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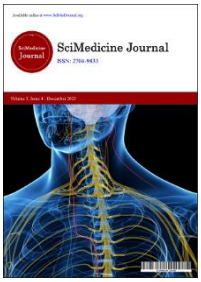

Diagnostic Accuracy of COVID-19 Antibody Tests Authorized by FDA Philippines: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Coronavirus Disease (COVID-19) is a highly infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which has infected many people all over the world. One of the best ways to lessen its spread is through early detection and diagnosis. Various serological tests are now being used as a surveillance tool in the detection of antibodies as a response to SARS-CoV-2. The aim of this study is to evaluate the diagnostic accuracy and performance of the available COVID-19 antibody tests authorized by the Food and Drug Administration (FDA) Philippines that make use of Enzyme-Linked Immunosorbent Assay (ELISA), Chemiluminescence Immunoassay (CLIA) and Lateral Flow Immunoassay (LFIA). *Method*: Complete published journal articles relevant to the diagnostic accuracy of the three antibody tests were collected using trusted medical journal search engines. The quality of journals was assessed using QUADAS-2 to determine the risk of bias and assess the applicability judgments of diagnostic accuracy studies. Forest plots were used to summarize the performance of LFIA, ELISA and CLIA according to their specificity and sensitivity in detecting various antibodies. Pooled sensitivity and specificity were also done using bivariate random-effects models with its log-likelihood, a corresponding chi-square test statistic, and area under the summary Receiver-Operating Characteristic curve to see the potential heterogeneity in the data and to assess the diagnostic accuracy of the COVID-19 antibody tests. *Results*: Bivariate random-effects model and areas under the sROC curve were used to evaluate the diagnostic accuracy of COVID-19 antibody tests. The pooled sensitivity in detecting IgG based on CLIA, ELISA, and LFIA were 81.7%, 58.7%, and 74.3% respectively, with an overall of 72.0%. For IgM detection, LFIA has a higher pooled sensitivity of 69.6% than CLIA with 61.0%. Overall, the pooled sensitivity is 68.5%. In IgA detection, only ELISA based test was included with a pooled sensitivity of 84.8%. Lastly, pooled sensitivities for combined antibodies based on ELISA and LFIA were 89.0% and 81.6% respectively, with an overall of 82.5%. On the other hand, all tests excluding ELISA-IgA displayed high pooled specificities with a range of 94.0% to 100.0%. Diagnostic accuracies of the test in detecting IgG, IgM, and combined antibodies were found out to be almost perfect based on the computed area under the sROC with values of 0.973, 0.953, and 0.966, respectively. *Conclusion*: In this systematic review and meta-analysis, existing evidence on the diagnostic accuracy of antibody tests for COVID-19 were found to be characterized by high risks of bias, consistency in the heterogeneity of sensitivities, and consistency in the homogeneity of high specificities except in IgA detection using ELISA. The bivariate random-effects models showed that there are no significant differences in terms of sensitivity among CLIA, ELISA and LFIA in detecting IgG, IgM, and combined antibodies at a 95% confidence interval. Nonetheless, CLIA, ELISA and LFIA were found to have excellent diagnostic accuracies in the detection of IgG, IgM and combined antibodies as reflected by their AUC values.

Keywords: COVID-19; Antibody Test; Enzyme-linked Immunosorbent Assay (ELISA); Chemiluminescence Immunoassay (CLIA); Lateral Flow Immunoassay (LFIA).

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1. Introduction

In December 2019, a number of pneumonia cases, with an unknown cause, were identified in Wuhan City, China. It was later identified that the pathogen of this pneumonia-like disease was the novel coronavirus which was later named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) named the disease, caused by this pathogen, as Coronavirus Disease (COVID-19). This disease is highly infectious and has infected many people all over the world. SARS-CoV-2 belongs to the virus family *Coronaviridae*, which causes diseases in the respiratory system. Patients who are infected with this virus usually present fever, dry cough, and tiredness. More symptoms include aches and pains, sore throat, diarrhea, conjunctivitis, headache, and loss of smell. Serious cases of COVID-19 may have difficulty breathing, chest pain or pressure or loss of speech or movement. However, there are also asymptomatic cases which may imminently cause more danger as they have no physical manifestations that they have acquired the virus and may unconsciously spread it to other people. As of January 28, 2021, there are 519,575 cases and 10,552 deaths in the Philippines while there are 101,400,862 cases and 2,182,193 deaths worldwide [1].

The diagnosis for COVID-19 is done either directly or indirectly. The direct approach involves the molecular detection of the viral genome through nucleic acid amplification techniques [2]. On the other hand, the indirect approach is termed as such because it does not explicitly discern the presence of the virus rather the indirect tests report the development of antibodies that correlate with former or present infections [3]. Currently, the gold standard in COVID-19 diagnosis is the direct approach, which is real-time reverse transcription PCR (rRT-PCR). Although rRT-PCR is already well-documented as an efficient diagnostic system, the significance of indirect methods, such as serological testing, should not be disregarded for it plays a substantial role in a different, but principal aspect in disease surveillance, and disease control.

Serological tests detect antibodies, the body's adaptive defense mechanism against infections. Its presence, however, is not entirely concurrent with that of a pathogen; instead, it may pertain to a past occurrence of an infection. This is crucial when it comes to disease mitigation, epidemiology, and even in vaccine formulation. With the information gathered from antibody detection through serological means, the nature of infection recurrences can be studied further. Antibody detection can be done through three different testing mechanisms: Enzyme-Linked Immunosorbent Assay (ELISA), Chemiluminescence Immunoassay (CLIA), and Lateral Flow Immunoassay (LFIA). This systematic review and meta-analysis aim to assess the overall diagnostic accuracy and performance of different Food and Drug Administration (FDA) Philippines-authorized antibody diagnostic test kits in terms of their overall diagnostic sensitivity, diagnostic specificity, and area under the summary Receiver-Operating Characteristics (sROC) curve.

2. Methods

2.1. Research Design

This study is a systematic review and meta-analysis of published articles about the diagnostic accuracy of COVID-19 antibody tests namely Enzyme-Linked Immunosorbent Assay (ELISA), Chemiluminescence Immunoassay (CLIA), and Lateral Flow Immunoassay (LFIA) [4-22].

2.2. Sampling Design

This study is a systematic review and meta-analysis of published articles about the diagnostic accuracy of COVID-19 antibody tests namely Enzyme-Linked Immunosorbent Assay (ELISA), Chemiluminescence Immunoassay (CLIA), and Lateral Flow Immunoassay (LFIA).

2.3. Research Instrument

The search engine is based on the four-phase systematic review adopted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Screening and evaluation of articles from trusted medical search engines are based on the inclusion and exclusion criteria listed below. This systematic review followed the guidelines provided in the Cochrane Handbook for Diagnostic Test Accuracy Reviews.

2.4. Selection Criteria

Table 1 shows the selection criteria for deciding whether a certain literature is to be included or excluded from this study. In addition to the aforementioned criteria, bibliographic databases from Beall's List of Potential Predatory Journals and Publishers were excluded from use. This study only utilized complete and original published articles. Editorials, narrative review, commentaries, textbook chapters were excluded. This paper is a systematic review and meta-analysis designed and structured to synthesize primary data. Retrospective, cohort, experimental, descriptive, and case series research designs with data including diagnostic sensitivity and specificity were the accepted research designs. Primary sources that satisfied the inclusion criteria focusing on the following tests were synthesized: Enzyme-

linked Immunosorbent Assays (ELISA), Chemiluminescence Immunoassays (CLIA), and Lateral Flow Immunoassays (LFIA). Other tests that are not mentioned were not included in this study.

Table 1. Inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Bibliographic Database	Trusted medical journal search engines such as, but not limited to: Medline (via PubMed or Ovid); Embase; CENTRAL (The Cochrane Central Register of Controlled Trials); Google Scholar; ScienceDirect	Databases included in the Beall's list (potential predatory journals)
Date of Publication	December 2019 up to March 2021	Publication date before December 2019
Authors	Minimum of two (2) authors	Articles with less than two (2) authors
Publication Type	Original published articles	Systematic review
Language	English	Non-English
Design of Study	Retrospective study, cohort study, experimental, descriptive, and case series research designs with data including diagnostic sensitivity and specificity	Editorials, narrative review and textbook chapters
Type of Antibody Test	Antibody tests authorized by FDA Philippines: Enzyme-linked Immunosorbent assays (ELISA), Chemiluminescence Immunoassays (CLIA), and Lateral Flow Immunoassays (LFIA)	Antibody tests not authorized by FDA Philippines
Participants of the Study	Patients with COVID-19 confirmed using RT-PCR	Articles that did not use RT-PCR to confirm COVID-19 cases

2.5. Data Extraction

In order to organize and collate data extraction from all studies involved, a custom Google spreadsheet was used. Two review authors, J.F. and S.A.E.O., separately performed the data extraction by collecting the following characteristics: general information about the study including the author/s, year of publication, study design, country of origin; target population including the age group, case severity, COVID-19 status; and details about the antibody-detection testing kit used such as the brand name, manufacturer, specimen used assay classification, sensitivity, and specificity. Conflicts or discrepancies between the data extraction of the review authors were resolved by a third reviewer (E.D.E.D.S.).

2.6. Quality Assessment

Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) is a structured tool used to determine the risk of bias and assess the applicability judgments of diagnostic accuracy studies. Three review authors, C.R.R.C., K.V.H.E. and R.LG.E., evaluated the articles based on four (4) domains: patient selection, index test, reference standard, and flow and timing. To assess the risk of bias, each domain included a set of signaling questions. The first three domains were also assessed as regards to applicability concerns. Conflicts among the authors were resolved through consensus. Review Manager (RevMan), the software certified by Cochrane Review to manage systematic reviews and meta-analyses, was used by the authors in the assessment of risk of bias and applicability concerns, as well as in the analysis of data.

