of type of test clusters, we noted more heterogeneity in the Realtime RT-PCR.

Types of Tests

In this review, all studies included used the Real-time polymerase chain reaction test (RT-PCR) as their reference test. Currently, RT-PCR is the gold standard and the recommended confirmatory test for COVID-19. 18.7% (n = 3) articles were determining the diagnostic accuracy of the PCR test. The remaining studies (n = 13) used other COVID-19 tests as the index tests including; IgM and IgG chemiluminescence immunoassay (CLIA) (n = 5), RT-LAMP-Reverse transcriptase loop-mediated isothermal amplification (n = 3), colloidal-gold lateral-flow immunoassays (CLFIA) (n = 2), Quantum dot immunofluorescent IgG and IgM kits (n = 1) and the enzyme-linked immunosorbent assay (n = 2).

Cost of Test

No study documented the cost of the diagnostic test used. In Uganda, the ministry of Health was initially using rapid diagnostic test kits (PCR) purchased at a cost of $65. This price included other accessories such as personal protective equipment (PPE) at USD 2.5, requirements for sample collection (oral and nasal swab each at $1.8), transportation media ($8.50) and triple packaging ($2.25). The unit costs for a test kit excluding the accessories varied based on the manufacturer and this was: - Altona PCR kits at $ 25, GeneXpert kits at $19.8, ABI kits at $17.2 and COBAS 6800/8800 kits at $18.9. Since October, 2020, the country has reduced the cost of a COVID-19 test from the initial $65 to $50. This cut was after the resumption of international flights reducing the cost of transportation of test kits and other supplies from the manufacturers.

Sensitivity and Specificity

It is generally observed that the tests were more specific than sensitive pooled sensitivity and specificity was 87.55 -95% CI (82.151–92.955), 98.105- 95% CI 96.441 -100.954) respectively and the RT-LAMP tests had the highest sensitivity as compared to Real time PCR, serological and CLIA (Figs. 2 and 3). In this review, the specificity and sensitivity of the tests were highest when bronchial lavage samples were used (26) and lowest with the use of serum specimens/samples (25, 27, 28). In populations where both IgG and IgM antibodies were used, a higher sensitivity was registered following the use of IgG tests compared to while using IgM tests (25, 27, 29, 30). For example, the studies that used *Serological test PCR (IgM*) (25, 29) reported a specificity score of 79.7% and 90.6% respectively. The two studies also used Serological test PCR (IgG) antibodies and consistently reported low scores for specificity, 0.840 (29) and 0.700 (25)

Discussion

Accurate covid-19 diagnosis is critical to the covid-19 response strategy. Early diagnosis improves care outcomes and reduces potential complications that may arise as a result of delayed diagnosis, which opens the door for disease progression into severity. However, accurate diagnosis is dependent on the accuracy of the available tests. The RT-PCR test was used as the reference standard by the various studies included in this review to determine the diagnostic accuracy of the index tests. RT-PCR is a Nucleic acid amplification test (NAAT) that is recommended as the gold standard for the confirmation of acute SARS-CoV-2 infections (3). The use of RT-PCR for COVID-19 diagnosis is limited in many settings due to its complexity, high cost compared to other assays, and longer sample-to-result turnaround time (31).

The other nucleic acid amplification tests whose diagnostic accuracy was determined in studies included in this review was the reverse transcriptase loop mediated isothermal amplification (RT-LAMP). In comparison to RT-PCR, RT-LAMP has higher sensitivity and specificity, is much faster, and does not require expensive reagents or instruments (32). In addition, studies in this review demonstrated the diagnostic accuracy of serological tests such as colloidal-gold lateral flow immunoassay (CLFIA), chemiluminescence immunoassay, enzyme linked immunosorbent assay (ELISA), and Quantum dot immunofluorescent assay. These tests detect antibodies produced by the human body in response to SARS-CoV-2 infection (3). For SARS-CoV-2, these tests rely on IgG/IgM affinity to recombinant spike (S) and nucleocapsid (N) proteins (31). They are particularly useful during the investigation of an ongoing outbreak and to support the retrospective assessment of an outbreak's attack rate or size (3). These tests, however, should not be used in isolation to identify acute cases in clinical care or for contact tracing (3).

