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A Comparison of the Performance of SARS-CoV-2 Antibody Assays in Healthcare Workers with COVID-19

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Abstract

Aims

Since its emergence, significant interest surrounds the use of SARS-CoV-2 serological tests as an alternative or as an adjunct to molecular testing. However, given the speed of this pandemic, paralleled with the pressure to develop and provide serological tests in an expediated manner, not every assay has undergone the rigorous evaluation that is usually associated with medical diagnostic assays. We aimed to examine the performance of several commercially available SARS-CoV-2 IgG antibody assays among participants with confirmed COVID-19 disease and negative controls.

Methods

Serum taken between day 17 and day 40 post onset of symptoms from 41 healthcare workers with RT-PCR confirmed COVID-19 disease, and pre-pandemic serum from 20 negative controls, were tested for the presence of SARS-CoV-2 IgG using 7 different assays including point-of-care (POC) and laboratory-based assays.

Results

Assay performance varied. The lab-based Abbott diagnostics SARS-CoV-2 IgG assay proved to be the assay with the best positive and negative predictive value, and overall accuracy. The POC Nal von Minden GmbH and Biozek assays also performed well.

Conclusion

Our research demonstrates the variations in performance of several commercially available SARS-CoV-2 antibody assays. These findings identify the limitations of some serological tests for SARS-CoV-2. This information will help inform test selection and may have particular relevance to providers operating beyond accredited laboratories.

Introduction

SARS-CoV-2 is the novel coronavirus which causes COVID-19 disease. As of early May 2021, over 150 million SARS-CoV-2 infections have been recorded globally, resulting in over 3 million deaths [1]. Since its emergence, significant interest surrounds the use of SARS-CoV-2 serological tests as an alternative or an adjunct to molecular testing. The major advantage of serological tests over their molecular counterparts is their assumed ability to identify individuals who have previously been infected. This information can enable better understanding of COVID-19 epidemiology. It may also have the potential to inform individual risk of future disease, though this depends on further research in the area of post-infection immunity [2].

The arrival of COVID-19 has brought with it the development of several novel laboratory-based and point-of-care (POC) serological tests that target different antigens of the SARS-CoV-2 virus. ELISA (enzyme linked immunosorbent assays), CLIA (Chemiluminescent immunoassay), CMIA (Chemiluminescent microparticle immunoassay - a subtype of CLIA) and ECLIA (electrochemiluminescence immunoassay) are laboratory-based tests that test serum or plasma samples for the presence of antibodies and can give results in hours. They detect antibodies to viral antigens by measuring the intensity of a colour or signal change upon the addition of an enzyme substrate. These are high-throughput tests and can give both quantitative and qualitative results. LFA (lateral flow assays) meanwhile can be carried out at the point-of-care (POC) using serum, plasma, whole blood or finger prick samples. These tests work by detecting antibodies via a colour change in the test strip. LFA are small, rapid tests that are used outside the laboratory and give results within minutes. However, they are low throughput tests and give a qualitative result only. Such tests were the subject of commercial promotion during the early days of the pandemic with some companies advertising their tests for sale to businesses and employers among others [3], though health agencies and regulatory authorities expressed caution over their use and interpretation outside of national testing strategies [4, 5].

The aim of our study was to examine the performance of several commercially available SARS-CoV-2 antibody assays.

Methods

Ethical approval for this study was granted by the St. James's Hospital and Tallaght University Hospital research ethics committee in April 2020 (reference 2020-04 List 15) with prior existing ethical approval in place to analyse pre-pandemic reference samples for assay quality and development purposes (reference 2016-09 (CA)2).

Symptomatic healthcare workers with COVID-19 disease confirmed by RT-PCR were randomly selected from an existing hospital database of COVID-19 positive patients and invited to participate in the study. Informed consent was obtained, and serum samples were collected from participants during April 2020. Stored serum samples predating the pandemic were included for analysis as negative controls. These samples were taken from outpatients in non-infectious/inflammatory states.