2.7. Data Analysis

To assess the diagnostic accuracy and performance of each antibody testing kit authorized by FDA Philippines, forests plots were used to summarize the performance of the three testing mechanisms namely LFIA, ELISA and CLIA, in terms of their specificity and sensitivity in detecting IgG, IgM, and IgA antibodies. To further investigate the reported results, both estimated pooled sensitivity and specificity were conducted using bivariate random-effects models including its log-likelihood, a corresponding chi-square test statistic, and area under the summary Receiver-Operating Characteristic (sROC) curve to see the potential heterogeneity in the data.

3. Result and Discussion

3.1. Study Selection

Figure 1 shows the study selection process. In the initial search, the researchers identified thirty-five (35) journal articles about COVID-19 antibody test kits from trusted medical journal search engines. After removal of duplicates, thirty-four (34) studies were then screened and nine (9) of these were excluded due to the following reasons: three (3) were published from databases included in the Beall's list of potential predatory journals, two (2) were published before December of 2019 and the study design of four (4) journals were part of the exclusion criteria. Twenty-five (25) full-text articles were further assessed for eligibility. Consequently, the researchers excluded three (3) articles that did not provide absolute data for specificity and sensitivity and another three (3) articles that did not use the gold

standard RT-PCR to diagnose COVID-19. After keen assessment and screening done by the researchers, a total of nineteen (19) journal articles [4-22] were found appropriate to be included in this systematic review and quantitative or meta-analysis.

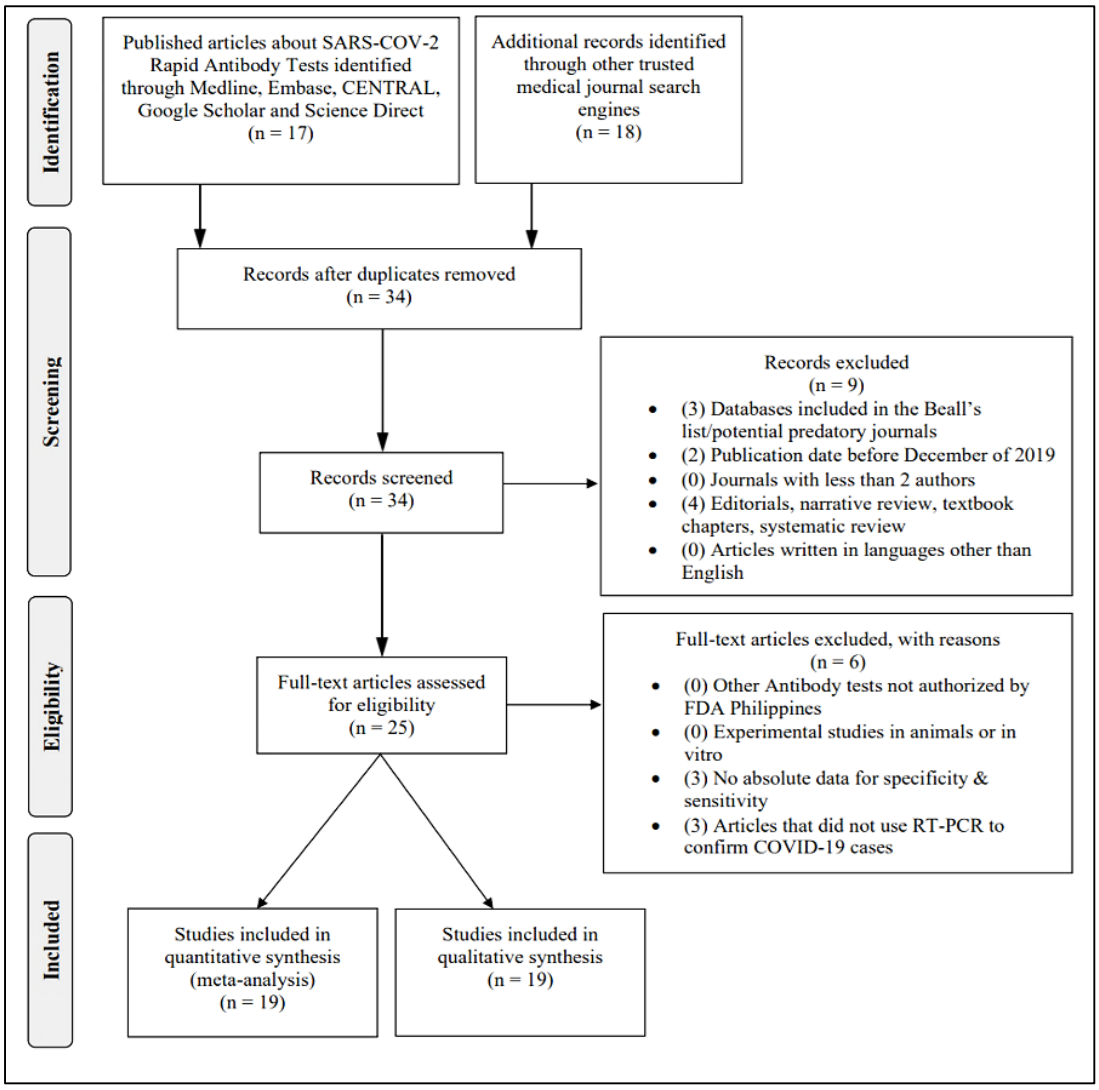

Figure 1. Schematic diagram of study selection process

3.2. Risk of Bias within Studies

The following figures display the risk of bias and applicability concerns for the included studies in this systematic review and meta-analysis. The unified decision of judgement for the risk of biases is done through answering signaling questions tailored by the researchers. This procedure is based on QUADAS-2, the current version of Quality Assessment of Diagnostic Accuracy Studies (QUADAS), a tool used in systematic reviews designed to assess and evaluate the risk of bias and applicability of primary diagnostic accuracy studies, as recommended by the University of Bristol.