Antigen tests, such as lateral flow immunoassays that detect the presence of SARS-CoV-2 viral proteins (antigens) in respiratory tract specimens, are also used in COVID diagnosis (3, 13). Due to the limitations of PCR, such as infrastructure, human resources, equipment, and reagents, WHO strongly encourages countries to begin using Antigen Rapid Diagnostic Tests (Ag-RDT) to detect infection as quickly as possible using the recommended testing algorithm (13) Currently, four WHO-approved Ag-RDTs are available for emergency use: SD Biosensor STANDARD Q, Sure Status COVID-19 Antigen Card Test, Abbott PanBio COVID-19 Ag Rapid Test Device (nasal), and Abbott PanBio COVID-19 Ag Rapid Test Device (nasopharyngeal swab) (13). The sensitivity and specificity of these antigen tests, however, were not determined in any of the studies included in this review.

It's surprising that none of the articles mentioned the costs of the tests. The fact that the majority of test kits in developing countries were donated or obtained through subsidized grants from international organizations/countries and collaborations (33) could explain why the costs were not stated. The cost of diagnostic tests is determined by several factors. For example, saliva collected samples have been found to be less expensive than nasopharyngeal collected samples (34). Costs are also affected by the type of test, as PCR tests are generally more expensive than rapid antigen tests (35). According to reports, PCR tests (which require an expensive laboratory to set up) have sometimes cost more than USD 100 in Sub-Saharan Africa (36). However, regardless of severity, testing people for COVID-19 is cost-effective and would reduce the overall risk of infections, hospitalization, and deaths (37). Importantly, there are ongoing efforts in Africa to make Covid-19 testing accessible and affordable. For example, the Access to COVID-19 Tools Accelerator (ACT-A) collaboration between UNICEF, COVID-19 test manufacturers, and other partners resulted in the procurement of some of the most affordable test kits for Africa. Each of these new kits costs $2.55, which is less than the $4.00 and $4.20 per test price of other COVID-19 rapid diagnostic tests currently available (38). Furthermore, the collaboration between Africa CDC and the Foundation for Innovative New Diagnostics is intended to strengthen the continent's capacity for developing COVID-19 diagnostic kits. Currently, nations such as Kenya, Morocco, Senegal and South Africa are manufacturing test kits (39).

The sensitivities of the diagnostic assays (the proportion of people with COVID-19 who were identified as positive) for RT-LAMP, real time RT-PCR, serological tests, and overall (all diagnostic tests combined) were 94.07%, 84.82%, 83.04%, and 87.55%, respectively. The specificities (proportion of people without COVID-19 who were identified as negative) for RT-LAMP, real time RT-PCR, serological tests, and overall (all diagnostic tests combined) was 99.60%, 96.79%, 96.97%, and 98.10%, respectively. In general, the diagnostic tests were better at identifying those without COVID-19 as negative than those with COVID-19 as positive, regardless of the population of interest tested. Our findings on serological test specificity are consistent with those of two systematic reviews of studies from both high-income and low- and middle-income countries which reported pooled sensitivities ranging from 66.0% (95%CI: 49.3–79.3%) for LFIAs measuring IgM and IgG to 84.3% (95%CI: 75.6–90.9%) for ELISAs measuring

IgM or IgG and pooled specificities ranging from 96.6% (95%CI: 94.3–98.2%) for LFIAs measuring IgM and IgG to 97.6% (95% CI: 93.2–99.4%) for ELISAs measuring IgM or IgG (14, 40), the presence of articles from high income countries in the above studies may cause a slight discrepancy in results since we exclusively assessed studies from low- and middle-income countries. Bronchial lavage samples demonstrated the highest specificity and sensitivity (26) compared serum specimens (25), this means that respiratory specimens are more appropriate in regard to accuracy of test results. These findings are consistent with those of a systematic review of studies from both high-income and low- and middle-income countries, which found that rectal stools/swabs, urine, and plasma were less sensitive than sputum for detecting COVID-19 (40).