Serum samples were processed and tested for the presence of SARS-CoV-2 IgG antibodies using the assays described in Table 1. The Abbott assay results were interpreted using the manufacturers recommended signal/cut off (S/CO) ratio at the time of 1.4. Samples at or above this S/CO were determined to be positive. Samples below the S/CO were determined to be negative. Results from the 2 other laboratory assays (DIA.PRO Diagnostic Bioprobes Srl and EUROIMMUN AG) were calculated according to their manufacturers specifications and reported as negative, borderline or positive. For the purposes of analysis, borderline results were interpreted as being positive. The lateral flow assay results were assessed and recorded by the authors as per their manufacturers' instructions. Only the IgG results from the lateral flow assays were included in this research.

Sensitivity and specificity were calculated for each assay. The positive and negative predictive values of each assay were calculated using a disease prevalence of 3.1%. This figure was the estimated SARS-CoV-2 seroprevalence in a Dublin population according to a national study carried out in July 2020 (Study to Investigate COVID-19 Infection in People Living in Ireland (SCOPI)) [6].

Table 1. List of assays tested, including the manufacturer, type of assay and platform involved. CMIA = Chemiluminescence microparticle immunoassay, ELISA = Enzyme-linked immunosorbent assay, LFIA = Lateral flow immunoassay.

Manufacturer	Name of Test	Format	Target	Platform
Abbott Diagnostics	SARS-CoV-2 IgG assay	CMIA	Nucleocapsid protein	Abbott Architect i4000sr
DIA.PRO Diagnostic Bioprobes Srl	COVID-19 IgG Enzyme Immunoassay	ELISA	Nucleocapsid and spike proteins 1 & 2	Dynex DS2 Automated ELISA system
EUROIMMUN AG	Anti-SARS-CoV-2 ELISA (IgG) assay	ELISA	S1 spike protein	Dynex DS2 Automated ELISA system
Biozek	COVID-19 IgG/IgM Rapid Test Cassette	LFIA	SARS-CoV-2 antigen-coated particles	Rapid Test Cassette
Hangzhou Testsea Biotechnology	SARS-CoV-2 IgG/IgM Test Cassette	LFIA	SARS-CoV-2 antigen-coated particles	Rapid Test Cassette
Nal von Minden GmbH	COVID-19 IgG/IgM Test	LFIA	SARS-CoV-2 antigen-coated particles	Rapid Test Cassette
Wuhan UNscience Biotechnology	COVID-19 IgG/IgM Rapid Test Kit	LFIA	SARS-CoV-2 antigen-coated particles	Rapid Test Cassette

Results

Forty one healthcare workers with COVID-19 disease confirmed by RT-PCR (13 male and 28 female) were recruited to this study. The median age of these participants was 42 years (IQR 34-50 years). All participants experienced symptomatic COVID-19 disease prior to serum sample collection. 4 participants (3 female and 1 male) were hospitalised during the course of their illness, though none were admitted to ICU. All participants were between 17 and 40 days post the onset of their symptoms at the time of sample collection (median 30 days, IQR 23-34 days). Stored pre-pandemic serum samples from 20 participants, 5 male and 15 female, were used as negative controls. The median age of these participants was 40 years (IQR 35-52 years).

Results from control participants are shown in Table 2. Several false positive results can be seen throughout the samples. This data suggests that false positive detections are not sample specific. Table 3 highlights the results of different assays tested on participants with confirmed COVID-19. As can be seen from this table, seropositivity does not always correlate with disease severity, as not all participants who were hospitalised due to COVID-19 disease had detectable antibodies across all assays, in contrast to several of the non-hospitalised participants.

Table 4 demonstrates the variability of sensitivity results across different platforms and manufacturers. There was significant variation in test sensitivity between assays; sensitivity ranged from 61% - 98%. The three lowest performing assays in terms of sensitivity were from the LFA group. These were the assays from Biozek (80%), Nal von Minden GmbH (76%) and Hangzhou Testsea Biotechnology (61%). The assays with the highest sensitivities were the lab-based DIA.PRO Diagnostic Bioprobes Srl (98%) and Euroimmun AG (93%) assays, followed by the point-of-care LFA from Wuhan UNscience Biotechnology (90%).