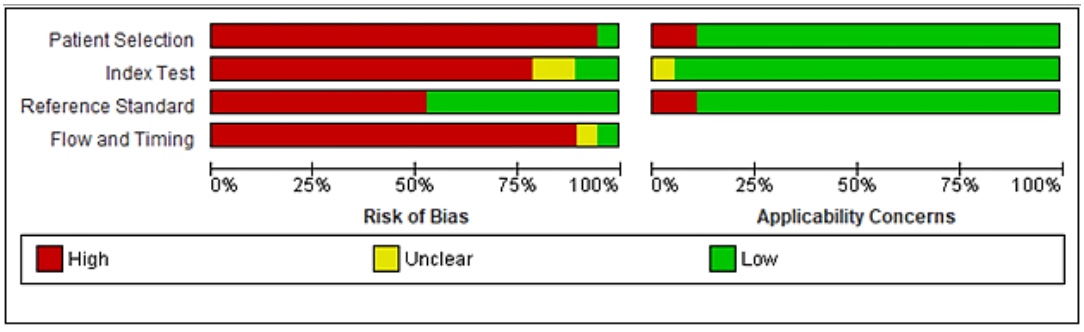

Figure 2. Summary of risk of bias and applicability concerns

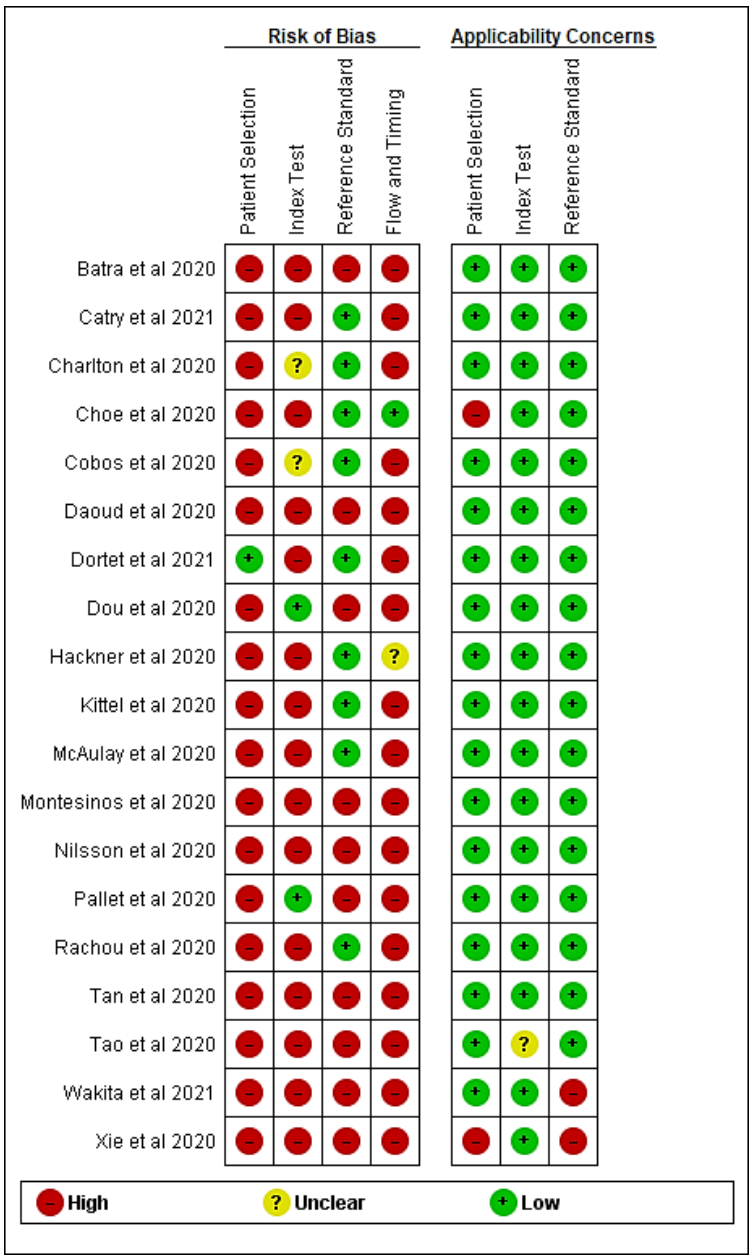

Figure 3. Risk of bias and applicability concerns by study author

Figure 2 presents the summary of the risk of bias and applicability concerns for each domain of quality assessment. More than 90% of the included studies have a high risk of bias in terms of patient selection. The majority of this can be attributed to the non-randomized or non-consecutive selection of patients/specimens. Then, about 80% of the studies have a high risk of bias in terms of the index test. For most of the studies, the status of the specimens (positive or negative via RT-PCR) is already known before the use of the index test namely CLIA, LFIA, and ELISA. In terms of the reference standard, about half of the studies showed a high risk of bias. Half of the studies did not state the use of RT-PCR as its reference standard or gold standard in obtaining a positive result for COVID-19. Lastly, about 90% of the included studies presented a high risk of bias in terms of flow and timing of the test. Bias may have been introduced in studies that did not explicitly state the timing or interval between the index test and the reference standard as well as in studies that faced withdrawal of participants during the course of the study. The breakdown of quality assessment for each study is seen in Figure 3.

3.3. Study Characteristics

Table 2 shows the summary of antibody test kits that was included in the study. It includes the authors of the nineteen (19) studies [4-22] that were included, along with its Rapid Diagnostic Test Identification (RDT-ID), the brands of the antibody test kits used per study, manufacturer, the types of assays namely LFIA, CLIA, and ELISA, and the type of antibody tested such as IgM, IgG, IgA, or Combined.

Table 2. Summary of antibody test kits included in the analysis

Author	RDT-ID	Brand	Manufacturer	Type of Assay	Type of Antibody Tested
Batra et al.	RDT-1	Abbott Panbio™ COVID-19 IgG/IgM RAPID TEST DEVICE	Abbott Rapid Diagnostics Jena GmbH – Orlaweg 1 07743 Jena, Germany	LFIA	IgG
Catry et al.	RDT-2	COVID-19 IgG/IgM Rapid Test Cassette (Whole Blood/ Serum/ Plasma)	Healgen Scientific Limited Liability Company – 3818 Fuqua Street Houston, TX 77047, USA	LFIA	Combined (IgM or IgG)
Charlton et al.	RDT-3	BIOLIDICS 2019-nCoV IgG/IgM DETECTION KIT	Biolidics Limited. – 37 Jalan Pemimpin, #02-07, Mapex, Singapore	LFIA	IgM, IgG, & Combined
	RDT-4	Genrui Novel Coronavirus (2019-nCoV) IgG/IgM Test Kit (Colloidal Gold)	Genrui Biotech Inc. – 4-10F, Building 3, Geya Technology Park Guangming District, 518106 Shenzhen China	LFIA	IgM, IgG, & Combined (IgM or IgG)
	RDT-5	2019-nCoV ANTIBODY TEST (COLLOIDAL GOLD)	Innovita (Tangshan) Biological Technology Co., Ltd. – No. 699 Juxin Street, High-Tech Industrial Development Zone, Qian'an 064400, Hebei, China	LFIA	IgM, IgG & Combined (IgM or IgG)
Choe et al.	RDT-6	PCL COVID19 IgG/IgM RAPID GOLD	PCL, Inc. – # 701, 99, Digital-ro 9-gil, Geumcheon-gu, Seoul, 08510, Republic of Korea	LFIA	IgM or IgG & IgM and IgG
Cobos et al.	RDT-7	SARS-CoV-2 ANTIBODY TEST (LATERAL FLOW METHOD)	Guangzhou Wondfo Biotech Co., Ltd. – No. 8 Lizhishan Road, Science City, Luogang District, 510663, Guangzhou, People's Republic of China	LFIA	IgM
	RDT-8	SGTi-flex COVID-19 IgM/IgG	Sugentech Inc. – 721-26 Jeongjungyeonje-ro Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do 28161, Republic of Korea	LFIA	IgM, IgG & Combined
	RDT-9	2019-nCoV ANTIBODY TEST (COLLOIDAL GOLD)	Innovita (Tangshan) Biological Technology Co., Ltd. – No. 699 Juxin Street, High-Tech Industrial Development Zone, Qian'an 064400, Hebei, China	LFIA	IgM, IgG & Combined
	RDT-10	EURORealTime SARS-CoV-2	EUROIMMUN Medizinische Labordiagnostika AG. – Seekamp 31 23560 Lubeck, Germany	ELISA	IgG
Cota et al.	RDT-11	HIGHTOP SARS-CoV-2 IgM/IgG ANTIBODY RAPID TEST	Qingdao Hightop Biotech Co., Ltd. – No. 369 Hedong Road, Hi-tech Industrial Development Zone, 266112 Qingdao, Shandong, Peoples Republic of China	LFIA	Combined
	RDT-12	EURORealTime SARS-CoV-2	EUROIMMUN Medizinische Labordiagnostika AG. – Seekamp 31 23560 Lubeck, Germany	ELISA	IgG and IgA
Daoud et al.	RDT-13	COVID-19 IgG/IgM Rapid Test Cassette (Whole Blood/ Serum/ Plasma)	Healgen Scientific Limited Liability Company – 3818 Fuqua Street Houston, TX 77047, USA	LFIA	IgM and IgG
Dortet et al.	RDT-14	NADAL COVID-19 IgG/IgM Test	nal von minden GmbH - Carl-Zeiss-Str. 12, 47445 Moers, Germany	LFIA	IgM, IgG & Combined
	RDT-15	NANJING VAZYME 2019-nCoV IgG/IgM DETECTION KIT	Biolidics Limited. – 37 Jalan Pemimpin, #02-07, Mapex, Singapore	LFIA	IgM, IgG & Combined
	RDT-16	2019-nCoV ANTIBODY TEST (COLLOIDAL GOLD)	Innovita (Tangshan) Biological Technology Co., Ltd. – No. 699 Juxin Street, High-Tech Industrial Development Zone, Qian'an 064400, Hebei, China	LFIA	IgM, IgG & Combined
	RDT-17	Anti-SARS-CoV-2 Rapid Test	Autobio Diagnostics Co., Ltd–No. 87, Jingbei Yi Rd, National Eco &Tech Zone, Zheng zhou, China	LFIA	IgM, IgG & Combined
Dou et al.	RDT-18	MAGLUMI 2019-nCoV IgM/IgG	Shenzhen New Industries Biomedical Engineering Co., Ltd. – Jinxiu East Road, Pingshan District, 518122 Shenzhen, P.R. China	CLIA	IgM and IgG
Hackner et al.	RDT-19	NADAL COVID-19 IgG/IgM Test	nal von minden GmbH - Carl-Zeiss-Str. 12, 47445 Moers, Germany	LFIA	IgM and IgG
Kittel et al.	RDT-20	EURORealTime SARS-CoV-2	EUROIMMUN Medizinische Labordiagnostika AG. – Seekamp 31 23560 Lubeck, Germany	ELISA	IgG and IgA
McAulay et al.	RDT-21	STANDARD Q COVID-19 IgM/IgG COMBO TEST	SD Biosensor, Inc.–C-4&5 Floor, 16, Deogyeong-daero 1556beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, 16690, Republic of Korea	LFIA	Combined
	RDT-22	ACON SARS-CoV-2 IgG/IgM Rapid Test	ACON Biotech (Hangzhou) Co., Ltd.– No.210 Zhenzhong Road, West Lake District, Hangzhou, P.R. China	LFIA	Combined