We noticed a dearth of evidence on accuracy, costs of tests and cost effectiveness of tests. We set out to evaluate the predictive value of tests, but we also noticed that studies did not report positive and negative predictive values, which are important when evaluating test accuracy. Because the costs of tests were

not mentioned in any of the included studies, the cost effectiveness could not be determined. Furthermore, none of the studies included were from Africa, indicating a significant gap in evidence on the availability and utility of laboratory tests in Africa. Given the slow pace of vaccine access in Africa (41), COVID-19 will continue to pose a significant global health security risk in the region. Member states should prioritize both increasing access to vaccines to vaccinate the population and generating evidence on cost-effective laboratory testing options, given the central role testing plays in the COVID-19 response. Patients must be correctly diagnosed before receiving appropriate treatment. Furthermore, despite a plethora of evidence on COVID-19, there is a scarcity of studies conducted on the African continent, particularly on COVID-19 testing, and thus there is room for research in terms of primary studies in this particular area that has yet to be adequately explored.

Strengths & Limitations

The study will help to strengthen the evidence base on the effectiveness of COVID-19 laboratory testing strategies in hospitals and community populations in low- and middle-income countries (LMICs). The protocol was written in accordance with the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Some of the articles did not report on key information required to make a comprehensive assessment of diagnostic test accuracy, for example, only 64.3% and 57.1% of the articles reported sensitivity and specificity, respectively, and the majority lacked information on negative predictive value (NPV) and positive predictive value (PPV), so we are unable to highlight a diagnostic test's ability to make a diagnosis in terms of the discriminatory value of the test. Our efforts to synthesize evidence on the cost effectiveness of COVID-19 strategies were also hampered by a lack of studies reporting on the subject. We excluded studies not published in English hence this may introduce bias.

Conclusion

The evidence on COVID-19 testing in LMICs is summarized in this systematic review. Real-time polymerase chain reaction (RT-PCR), IgM and IgG chemiluminescence immunoassay (CLIA), reverse transcriptase loop-mediated isothermal amplification (RT-LAMP), colloidal-gold lateral-flow immunoassays (CLFIA), quantum dot immunofluorescent IgG and IgM kits, and the enzyme-linked immunosorbent assay (ELISA) were among the diagnostic tests reported. The RT-PCR was used as the reference test in all studies. The diagnostic assays' combined sensitivity and specificity were 87.55% and 98.10%, respectively. The diagnostic tests were more accurate in identifying those who did not have COVID-19 than those who did. In the reviewed literature, no study reported on the cost and cost effectiveness of diagnostic tests. Finally, no studies were carried out on the African continent.

Abbreviations

1. ACT-A –Access to COVID-19 Tools Accelerator
2. CDC—Centers for Disease Control & Prevention
3. CLFIA–Colloidal-gold Lateral-Flow Immunoassays
4. CLIA–Chemiluminescence Immunoassay
5. COVID-19–Corona Virus Disease 2019
6. COVID-END–COVID-19 Evidence Network to support Decision-making
7. ELISA–Enzyme-Linked Immunosorbent Assay
8. LFIA–Lateral Flow Immunoassays
9. LMICs–Low and Middle In-Come Countries
10. NAATs– Nucleic Acid Amplification Tests
11. NPV–Negative Predictive Value
12. PCR–Polymerase Chain Reaction
13. PPV–Positive Predictive Value
14. PRISMA– Preferred Reporting Items for Systematic Reviews & Meta-Analysis
15. PRISMA-DTA–Preferred Reporting Items for Systematic Reviews & Meta-Analysis Guidelines for Diagnostic Test Accuracy studies
16. PROSPERO– International prospective register of systematic reviews
17. QUADAS–Quality Assessment of Diagnostic Accuracy Studies
18. RT-LAMP–Reverse Transcriptase Loop-Mediated Isothermal Amplification
19. RT-PCR–Real-time polymerase chain reaction
20. SARS-CoV-2– Severe Acute respiratory Syndrome coronavirus 2
21. TAT—Turn Around Time
22. WHO—World Health Organization

Declarations

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Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interests.