Specificity also varied, though not as widely as sensitivity, across all the assays tested, ranging between 90% - 100%. The assay with the lowest specificity was the lab based DIA.PRO Diagnostic Bioprobes Srl, which had a specificity of 90%, followed by the lab based Euroimmun AG and LFA Wuhan UNscience Biotechnology, both at 95%. The three other point-of-care LFAs (Biozek, Nal von Minden GmbH and Hangzhou Testsea Biotechnology) had the highest specificities at 100%, along with the lab-based assays from Abbott.

Negative predictive values (calculated using a disease prevalence of 3.1% (6)) were consistently high (with the lowest calculated negative predictive value being 99% (shared by the three LFAs from Biozek, Nal von Minden GmbH and Hangzhou Testsea Biotechnology). However, significant differences were noted between the positive predictive values of the assays, with results ranging from 24% - 100%. Given the low estimated disease prevalence, any false positive results among control samples led to a drastic reduction in the positive predictive value of the assay. False positive results in the control group resulted in 3 assays performing poorly in this category (DIA.PRO Diagnostic Bioprobes Srl at 24 %, and Euroimmun and Wuhan UNscience Biotechnology assays at 37%. The lab-based Abbott assays, as well as the point-of-care LFAs from Nal von Minden GmbH, Biozek and Hangzhou Testsea Biotechnology, performed best with positive predictive values of 100%.

Table 2. Overview of basic participant demographics and results from assays tested on "pre-pandemic" negative control samples. "Positive" results are highlighted in red font and "negative" results in black font. "Borderline" results are highlighted in blue font and were considered "positive" in terms of analysis.

Sample number	Gender	Age	Abbott Diagnostics	DIA.PRO Diagnostic Bioprobes Srl	EUROIMMUN AG	NaI von Minden GmbH (IgG only)	Wuhan UNscience Biotechnology (IgG only)	Biozek (IgG only)	Hangzhou Testsea Biotechnology (IgG only)
1	F	38	Neg	Borderline	Neg	Neg	Neg	Neg	Neg
2	F	33	Neg	Neg	Neg	Neg	Neg	Neg	Neg
3	F	51	Neg	Neg	Neg	Neg	Neg	Neg	Neg
4	M	17	Neg	Neg	Neg	Neg	Neg	Neg	Neg
5	M	71	Neg	Neg	Neg	Neg	Neg	Neg	Neg
6	F	35	Neg	Neg	Neg	Neg	Neg	Neg	Neg
7	M	39	Neg	Neg	Neg	Neg	Neg	Neg	Neg
8	F	36	Neg	Neg	Neg	Neg	Neg	Neg	Neg
9	M	49	Neg	Neg	Neg	Neg	Neg	Neg	Neg
10	F	44	Neg	Neg	Neg	Neg	Neg	Neg	Neg
11	F	40	Neg	Neg	Neg	Neg	Neg	Neg	Neg
12	F	21	Neg	Neg	Neg	Neg	Neg	Neg	Neg
13	M	41	Neg	Neg	Neg	Neg	Neg	Neg	Neg
14	F	56	Neg	Neg	Neg	Neg	Neg	Neg	Neg
15	F	62	Neg	Pos	Neg	Neg	Neg	Neg	Neg
16	F	39	Neg	Neg	Neg	Neg	Neg	Neg	Neg
17	F	55	Neg	Neg	Neg	Neg	Pos	Neg	Neg
18	F	30	Neg	Neg	Pos	Neg	Neg	Neg	Neg
19	F	71	Neg	Neg	Neg	Neg	Neg	Neg	Neg
20	F	30	Neg	Neg	Neg	Neg	Neg	Neg	Neg

Table 3. Overview of basic participant demographics and results from the various assays tested on symptomatic participants with proven COVID-19. "Positive" results are highlighted in red font and "negative" results are highlighted in black font. "Borderline" results are highlighted in blue font ("borderline" results were considered "positive" in terms of analysis).