Montesinos et al.	RDT-23	MAGLUMI 2019-nCoV IgM/IgG	Shenzhen New Industries Biomedical Engineering Co., Ltd. – Jinxiu East Road, Pingshan District, 518122 Shenzhen, P.R. China	CLIA	IgG, IgM & Combined
	RDT-24	EURORealTime SARS-CoV-2	EUROIMMUN Medizinische Labordiagnostika AG. – Seekamp 31 23560 Lubeck, Germany	ELISA	IgG, IgA & Combined
Nilsson et al.	RDT-25	WANTAI SARS- CoV Ab RAPID TEST KIT	Beijing Wantai Biological Pharmacy Enterprise Co., Ltd. – 31 Kexueyuan Road, Changping District Beijing, People's Republic of China	ELISA	IgM
	RDT-26	DIAGNOSTIC KIT FOR IgM/IgG ANTIBODY TO CORONAVIRUS (SARS-CoV-2)	Zhuhai Livzon Diagnostic Inc. – 1st Building, No. 266, Tongchang Road, Xiangzhou District, Zhuhai, Guangdong Province, People's Republic of China	LFIA	IgG and IgM
	RDT-27	OnSite COVID-19 IgG/IgM Rapid Test	CTK Biotech, Inc. – 13855 Stowe Dr. Poway California, USA	LFIA	IgG and IgM
Pallett et al.	RDT-28	ENCODE SARS-CoV-2 IgG/IgM Rapid Test	Zhuhai Encode Medical Engineering Co., Ltd – No. 20, Honghui 2nd Road, Hongqi Industrial Zone, Jinwan District, Zhuhai, China	LFIA	IgG
	RDT-29	OnSite COVID-19 IgG/IgM Rapid Test	CTK Biotech, Inc. – 13855 Stowe Dr. Poway California, USA	LFIA	IgG
Tan et al.	RDT-30	cPassTM SARS-CoV-2 Neutralization Antibody Detection Kit	Accelerate Technologies Pte Ltd (DxD Hub) – 10 Biopolis Road #03-01/02 Chromos Building, Singapore	ELISA	IgG
Tao et al.	RDT-31	Biohit SARS-CoV-2 IgM/IgG Antibody Test Kit	Biohit Healthcare (Hefei) Co., Ltd. – Building D9, Innovation Park, No.800 West Wangjiang Road, High-Tech Zones, Hefei, Anhui Province, P.R. China	ELISA	Combined (IgG and IgM)
Wakita et al.	RDT-32	NADAL COVID-19 IgG/IgM Test	nal von minden GmbH - Carl-Zeiss-Str. 12, 47445 Moers, Germany	LFIA	IgG and IgM
	RDT-33	LYHER Novel Coronavirus (2019-nCoV) IgM/IgG Antibody Combo Test Kit (Colloidal Gold)	Hangzhou Laihe Biotech Co Ltd. – Floor 1 Room 505-512 Floor, 5 Building B 688 Bin'an Road, Binjiang District, Hangzhou, 310052, China	LFIA	IgG and IgM
	RDT-34	COVID-19 IgG/IgM Rapid Test Cassette	CHIL TIBBİ MAL. SAN. TİC. LTD. ŞTİ. -10028 sok. No.11 AOSB 35620 Cigli-Izmir/Turkey	LFIA	IgG and IgM
Xie et al.	RDT-35	NOVEL CORONAVIRUS (2019-NCOV) IgM/IgG ANTIBODY DETECTION KIT (COLLOIDAL GOLD METHOD)	Nanjing Vazyme Medical Technology Co., Ltd – Level 1-3, Bldg. C2, Red Maple Sci-Tech Park, Kechuang Road, Nanjing China	LFIA	Combined

Table 3 shows the summary of characteristics of the nineteen (19) studies [4-22] included for this systematic review and meta-analysis. Displayed above is the author of each study with his corresponding Rapid Diagnostic Test Identification (RDT-ID) patterned in Table 2. For every article, the characteristics included were the Location, Study Design, Sample Size, and Reference Standard. There were no limitations in the setting as long as the brand of the FDA Philippines-approved test kits are present in the journal. Additionally, the study designs included were cohort, retrospective, experimental, descriptive, and case series studies. Sample sizes were based on the number of samples used in every article, which can be either whole blood, serum, or plasma. Lastly, the reference standard was also noted for each article. Samples used must be confirmed with Real-Time Polymerase Chain Reaction (RT-PCR) in accordance with the inclusion criteria.

Table 3. Summary of the characteristics of articles included in the analysis

Author	RDT ID	Location	Study Design	Sample Size	Confirmed by Reference Standard
Batra et. al	RDT-1	London, UK; Huston Texas; Hunstville, Alabama	Cohort study	272	Yes
Catry et. al	RDT-2	Belgium	Retrospective Study	123	Yes
	RDT-3				
Charlton et. al.	RDT-4	Alberta, Canada	Experimental Study	92	Yes
	RDT-5				
Choe et. al.	RDT-6	Daegu, Republic of Korea	Retrospective Study	149	Yes
Cobos et. al.	RDT-7	Madrid, Spain	Descriptive Study	100	Yes
	RDT-8				
	RDT-9				
	RDT-10				

Cota et. Al	RDT-11	Minas Gerais, Brazil	Retrospective study	207	Yes
	RDT-12			420	
Daoud et. al	RDT-13	Not stated	Retrospective Study	195	Yes
	RDT-14				
	RDT-15				
Dortet et.al.	RDT-16	Paris	Retrospective Study	504	Yes
	RDT-17				
Dou et. al.	RDT-18	China	Cohort Study	205	Yes
Hackner et. al	RDT-19	Krems, Austria	Case report	260	Yes
Kittel et. al.	RDT-20	Mannheim, Germany	Retrospective study	280	Yes
McAulay et. al	RDT-21	Seattle, WA, USA	Retrospective study	200	Yes
	RDT-22				
Montesinos et. al	RDT-23	Brussels, Belgium	Retrospective study	72	Yes
	RDT-24				
Nilsson et. al.	RDT-25	Odense, Denmark	Cohort study	200	Yes
	RDT-26				
	RDT-27				
Pallett et. al	RDT-28	London, UK	Cohort study	236	Yes
	RDT-29				
Tan et. al.	RDT-30	Singapore	Cohort study	336	Yes
Tao et. al.	RDT-31	Hefei, China	Cohort study	703	Yes
Wakita et. al	RDT-32	Japan	Case control	214	Yes
	RDT-33				
	RDT-34				
Xie et. al.	RDT-35	Not stated	Experimental	92	Yes

Table 4 shows the individual sensitivity and specificity of the antibody tests included in the analysis. Data for the number of positive sera confirmed by RT-PCR (N_+) and the number of control serum or samples from non-COVID patients (N_-) were gathered to compute the true positive, false negative, false positive, and true negative values. Sensitivity and specificity for each brand of assay were indicated based on the type of antibody tested.

Table 4. Individual sensitivity and specificity of antibody test kit and immunoglobulin class detected

RDT	Type of Antibody Tested	Total Samples		True Positive	False Negative	False Positive	True Negative	Sensitivity	Specificity
		N+	N-						
RDT-1	IgG	108	164	106	2	1	163	98.20%	99.40%
RDT-2	Combined	126	100	126	0	6	94	100.00%	94.00%
RDT-3	IgM	40	50	7	33	2	48	18.00%	96.00%
	IgG	40	50	31	9	0	50	78.00%	100.00%
	Combined	40	50	31	9	0	50	78.00%	100.00%
RDT-4	IgM	40	50	32	8	2	48	80.00%	96.00%
	IgG	40	50	26	14	0	50	65.00%	100.00%
	Combined	40	50	32	8	0	50	80.00%	100.00%
RDT-5	IgM	40	50	8	32	0	50	20.00%	100.00%
	IgG	40	50	16	24	0	50	40.00%	100.00%
	Combined	40	50	18	11	0	50	45.00%	100.00%
RTD-6	IgM or IgG	70	79	65	5	3	76	92.90%	96.20%
	IgM and IgG	70	79	46	24	0	79	65.70%	100.00%
RDT-7	IgM	50	50	50	0	12	38	100%	76.00%
RDT-8	IgM	50	50	35	15	5	45	70.00%	90.00%
	IgG	50	50	20	30	0	50	40.00%	100.00%
	Combined	50	50	37	13	5	45	74.00%	90.00%
RDT-9	IgM	50	50	26	24	0	50	52.00%	100.00%
	IgG	50	50	22	28	1	49	44.00%	98.00%
	Combined	50	50	29	21	1	49	58.00%	98.00%

RDT-10	IgG	50	50	19	31	0	50	37.78%	100.00%
RDT-11	Combined	91	116	54	37	0	116	59.50%	100.00%
RDT-12	IgG	64	116	43	21	5	111	67.00%	82.20%
	IgA	133	116	69	14	48	68	82.90%	82.20%
RDT-13	IgM	49	146	49	25	0	121	66.20%	100.00%
	IgG	51	141	54	19	0	122	74.00%	100.00%
RDT-14	IgM	250	254	188	62	0	254	75.20%	100.00%
	IgG	250	254	123	127	2	252	49.20%	99.20%
	Combined	249	254	192	58	2	252	76.80%	99.20%
RDT-15	IgM	250	79	82	168	2	77	32.80%	97.50%
	IgG	250	79	158	92	4	75	63.20%	94.90%
	Combined	167	79	163	87	6	73	65.20%	92.40%
RDT-16	IgM	250	253	109	141	2	251	43.60%	99.20%
	IgG	250	253	119	131	3	250	47.60%	98.80%
	Combined	249	253	140	110	4	249	56.00%	98.40%
RDT-17	IgM	250	253	168	82	10	243	67.20%	96.00%
	IgG	250	253	169	81	6	247	67.60%	97.60%
	Combined	247	253	184	66	14	239	73.60%	94.50%
RDT-18	IgM	97	100	62	35	0	100	63.90%	100.00%
	IgG	97	100	92	5	3	97	94.80%	97.00%
RDT-19	IgG	4	126	4	0	0	126	100.00%	100.00%
	IgM	4	126	4	0	3	123	100.00%	97.60%
RDT-20	IgG	183	97	137	46	6	91	94.00%	94.00%
	IgA	183	97	159	24	16	81	83.00%	83.00%
RDT-21	Combined	95	105	87	8	0	105	92.00%	100.00%
RDT-22	Combined	95	100	90	5	2	103	95.00%	98.00%
RDT-23	IgG	126	72	67	59	0	72	53.20%	100.00%
	IgM	126	72	74	52	0	72	58.70%	100.00%
	Combined	122	72	77	45	0	72	64.30%	100.00%
RDT-24	IgG	128	72	79	49	1	71	61.70%	98.60%
	IgA	128	72	107	121	10	62	83.60%	86.10%
	Combined	128	72	108	20	9	63	84.40%	87.50%
RDT-25	IgM	98	200	91	7	2	98	92.86%	98.00%
RDT-26	IgG	98	200	77	21	0	100	78.57%	100.00%
	IgM	98	200	71	27	1	99	72.45%	99.00%
RDT-27	IgG	98	200	84	14	7	93	85.71%	93.00%
	IgM	98	200	82	16	1	99	83.67%	99.00%
RDT-28	IgG	136	100	127	9	1	99	93.40%	99.00%
RDT-29	IgG	136	100	120	16	6	94	88.20%	94.00%
RDT-30	IgG	170	163	77	93	0	163	45.29%	100.00%
RDT-31	Combined	70	633	65	5	20	613	92.00%	96.94%
RDT-32	IgG	114	100	97	17	1	99	85.21%	99.00%
	IgM	114	100	96	18	3	123	84.36%	97.00%
RDT-33	IgG	114	100	87	27	1	99	76.71%	99.00%
	IgM	114	100	97	17	1	99	85.21%	99.00%
RDT-34	IgG	114	100	88	26	2	98	76.79%	98.00%
	IgM	114	100	83	31	0	100	72.86%	100.00%
RDT-35	Combined	49	51	47	2	2	49	95.90%	96.10%