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Figures

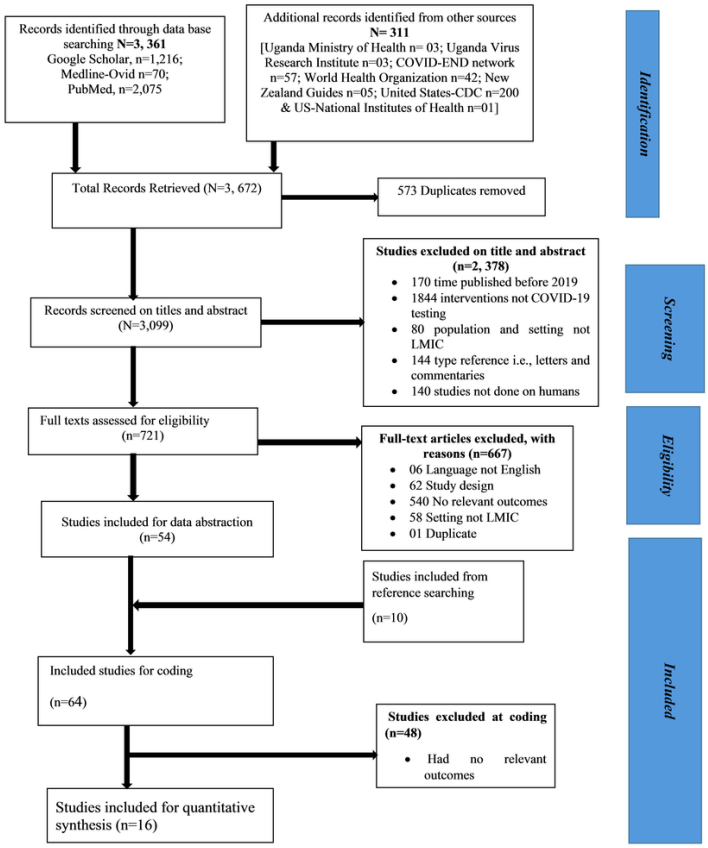

Figure 1

Prisma flow diagram showing article selection for the review