Participant number	Admitted to Hospital?	Gender	Age	Days Post symptom onset	Abbott Diagnostics	DIA.PRO Diagnostic Bioprobes Srl	EUROIMMUN AG	Nal von Minden GmbH (IgG only)	Wuhan UNscience Biotechnology	Biozek (IgG only)	Hangzhou Testsea Biotechnology (IgG only)
1	Yes	F	59	18	Pos	Pos	Pos	Pos	Pos	Pos	Pos
2	No	M	28	23	Pos	Pos	Pos	Pos	Pos	Pos	Pos
3	No	F	27	21	Pos	Pos	Pos	Pos	Pos	Pos	Pos
4	No	F	35	34	Pos	Pos	Pos	Neg	Pos	Neg	Neg
5	No	F	50	21	Pos	Pos	Pos	Pos	Pos	Pos	Pos
6	No	F	41	35	Pos	Pos	Pos	Pos	Pos	Pos	Pos
7	No	F	43	23	Neg	Pos	Borderline	Pos	Neg	Pos	Pos
8	No	M	35	32	Pos	Pos	Pos	Pos	Pos	Neg	Neg
9	No	F	64	29	Pos	Pos	Pos	Pos	Pos	Pos	Pos
10	No	M	49	26	Pos	Pos	Neg	Neg	Pos	Pos	Neg
11	Yes	F	26	26	Neg	Neg	Neg	Neg	Neg	Neg	Pos
12	Yes	F	31	21	Pos	Pos	Pos	Pos	Pos	Pos	Neg
13	No	M	35	30	Pos	Pos	Pos	Neg	Pos	Pos	Neg
14	No	F	40	30	Pos	Pos	Pos	Pos	Pos	Neg	Pos
15	No	M	50	23	Pos	Pos	Pos	Pos	Pos	Pos	Pos
16	Yes	M	48	25	Neg	Pos	Pos	Neg	Neg	Neg	Neg
17	No	F	27	27	Pos	Pos	Pos	Pos	Pos	Pos	Pos
18	No	F	59	31	Pos	Pos	Pos	Pos	Pos	Pos	Pos
19	No	F	29	31	Pos	Pos	Pos	Pos	Pos	Pos	Pos
20	No	F	28	39	Pos	Pos	Pos	Pos	Pos	Pos	Pos
21	No	F	62	34	Pos	Pos	Pos	Pos	Pos	Pos	Neg
22	No	F	42	28	Pos	Pos	Pos	Pos	Pos	Pos	Pos
23	No	F	37	35	Pos	Pos	Pos	Neg	Pos	Pos	Neg
24	No	F	24	32	Pos	Pos	Pos	Pos	Pos	Pos	Pos
25	No	F	46	30	Pos	Pos	Pos	Pos	Pos	Pos	Neg
26	No	M	43	17	Neg	Pos	Borderline	Neg	Neg	Neg	Neg
27	No	F	57	32	Pos	Pos	Pos	Pos	Pos	Pos	Pos
28	No	F	48	23	Pos	Pos	Pos	Pos	Pos	Pos	Pos
29	No	F	40	34	Pos	Pos	Pos	Neg	Pos	Pos	Neg
30	No	M	24	40	Pos	Pos	Pos	Neg	Pos	Pos	Neg
31	No	F	45	34	Pos	Pos	Pos	Pos	Pos	Pos	Pos
32	No	F	43	33	Pos	Pos	Pos	Pos	Pos	Pos	Pos
33	No	M	53	36	Pos	Pos	Pos	Pos	Pos	Pos	Pos
34	No	M	40	40	Pos	Pos	Pos	Pos	Pos	Pos	Pos
35	No	F	27	31	Pos	Pos	Pos	Pos	Pos	Pos	Neg
36	No	F	51	35	Neg	Pos	Pos	Pos	Pos	Neg	Pos
37	No	M	52	21	Pos	Pos	Pos	Pos	Pos	Pos	Neg
38	No	F	34	25	Neg	Borderline	Neg	Pos	Pos	Pos	Neg
39	No	F	59	27	Pos	Pos	Borderline	Neg	Pos	Neg	Neg
40	No	M	38	27	Pos	Pos	Pos	Pos	Pos	Pos	Pos
41	No	M	54	21	Pos	Pos	Pos	Pos	Pos	Pos	Pos

Table 4. Assay results for pre-pandemic (negative control) and COVID-19 positive participant samples are shown here, as well as calculations for assay sensitivity, specificity, positive & negative predictive value and accuracy. * = includes one result reported as "borderline". ** = includes three results reported as "borderline".