RDT, rapid diagnostic test; *N+*, number of positive sera confirmed by RT-PCR; *N-*, number of control serum (non-COVID)

3.4. Meta-analysis of Diagnostic Accuracy of COVID-19 Antibody Tests

This chapter presents the results of the meta-analysis of the diagnostic accuracy and performance of COVID-19 antibody tests authorized by FDA Philippines which focuses on the comparisons of the performance of CLIA, ELISA, and LFIA. This chapter is divided into four (4) parts: (a) forest plots of sensitivity and specificity of individual studies,

(b) summary receiver operating characteristics (sROC) curves with its corresponding area under the curve (AUC), (c) pooled sensitivity and specificity estimated using a bivariate random-effects model and (d) subgroup analysis.

Table 5. Summary of number of studies that have data on the performance of COVID-19 antibody tests

Antibody	CLIA	ELISA	LFIA	Total
IgG	2	5	9	16
IgM	2	0	7	9
IgA	0	3	0	3
Combined	0	2	8	10

Table 5 presents a summary of the number of studies that have data on the performance of different COVID-19 antibody tests. A total of sixteen (16) studies for IgG detection, nine (9) studies for IgM, three (3) studies for IgA, and ten (10) studies for combined antibodies detection. Note that for LFIA, some studies tested multiple brands of the same test type which were reflected on the forest plot or multiple entries from one study. To avoid bias, the results were not pooled within those studies.

3.4.1. Forest Plots of Diagnostics Performance of COVID-19 Antibody Tests

The following figures are the forest plots of diagnostic performance of COVID-19 antibody tests of the individual studies included in the meta-analysis. The plots include the number of true positives, false positives, false negatives, and true negatives, as well as the computed sensitivities and specificities with their corresponding confidence intervals. Visual plots of the estimated sensitivity and specificity are also shown in the forest plots. Figure 4 shows the forest plot of the individual studies included in detecting IgG antibodies. For the studies that reported the performance of CLIA, sensitivity ranges from 53.0 to 95.0%. Notice that the two (2) records for CLIA have statistically different sensitivities as shown by their non-overlapping confidence intervals. In comparison, the range of sensitivities for ELISA is lower at 38.0 to 75.0% while for LFIA, the range is as low as 44.0% and as high as 100.0%. On the other hand, in terms of specificity, all reported data do not vary much with a range of 93.0 to 100.0% for all types of tests.

Figure 5 shows the forest plot of the individual studies included in detecting IgM antibodies. For the studies that reported the performance of CLIA, sensitivity ranges from 59.0 to 64.0% while all reported specificities are 100.0%. Both sensitivity and specificity from the two (2) included studies for CLIA are not statistically different at a 95% level of confidence. On the other hand, sensitivities for LFIA ranges from 17.0 to 100.0%. Meanwhile, in terms of specificity, all reported data do not vary much with a range of 76.0 to 100.0% for all types of tests.

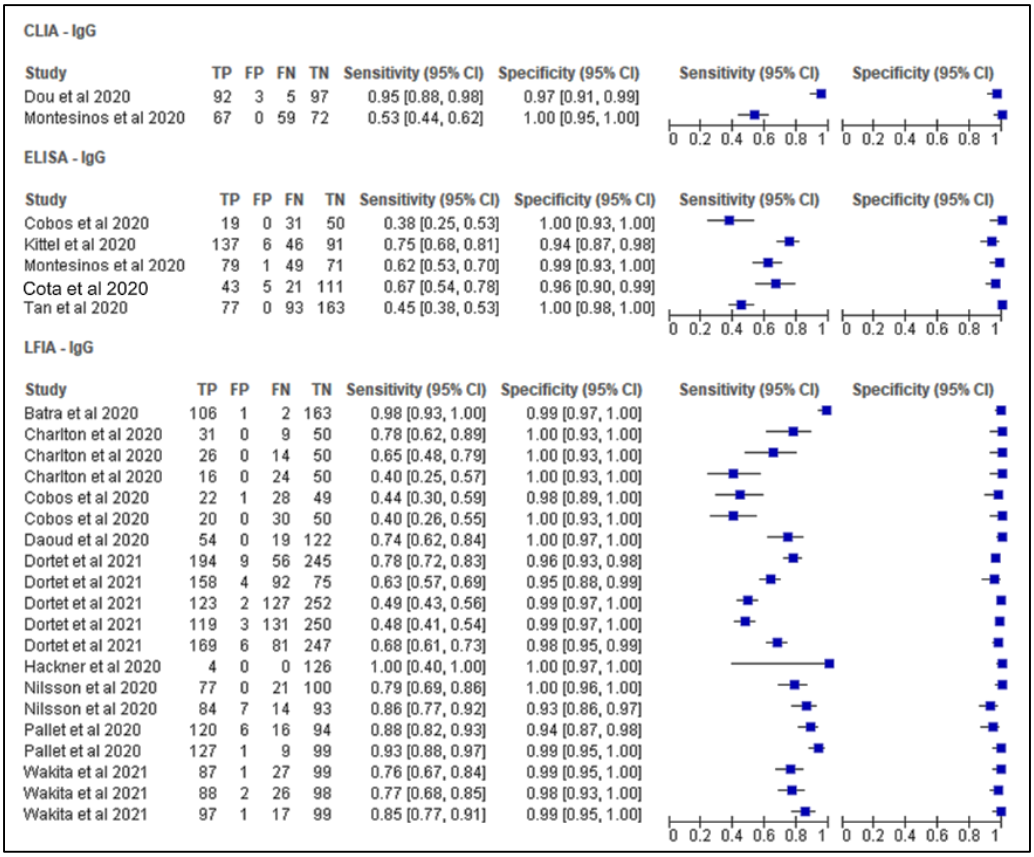

Figure 4. Forest plot of diagnostic performance of CLIA, ELISA and LFIA in detecting IgG antibodies

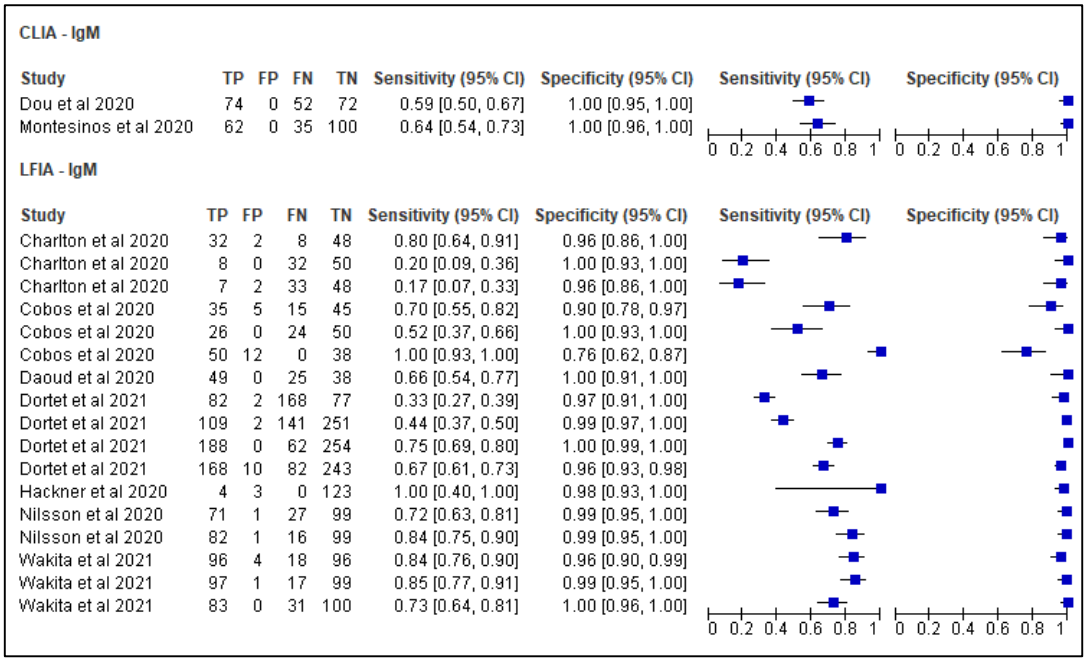

Figure 5. Forest plot of diagnostic performance of CLIA and LFIA in detecting IgM antibodies

In terms of IgA antibodies detection, Figure 6 shows that the sensitivity of ELISA ranges from 83.0% to 87.0%, which is higher and more compact than the reported sensitivities for IgG and IgM. On the other hand, specificities range from 59.0% up to 86.0%, which is slightly at a disadvantage when compared to the results of the other two (2) antibodies.