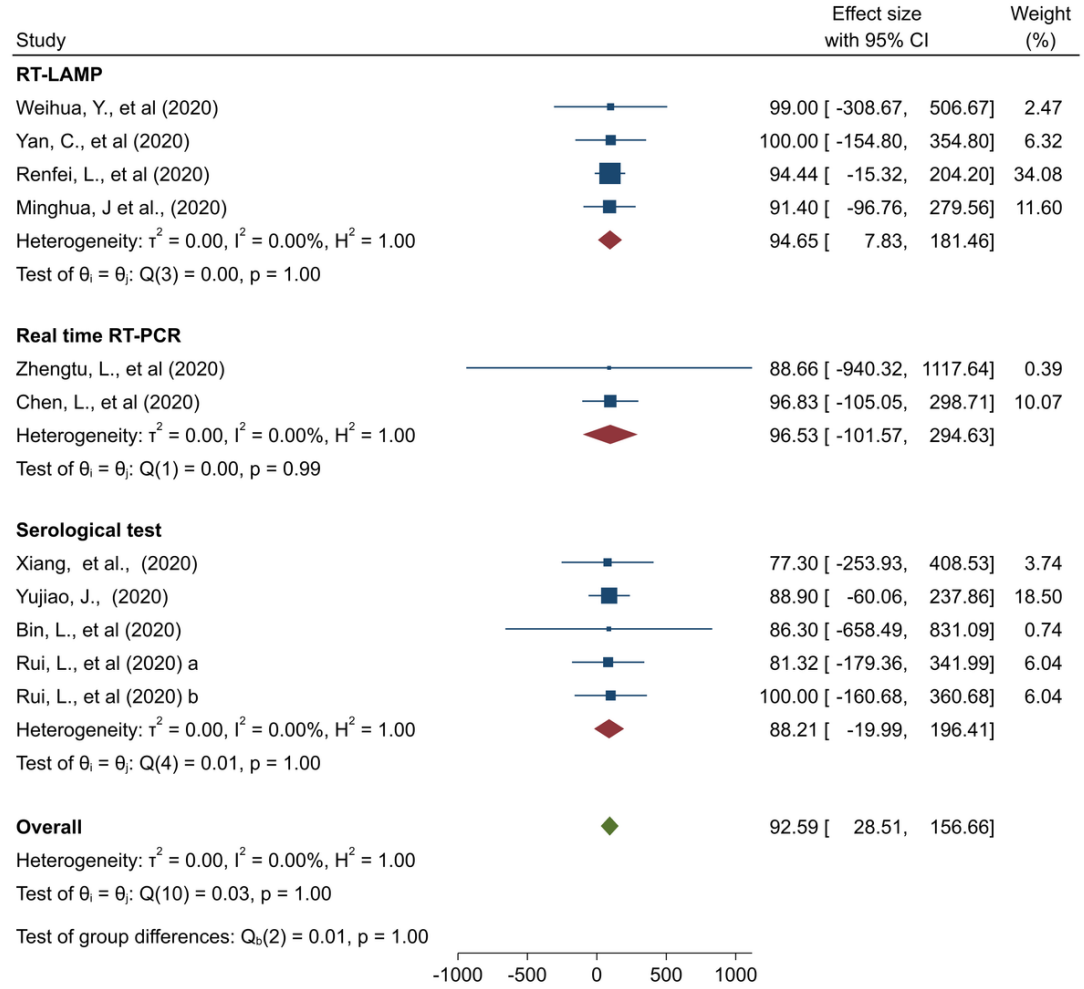

Figure 2

Sensitivity

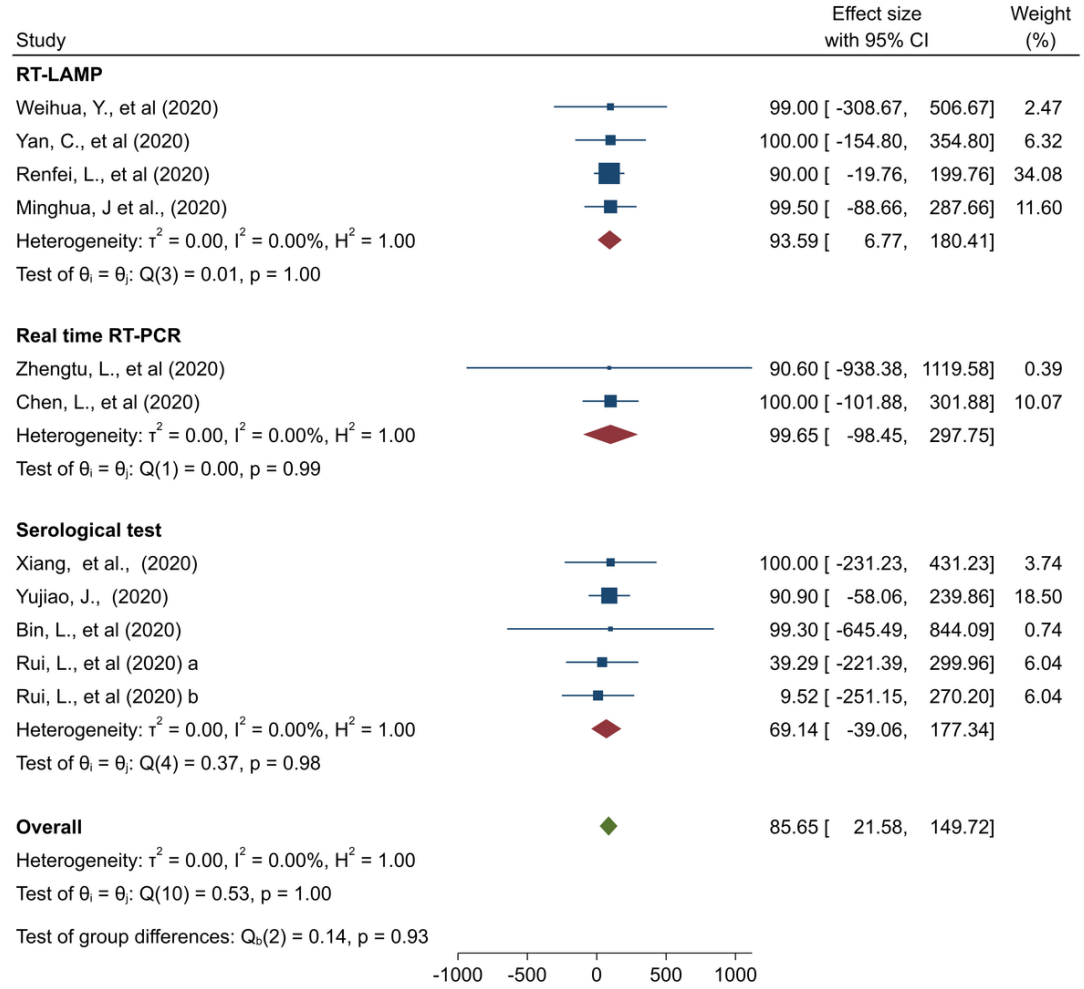

Figure 3

Specificity

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