Manufacturer	Name of Test	Total no. of COVID-19 samples	True Positive	False Negative	Total no. of Controls	True Negative	False Positive	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value(95% CI)	Negative Predictive Value (95% CI)	Accuracy (95% CI)
Abbott Diagnostics	SARS-CoV-2 IgG assay	41	35	6	20	20	0	85% (71% - 94%)	100% (83%-100%)	100%	100% (99%-100%)	100% (93%-100%)
DIA.PRO Diagnostic Bioprobes Srl	COVID-19 IgG Enzyme Immunoassay	41	40*	1	20	18	2	98% (87%-100%)	90% (68%-99%)	24% (8%-54%)	100% (99%-100%)	90% (80%-96%)
EUROIMMUN AG	Anti-SARS-CoV-2 ELISA (IgG) assay	41	38**	3	20	19	1	93% (80%-98%)	95% (75%-99%)	37% (8%-80%)	100% (99%-100%)	95% (86%-99%)
Nal von Minden GmbH	IgG only	41	31	10	20	20	0	76% (60%-88%)	100% (83%-100%)	100%	99% (99%-100%)	99% (93%-100%)
Wuhan UNscience Biotechnology	IgG only	41	37	4	20	19	1	90% (77%-97%)	95% (75%-100%)	37% (8%-80%)	100% (99%-100%)	95% (86%-99%)
Biozek	IgG only	41	33	8	20	20	0	80% (65%-91%)	100% (83%-100%)	100%	99% (99%-100%)	99% (93%-100%)
Hangzhou Testsea Biotechnology	IgG only	41	25	16	20	20	0	61% (45%-76%)	100% (83%-100%)	100%	99% (98%-99%)	99% (92%-100%)

Discussion

Our research demonstrates the variations in the performance of several commercially available SARS-CoV-2 antibody assays, which has implications for assay selection and interpretation in clinical practice.

Accuracy describes the overall probability that a sample result is correctly classified and considers the specificity and sensitivity of an assay in light of an overall disease prevalence. The assay in our study which demonstrated the highest accuracy was the Abbott assay at 100%, followed by the assays from Nal von Minden GmbH, Biozek and Hangzhou Testsea Biotechnology. However, the small samples size of our study and this must be borne in mind when interpreting accuracy, which favours specificity in regard to disease prevalence.

Serological assays are being investigated to explore their utility in complementing RT-PCR tests in the confirmation of COVID-19 disease. These assays potentially have a very important role to play in our response to the COVID-19 pandemic, enabling us to gain a better understanding of disease epidemiology by allowing us to gather data on disease spread through national epidemiological studies. At the time of writing, four SARS-CoV-2 vaccines have been licensed by the EMA and several more are in phase 3 clinical trials with dozens in earlier stages of development. Serological assays will be integral to assessing host vaccine response among vaccine recipients. They can possibly help in informing individual risk of future disease, though this latter point depends on further research in the area of post-infection immunity [2]. Caution is however advised with regards to the use of antibody tests outside of national testing strategies [5], in particular the inappropriate unsupervised use of point-of-care LFAs.

Knowledge of future disease risk could be of importance in informing future workforce planning, especially in the healthcare sector. Healthcare workers (HCWs) are particularly at risk of contracting COVID-19 in the course of their duties [7] and through social risks and, as such, may be considered a vulnerable group in the context of the global COVID-19 pandemic. [8] HCWs may contract COVID-19 through symptomatic [9] or asymptomatic [10, 11] transmission and may in turn be asymptomatic carriers of the virus. Though molecular testing via oro- and nasopharyngeal swabs is the recommended diagnostic and surveillance method to detect current COVID-19 infection in symptomatic individuals, serological testing may be a sensitive method to detect the presence of prior exposure to COVID-19, especially in the asymptomatic or mildly symptomatic population. [12]. SARS-CoV-2 antibody testing studies conducted in individual healthcare centres in the UK [13] and Europe [14] have revealed significant seropositivity in asymptomatic staff as well as interesting findings related to seroconversion rates among different staff sectors. Public Health England (PHE) have implemented a country wide programme of community based HCW COVID-19 antibody testing in order to better understand the trend of infection within the HCW population [15].