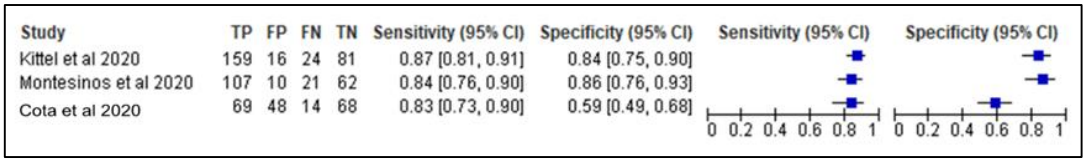

Figure 6. Forest plot of diagnostic performance of ELISA in detecting IgA antibodies

Figure 7 presents the forest plot of the studies that reported the diagnostic performance of ELISA and LFIA in detecting combined antibodies. For ELISA, sensitivity ranges from 84.0 to 93.0% which is considerably high compared to the previous reports. Specificities range from 88.0 to 97.0%. Both sensitivity and specificity from the two (2) included studies for ELISA do not have statistical difference at a 95% level of confidence. On the other hand, sensitivities for LFIA ranges from as low as 57.0% up to as high as 100.0%. All reported data for specificity do not have variation, ranging from 90.0 to 100.0% for all types of tests.

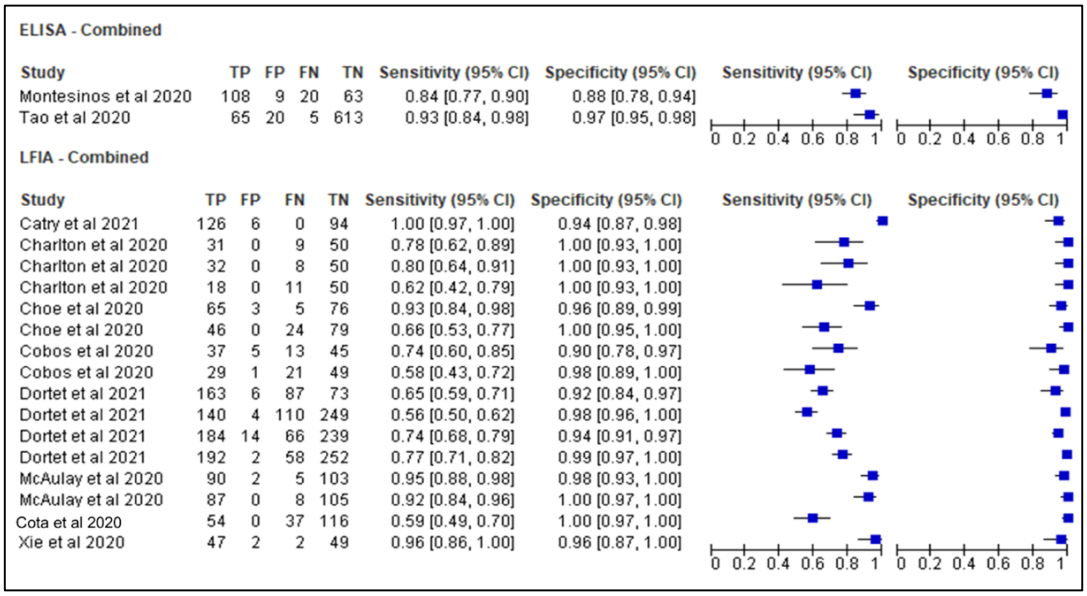

Figure 7. Forest plot of diagnostic performance of ELISA and LFIA in detecting combined antibodies

To summarize, the forest plots of the diagnostic performance of COVID-19 Antibody tests in detecting IgG, IgM, and combined antibodies indicate that the data for sensitivity show a low to moderate level of heterogeneity, while data for specificity are highly homogeneous. On the other hand, data for sensitivities in detecting IgA antibodies are more homogenous than their corresponding specificities. To further test this claim, the authors estimated a bivariate random-effects model and conducted a subgroup analysis to determine whether heterogeneity is present in the data. The results of the models are presented in Tables 6 to 9 of this chapter.

3.4.2. Summary Receiver-operating Characteristics Curves of COVID-19 Antibody Tests

The following figures display the summary ROC (sROC) curve generated from all the included studies of each testing mechanism. From each figure, all testing mechanisms are analyzed by their performance in detecting the same immunoglobulin type through the sensitivity and specificity reported by each study that represents the said testing mechanism. The hollow shapes inside the plot indicate the reported sensitivity against (1-specificity) from every included study in the review and are scaled by the inverse variance of the study, while the solid curved lines are the ROC curves. The Area Under the Curve (AUC) was also computed to summarize the overall diagnostic accuracy of the test. It ranges from 0-1 wherein an AUC of 0 pertains to a perfectly inaccurate test whereas an AUC of 1 pertains to a perfectly accurate test [23].

Figure 8 shows the sROC curve generated by studies that have antibody test kits that detect IgG antibodies. The black circles and black curved line represent the studies that represent CLIA test kits, the red diamonds and red curved line represent ELISA, and lastly, the green boxes and curved line represent LFIA. Based on the figure, both CLIA and LFIA seem to have an almost equal diagnostic performance in detecting IgGs due to their nearly overlapping sROCs. On the other hand, ELISA is shown to have poorer diagnostic performance as compared to the other two antibody tests due to it being relatively father from the upper left corner indicating a perfect test and is relatively closer to the dotted diagonal line or line of no effect. Additionally, an AUC value of 0.973 was computed and this denotes that the diagnostic tests can sufficiently differentiate diseased from healthy individuals.

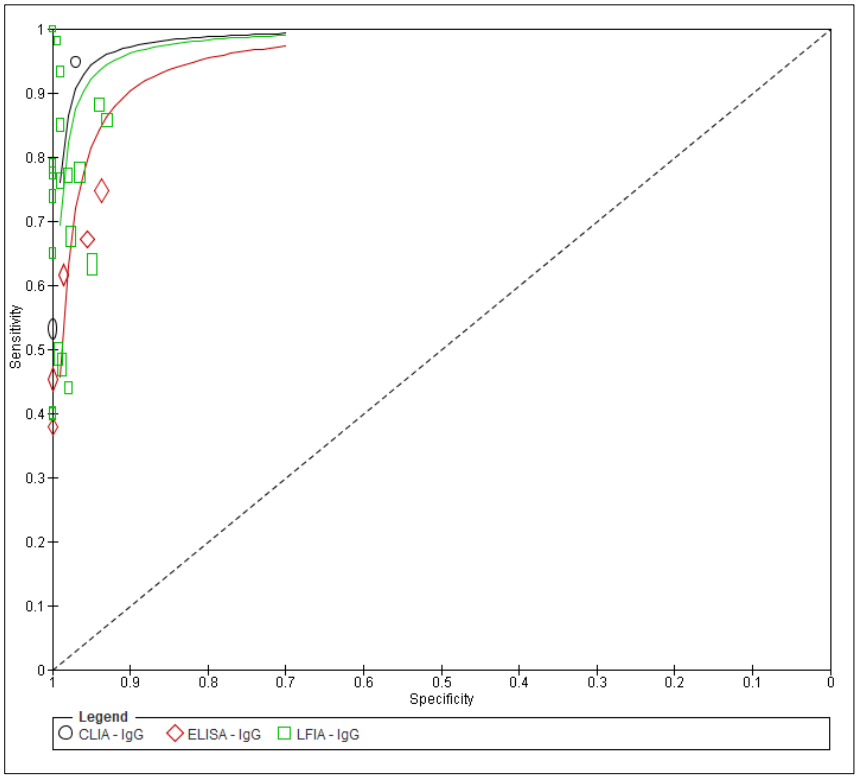

Figure 8. Summary ROC curve of COVID-19 antibody test for IgG antibodies

Figure 9 shows the sROC curve showing the performance of test kits in detecting IgM antibodies. The black circles and black curved line represent the studies that represent CLIA test kits, while the red diamonds and red curved line represent LFIA. LFIA is seen to have a lower diagnostic performance as compared to CLIA due to its sROC curve being relatively closer to the line of no effect. Nonetheless, the performance of the two test types is statistically tied as per the bivariate random-effects model. From the computation for AUC, a value of 0.953 was obtained and infers that the diagnostic test is can reliably discriminate diseased from healthy individuals.

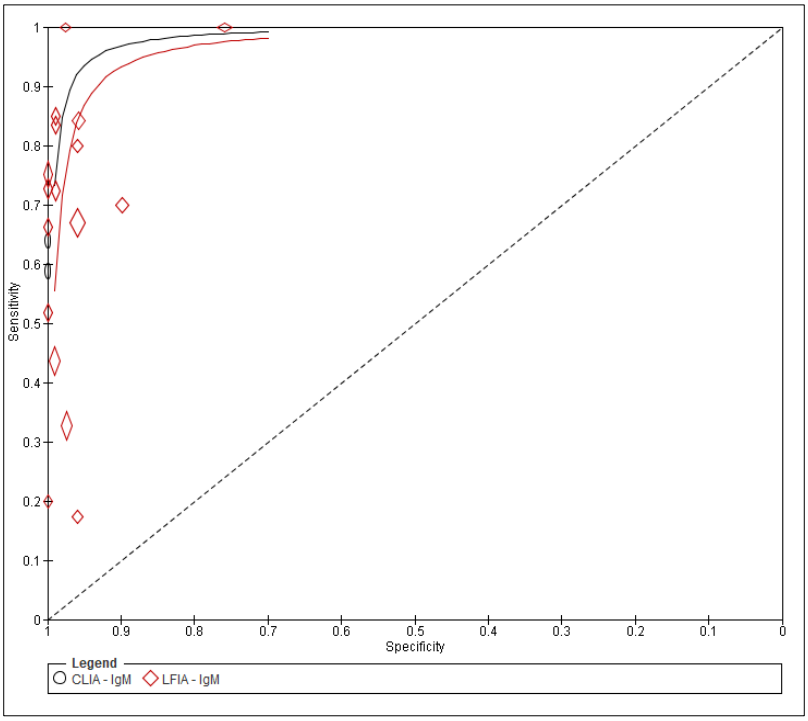

Figure 9. Summary ROC curve of COVID-19 antibody test for IgM antibodies

The black dots and the black line represent the studies for ELISA. Based on Figure 10, the dots occupied the upper middle portion of the graph which shows a good balance between the sensitivity and specificity of the test. In contrast, the previous sROC charts are too clustered on the far left of the chart which shows very high specificities but also compromised the sensitivity of the test. As for its AUC, it cannot be computed due to the limited number of studies available.

