

1 **Evaluation of six commercial mid to high volume antibody and six point of care**
2 **lateral flow assays for detection of SARS-CoV-2 antibodies**

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33 **Abstract**

34 **Background:** COVID serological tests are essential to determine the overall
35 seroprevalence of a population, and to facilitate exposure estimates within that
36 population.

37 **Methods:** We performed a head-to-head assessment of enzyme immunoassays (EIA)
38 and point of care lateral flow assays (POCT) to detect SARS-CoV-2 antibodies.
39 Demographics, symptoms, co-morbidities, treatment, and mortality of patients whose
40 sera was used were also reviewed.

41 **Results:** Six EIAs (Abbott, Affinity, BioRad, DiaSorin, Euroimmun, and Roche), and six
42 POCTs (BTNX, Biolidics, Deep Blue, Genrui, Getein BioTech, and Innovita) were
43 evaluated for the detection of SARS-CoV-2 antibodies in known COVID-19 infected
44 individuals. Sensitivity of EIAs ranged from 50-100%, with only four assays having
45 overall sensitivities >95% after 21 days post symptom onset. Notably, cross-reactivity
46 with other respiratory viruses (PIV-4 (n=5), hMPV (n=3), rhinovirus/enterovirus (n=1),
47 CoV-229E (n=2), CoV-NL63 (n=2), and CoV-OC43 (n=2) was observed; however,
48 overall specificity for EIAs was good (92-100%; where all but one assay had specificity
49 above 95%). POCTs were 0-100% sensitive >21 days post onset, with specificity
50 ranging from 96-100%. However, many POCTs had faint banding and were often
51 difficult to interpret.

52 **Conclusions:** Serology assays can detect SARS-CoV-2 antibodies as early as 10 days
53 post onset. Serology assays vary in their sensitivity based on the marker (IgA/M vs. IgG
54 vs. total) and by manufacturer; however, overall only 4 EIA and 4 POCT assays had
55 sensitivities >95% >21 days post symptom onset. Cross-reactivity with other seasonal

56 coronaviruses is of concern. The use of serology assays should not be used for the
57 diagnosis of acute infection, but rather for use in carefully designed serosurveys to
58 facilitate understanding of seroprevalence in a population and to identify previous
59 exposure to SARS-CoV-2.
60

61 Introduction

62 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected as
63 an unknown cause of pneumonia in December 2019¹. By January 8, 2020, the Chinese
64 Center for Disease Control and Prevention officially announced a novel coronavirus to
65 be the cause of the outbreak seen in Hubei province². The disease spread quickly; by
66 the writing of this paper (July 1, 2020), there were 10,357,662 confirmed cases and
67 508,055 deaths associated with SARS-CoV-2 globally, which has affected nearly every
68 country in the world³.

69

70 The ability to rapidly diagnose disease, isolate infected patients, and employ contact
71 tracing strategies to mitigate spread of the virus is paramount to slowing the spread.
72 Public health laboratories and acute diagnostic laboratories globally have rapidly
73 developed and implemented diagnostic tests to identify COVID-19 disease. In the acute
74 phases of illness, molecular detection of the virus is the primary tool for early and
75 accurate diagnosis of disease^{4,5}, as antibody production is usually delayed or absent in
76 the acute phase. Serological assays are now being developed as an epidemiological
77 tool for population based serosurveys and identification of remote infection⁶. However,
78 the full extent of SARS-CoV-2 infection in large populations has yet to be determined
79 due to limited testing^{5,7} and the presence of asymptomatic infection. Therefore,
80 serosurveys must be well-designed to best represent the population of interest. To this
81 end, accurate and high-throughput serology assays that can be integrated into
82 laboratory information systems are key to facilitating these large-scale studies, and

improving the understanding of the true proportion of the population that has recovered from COVID-19.