The rapid spread of the pandemic fostered pressure to develop and roll out new serological tests in an expedited manner, and thus certain assays may not have undergone the same regulatory scrutiny that is usually associated with medical diagnostic approval. As a result, uncertainty exists around the accuracy of some serological tests that have become available since the advent of the pandemic [16]. The pace of serological diagnostic development in the face of pressing demand has also meant that some tests may not have undergone extensive validation, which is required to put their clinical relevance in context before they are made commercially available. At the time of the commencement of this research (April 2020), 91 different manufacturers had notified the Food and Drug Administration (FDA) of their intention to offer internally validated tests for commercial use [17]. At that time, the FDA indicated that the laboratories should, after notifying the FDA, validate their assays as appropriate and include a report commenting on the limitation of their tests [17, 18]. Such an absence of oversight raises concerns about the performance of some of the commercially available assays.

Further concerns exist around the performance of unvalidated POC tests which are used outside of regulated environments such as accredited laboratories. The relative inferiority of lateral flow assays in this regard means their use should be met with caution, and perhaps even discouraged unless accompanied by expert oversight.

Our research analysed four such POC tests (the four lateral flow assays). The three poorest performing assays in terms of sensitivity in this small study were from the POC group.

Caution should be advised in the interpretation of COVID-19 serology results. Accurate serological interpretation requires robust assay validation as well as an understanding of immunobiology and knowledge of the relevant clinical details. The clinical scenario pertaining to the person undergoing testing, and details on symptomatology, play an extremely important role in the accurate interpretation of serological results. A study published in Clinical Medicine [19] showed that serological result interpretation for SARS-CoV-2 can vary significantly, even among clinicians. This highlights the need for expert guidance in the interpretation of results, especially in the context of a novel disease and new assays. Input from expert clinical and laboratory scientists should be sought if doubt exists around assay result interpretation. This point should be borne in mind when choosing a serological assay to test patients for SARS-CoV-2 seropositivity, teamed with knowledge of different assay performances and optimal testing timeframes.

Studies continue to emerge showing the potential for false positive and false negative antibody results. One case report showed how cross reactivity and a false positive result occurred in a case of granulomatosis with polyangiitis [20]. Incidences of false positive results have been seen in patients suffering from acute infectious conditions, especially infection with Epstein-Barr virus and hepatitis B virus [21]. Other causes of false positive results include rheumatoid factor, human anti-animal antibodies (produced through animal contact, vaccination, blood transfusion, use of drugs of animal origin etc.), and cross reactions between coronaviruses in the same subgenus or different subgenuses (though this is thought to be relatively rare in clinical practice) [22]. False negative results have been attributed to issues around assay formats, the selection of viral antigens and antibody types, diagnostic testing windows, antibody level fluctuation and individual variance [23].

There are limitations to this study. Firstly, this is a small study. Any false positive or false negative results in a small sample among a population with a low disease prevalence can lead to wide ranging results in terms of sensitivity and specificity. Details of the presence of pre-existing infectious or inflammatory conditions in the control group were not recorded. However, the control samples were taken from patients in non-infectious/inflammatory states.

Despite the limitations, our research found that the lab-based Abbott diagnostics SARS-CoV-2 IgG assay proved to be the assay with the best positive and negative predictive value, and overall accuracy, when tested among participants with confirmed COVID-19 disease and negative controls. The point-of-care Nal von Minden GmbH IgG and Biozek assays also performed well. Serological assays for SARS-CoV-2 have multiple potential roles to play in the response to the COVID-19 pandemic, including complementing RT-PCR testing, assessing previous exposure, augmenting epidemiological COVID-19 research, evaluating vaccine efficacy or informing future workforce planning and individual risk of future disease. However, the rapidly evolving nature of the pandemic has expedited the introduction of many diagnostic assays for SARS-CoV-2 antibodies, some of which may not have undergone rigorous validation. Assay result interpretation requires a knowledge of the type of assay employed, the environment in which it is used, its accuracy and an understanding of its limitations.

Declaration of Conflicts of Interest:

None of the authors have any conflicts of interest to declare.

Ethics Approval:

Full ethical approval for this study was granted by the St. James's Hospital and Tallaght University Hospital research ethics committee in April 2020 (reference 2020-04 List 15) with prior existing ethical approval to analyse pre-pandemic reference samples for assay quality and development purposes (reference 2016-09 (CA)2).

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