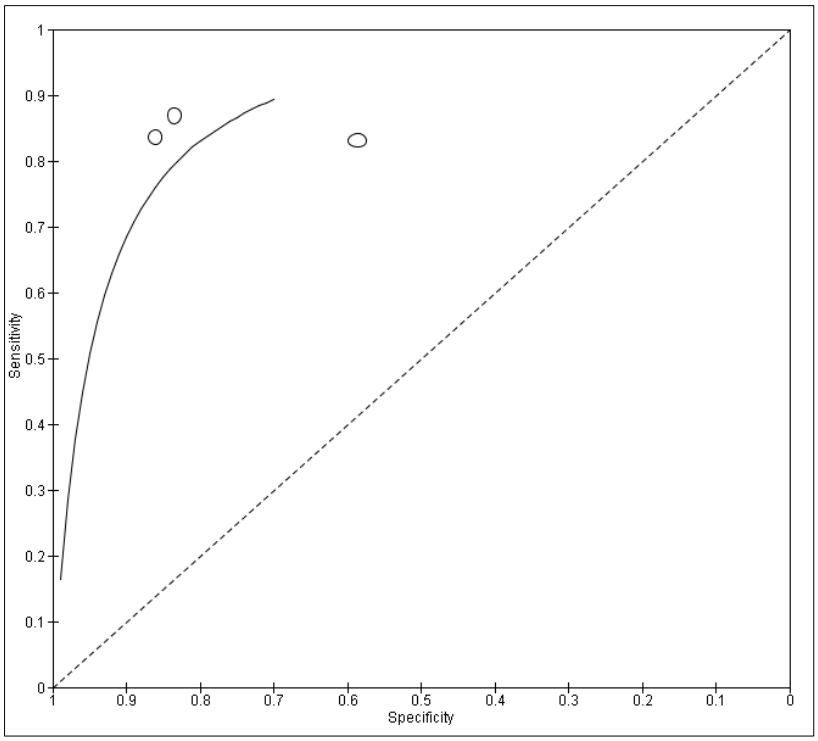

Figure 10. Summary ROC curve of COVID-19 antibody test for IgA antibodies

The black dots and line represent the studies for ELISA while the red dots and line represent the studies for LFIA. Based on Figure 11, LFIA has better diagnostic performance compared to ELISA although the difference is only slight. Nonetheless, the performance of the two test types is statistically tied as per the bivariate random-effects model. As for its AUC, it obtained a value of 0.966 which also indicates a high performing and accurate test.

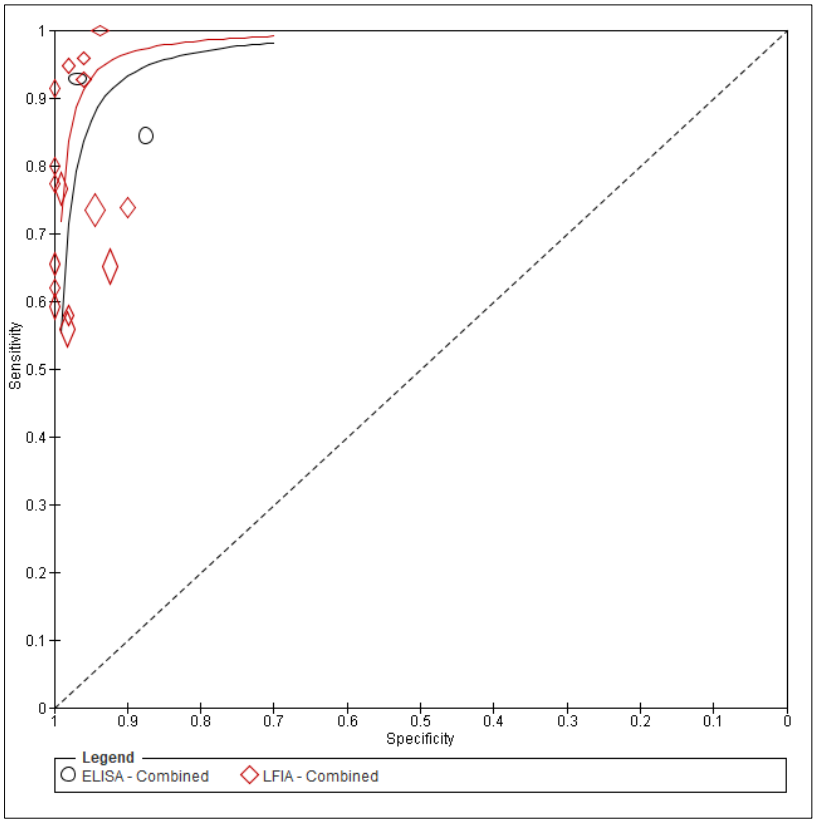

Figure 11. Summary ROC curve of COVID-19 antibody test for combined antibodies

3.4.3. Pooled Sensitivities and Specificities of COVID-19 Antibody Tests from the Bivariate Random Effects Model

The following tables present the estimated pooled sensitivity and specificity of different COVID-19 antibody tests using the bivariate random-effects model as this is the preferred method for the estimation of a summary value of sensitivity and specificity, their direct correlation, as well as for the evaluation of how their expected values may vary with study level covariates [24].

Table 6. Pooled sensitivities and specificities of COVID-19 antibody tests for IgG antibody from the bivariate random effects model

Test	Sensitivity	95% Confidence Intervals		Specificity	95% Confidence Intervals	
		Lower	Upper		Lower	Upper
CLIA	81.7%	38.4%	97.0%	99.3%	82.1%	100.0%
ELISA	58.7%	45.8%	70.4%	98.9%	93.7%	99.8%
LFIA	74.3%	64.8%	82.0%	98.8%	97.7%	99.3%
Overall	72.0%	63.5%	79.1%	98.8%	97.8%	99.3%

A huge variation in the pooled sensitivities is seen as presented in Table 6. ELISA has the lowest pooled sensitivity at 58.7% while CLIA has the highest pooled sensitivity at 81.7%, although it also has the widest confidence interval estimate with a lower bound of 38.4% and an upper bound of 97.0%. Overall, the pooled sensitivity of all COVID-19 antibody test in detecting IgG antibody is 72.0% (95% CI: [63.5%, 79.1%]). From the given data, there is no significant difference seen in the pooled sensitivities of the antibody tests at a 95% confidence level.

On the other hand, the pooled specificities of the tests are nearer to one another as compared to their sensitivities. CLIA has the highest average specificity at 99.3% followed by ELISA at 98.9% and finally by LFIA at 98.8%. Overall, the pooled specificity for all tests is 98.8% with a 95% confidence interval: a lower bound of 97.8% and an upper bound of 99.3%. In any case, the COVID-19 antibody tests are very reliable in predicting specimens negative from COVID-19.

Table 7. Pooled sensitivities and specificities of COVID-19 antibody tests for IgM antibody from the bivariate random effects model

Test	Sensitivity	95% Confidence Intervals		Specificity	95% Confidence Intervals	
		Lower	Upper		Lower	Upper
CLIA	61.0%	54.4%	67.2%	100.0%	0.0%	100.0%
LFIA	69.6%	54.5%	81.3%	98.4%	96.6%	99.2%
Overall	68.5%	55.4%	79.2%	98.7%	97.2%	99.4%

Based on Table 7, CLIA has a lower pooled sensitivity of 61.0% compared to LFIA with a pooled sensitivity of 69.6%. Overall, the pooled sensitivity of all COVID-19 antibody tests in detecting IgM antibodies is 68.5% (95% CI: [55.4%, 79.2%]). No significant difference is seen in the pooled sensitivities of the antibody tests at a 95% confidence level.

On the other hand, the pooled specificities of the tests are nearer to one another compared to their sensitivities. Both studies for CLIA reported a 100.0% specificity, hence the pooled specificity stayed at 100.0% while the pooled specificity of LFIA is 98.4% with a 95% confidence interval of 96.6% to 99.2%. Overall, the pooled specificity for all tests is 98.7% with a 95% confidence interval lower bound of 97.2% and an upper bound of 99.4%. Nonetheless, the COVID-19 antibody tests are very reliable in predicting specimens negative from COVID-19.

Table 8. Pooled sensitivity and specificity of COVID-19 antibody tests for IgA antibody from the bivariate random effects model

ELISA	Sensitivity	95% Confidence Intervals	
		Lower	Upper
Sensitivity	84.8%	80.7%	88.2%
Specificity	77.5%	61.5%	88.2%

Based on Table 8, the average sensitivity of the test is 84.8% with a 95% confidence interval of 80.7% to 88.2%. Meanwhile, the pooled specificity is 77.5% with a 95% confidence interval of 61.5% to 88.2%. These results suggest that detecting IgA antibodies using the ELISA test kits is considerably more reliable compared to detecting IgG or IgM antibodies. However, the specificity of the test is less efficient for IgA compared to IgG and IgM despite having higher sensitivity.

Table 9. Pooled sensitivities and specificities of COVID-19 antibody tests for combined antibodies from the bivariate random effects model

Test	Sensitivity	95% Confidence Intervals		Specificity	95% Confidence Intervals	
		Lower	Upper		Lower	Upper
ELISA	89.0%	79.6%	94.4%	94.0%	84.8%	97.8%
LFIA	81.6%	70.8%	89.0%	98.3%	96.5%	99.2%
Overall	82.5%	73.3%	89.0%	97.9%	96.0%	98.9%

Table 9 presents the estimated pooled sensitivity and specificity of different COVID-19 antibody tests in detecting a combination of IgG, IgM, or IgA antibodies using the bivariate random-effects model. LFIA has a lower pooled sensitivity of 81.6% compared to ELISA with a pooled sensitivity of 89.0%. Overall, the pooled sensitivity of all COVID-19 antibody tests in detecting combined antibodies is 82.5% (95% CI: [73.3%, 89.0%]). Hence, it can be derived in the given data that there is no significant difference in the pooled sensitivities of the antibody tests at a 95% confidence level.

On the other hand, the pooled specificities of the tests are nearly similar compared to their sensitivities. Pooled specificity for ELISA is lower at 94.0% with a confidence interval of 84.8% to 97.8% compared to the pooled specificity of LFIA at 98.3% with a 95% confidence interval of 96.5% to 99.2%. Overall, the pooled specificity for all tests is 97.9%, with a 95% confidence interval lower bound of 96.0% and an upper bound of 98.9%. Nonetheless, the COVID-19 antibody tests are very reliable in predicting specimens negative from COVID-19.

3.4.4. Subgroup Analysis using Bivariate Random-effects Model with Covariates

Since there are huge gaps and differences in the reported sensitivities for the detection of IgG, IgM and combined antibodies, the researchers conducted a subgroup analysis to further investigate the potential heterogeneity in the data.

Using the bivariate random-effects model with covariates, wherein the test types are used as covariates, the proponents tested for the significant difference of the estimated parameter for sensitivity for each test type while fixing the specificity.

Table 10. Subgroup analysis using bivariate random effects model with covariates

Antibodies detected	Log-likelihood		Chi-square Test Statistic	Degrees of Freedom	p-value
	Original Model	With Covariates			
IgG	-164.07	-162.32	3.4989	2	0.1739
IgM	-118.11	-118.09	0.0424	1	0.8368
Combined	-113.57	-113.50	0.154	1	0.7129

Notice that the log-likelihood of the models slightly increased. In addition, all the p-values of the test statistic are not less than or equal to 0.05, hence, there is no sufficient evidence to conclude that the models with covariates are better than the full model. Therefore, the type of test does not affect the diagnostic performance of the antibody test and thus, there is no significant difference between the true sensitivities of CLIA, ELISA, and LFIA in detecting COVID-19 IgG antibodies, CLIA and LFIA in detecting COVID-19 IgM antibodies, and ELISA and LFIA in detecting combined antibodies.

4. Summary

Based on the included studies, the forest plots of the reported diagnostic performance of COVID-19 antibody tests showed that CLIA has the highest sensitivity range in detecting IgG antibodies. The highest sensitivity ranges for ELISA and LFIA were seen in the detection of combined antibodies. However, the reported sensitivity in detecting IgA antibodies using ELISA is higher and more compact than any of the reported sensitivities for IgG and IgM. In terms of specificity, all reported ranges do not vary for all the types of tests. This indicates that the data for sensitivity shows a low to moderate level of heterogeneity while the data for specificity are highly homogeneous.

Summary ROC curves were used to visually assess the heterogeneity of the given data for each test type in terms of their diagnostic performance. In IgG detection, CLIA and LFIA have an almost equal diagnostic performance since their summary ROC curves are nearly overlapping. For IgM detection, LFIA has a slightly lower diagnostic performance compared to CLIA. The use of ELISA in IgA detection, on the other hand, shows a good balance between the sensitivity and specificity of the test. In contrast, the summary ROC curves of IgG and IgM detection shows very high specificities but compromises the sensitivity of the test. Lastly, LFIA has a better diagnostic performance compared to ELISA with a minimal difference in the detection of combined antibodies. In addition, area under the curve was computed to evaluate each test type in terms of their diagnostic accuracy. Most of their values are near to the value of 1 which indicates that the tests are almost perfectly accurate. The detection of IgG has the highest computed value followed by combined antibodies and lastly by IgM. However, the AUC value for IgA cannot be computed due to the limited number of studies available.

To investigate the potential heterogeneity in the data, estimated pooled sensitivity and specificity were done using bivariate random-effects models. This showed that there are no significant differences in terms of sensitivity among CLIA, ELISA and LFIA in detecting IgG, IgM, and combined antibodies at a 95% confidence interval. For IgA antibody detection, ELISA showed better sensitivity compared to the detection of IgG and IgM antibodies. Since there were huge gaps in the reported sensitivities, a subgroup analysis was conducted wherein the computed p-values are not less than or equal to 0.05. Therefore, the sensitivity of the antibody test in the detection of IgG, IgM and combined antibodies do not significantly vary in terms of test type. All tests are considered to have high specificities in detecting specimens negative from COVID-19 but is relatively lower for IgA antibodies despite having a higher sensitivity.

5. Conclusion and Recommendations

In this systematic review and meta-analysis, existing evidence on the diagnostic accuracy of antibody tests for COVID-19 were found to be characterized by high risks of bias. Consistency in the heterogeneity of sensitivities is factored by the differences in the number of available studies and patient characteristics such as time of sample collection and symptom onset. On the other hand, consistency in the homogeneity of high specificities was observed except in IgA detection using ELISA which may be influenced by the number of available studies and the possible presence of other viral infections at the time of sample collection. Based on their AUC values, all test types, CLIA, ELISA and LFIA, in the detection of IgG, IgM and combined antibodies were found to have excellent diagnostic accuracies, mostly influenced by their outstanding specificities.

Future studies that aim to evaluate the diagnostic accuracy of SARS-CoV-2 antibody test kits through systematic reviews should design a more well-balanced approach in gathering significant studies. This can be accomplished by

collecting articles across a wider platform of journal databases and by implementing a more flexible, yet structured inclusion and exclusion criteria. It is also notable that the sensitivity and specificity of the CLIA antibody testing kits are the highest among the three testing mechanisms. The results may be skewed in this manner due to the lack of journal articles that represent specific brands for CLIA. This partiality can be resolved by gathering the same number of articles for each testing mechanism to reduce the disparity regarding the number of references and its effect on the results.

6. Declarations

6.1. Author Contributions

Conceptualization, C.R.R.C., E.D.E.D.S., K.V.H.E., R.L.G.E., J.F., S.A.E.O., C.L., J.E.D.L. and S.D.T.; methodology, C.R.R.C., E.D.E.D.S., K.V.H.E., R.L.G.E., J.F. and S.A.E.O.; formal analysis, C.R.R.C., E.D.E.D.S., K.V.H.E., R.L.G.E., J.F., S.A.E.O. and J.E.D.L.; investigation, C.R.R.C., E.D.E.D.S., K.V.H.E., R.L.G.E., J.F. and S.A.E.O; data curation, C.R.R.C., E.D.E.D.S., K.V.H.E., R.L.G.E., J.F., S.A.E.O. and J.E.D.L.; writing—original draft preparation, C.R.R.C., E.D.E.D.S., K.V.H.E., R.L.G.E., J.F. and S.A.E.O.; writing—review and editing, C.R.R.C., E.D.E.D.S., K.V.H.E., R.L.G.E., J.F. and S.A.E.O.; supervision, S.D.T. and C.L.; project administration, K.V.H.E. and R.L.G.E. All authors have read and agreed to the published version of the manuscript.

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The authors received no financial support for the research, authorship, and/or publication of this article.

6.3. Ethical Approval

This study does not involve the use of animals and humans therefore ethical permission is not required.

6.4. Data Availability Statement

Data available in a publicly accessible repository: The data presented in this study are openly available in Elsevier at https://doi.org/10.1016/j.jcv.2020.104645 [4]; Elsevier at https://doi.org/10.1016/j.jviromet.2020.114060 [5]; ASM Journals at https://doi.org/10.1128/JCM.01361-20 [6]; Wiley Online Library at https://doi.org/10.1002/jmv.26060 [7]; Springer at https://doi.org/10.1007/s10096-020-04092-3 [8]; International Journal of Infectious Diseases at https://doi.org/ 10.1016/j.ijid.2020.10.008 [9]; Frontiers at https://doi.org/10.3389/fcimb.2020.00479 [10]; ASM Journals at https://doi.org/10.1128/JCM.02342-20 [11]; Wiley Online Library at https://doi.org/10.1002/jcla.23681 [12]; German Medical Science at https://doi.org/10.3205/dgkh000363, [13]; International Journal of Infectious at https://doi.org/10.1016/j.ijid.2020.12.003 [14]; Wiley Online Library at https://doi.org/10.1002/jmv.26060 [15]; Elsevier at https://doi.org/10.1016/j.jcv.2020.104413, [16]; International Journal of Infectious Diseases at https://doi.org/10.1016/j.ijid.2020.12.017 [17]; The Lancet at https://doi.org/10.1016/S2213-2600(20)30315-5 [18]; Pathology Journal at https://doi.org/10.1016/j.pathol.2020.09.007, [19]; Frontiers at https://doi.org/10.3389/fcimb.2020.00470, [20]; PLOS One at https://doi.org/10.1371/journal.pone.0246536 [21]; Elsevier at https://doi.org/10.1016/j.diagmicrobio.2020.115248 [22].

6.5. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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