The primary objective of this study was to conduct a direct comparison of six high- to mid-volume commercial enzyme immunoassays (IgG only or IgG with IgM or IgA or total antibody) and six lateral flow point of care assays (IgG/IgM) for detection of SARS-CoV-2 antibodies. All assays were tested against the same panel of serology samples from patients with confirmed COVID-19 and a group of negative controls. High- to mid-volume enzyme immunoassays were also evaluated with a separate panel of convalescent sera to evaluate cross-reactivity to common respiratory viruses and non-SARS-CoV-2 coronaviruses. This performance data, coupled with clinical data from SARS-CoV-2 positive patients, makes our evaluation panel particularly robust, and significantly adds to the current understanding of serology assays for SARS-CoV-2.

Materials and Methods

Assay evaluation:

We evaluated six commercial high- to mid-volume kits: two chemiluminescence immunoassays (CMIA/CLIA; SARS-CoV-2 IgG assay (Abbott Laboratories, Abbott Park, IL, USA); and SARS-CoV-2 S1/S2 IgG (DiaSorin, Stillwater, MN, USA)), three enzyme-linked immunosorbent assays (ELISA; EDI Novel coronavirus COVID-19 IgM and IgG ELISA (Epitope Diagnostics Inc., supplied by AFFINITY Diagnostics Corp, Toronto, ON, Canada); Novel Coronavirus COVID-19 IgM and IgG (DRG International Inc., supplied

106 by BioRad, Hercules, CA, USA); and Anti-SARS-CoV-2 ELISA IgA and IgG assay
107 (Euroimmun, Mississauga, ON, Canada)) and one electrochemiluminescence
108 immunoassay (ECLIA; Anti-SARS-CoV-2 (Roche Diagnostics, Indianapolis, IN, USA))
109 for detection of SARS-CoV-2 antibodies. All assays were assessed for detection of
110 SARS-CoV-2 IgG antibodies. Additionally, Affinity and BioRad were assessed for
111 detection of IgM, and Euroimmun was assessed for detection of IgA antibodies. Testing
112 was performed as per manufacturer specifications and cut-offs were determined as
113 described in the package insert. All values greater than the published cut-off were
114 considered positive. Importantly, all kits were assessed using the same patient samples
115 from single-use aliquots, which negated analyte degradation due to increased
116 freeze/thaw cycles, and allowed for a direct comparison amongst a large number of
117 commercially available serology assays. For the purposes of this study,
118 CLIA/ECLIA/ELISA assays will be referred to as enzyme immunoassays (EIA). Where
119 specified, targets of EIAs are listed in Table 1.

120

121 Additionally, we assessed six point of care lateral flow tests (POCT): Rapid Response
122 (BTNX; BTNX Markham, Ont, Canada), 2019 nCoV IgM/IgG Detection Kit (Biolidics;
123 Biolidics Limited, Mapex, Singapore), SARS-CoV-2 IgG/IgM Ab Test Kit (Deep Blue;
124 Anhui Deep Blue Medical Technology Co., Ltd., Anhui, China), Novel Coronavirus
125 IgG/IgM Test Kit (Genrui; Genrui Biotech Inc., Shenzhen, China), One Step Test for
126 Novel Coronavirus (Geitein; Geitein Biotech Inc. Nanjing, China), and 2019-nCoV Ab
127 test (Innovita; Innovita Biological Technology Co. Ltd., Qian'an, Hebei, China). All
128 assays were assessed for the detection of IgM and IgG antibodies. A positive result

129 was determined by any banding detected for either IgM, IgG. Faint banding was
130 considered positive. Assays where the control line was absent were considered invalid.
131 Testing was performed as per manufacturer specifications. Results were read
132 independently by two laboratorians, and when there was a discrepancy, a third
133 laboratorian reading was used as an arbitrator (+/-/- was considered equivocal, +/-/+
134 was considered positive). Sensitivities at various time intervals and specificities, as well
135 as binomial exact 95% confidence intervals and Fisher's exact tests were calculated
136 (Microsoft Excel and STATA v.15 (StataCorp. 2017. College Station, TX, USA).

137

138 *Precision and reproducibility studies*

139 Patient sera from 4 patients positive for SARS-CoV-2 by reverse transcriptase real-time
140 polymerase chain reaction (rRT-PCR) were pooled and used as the positive control,
141 while patient sera from 4 patients with sera collected prior to November 1, 2019 (from
142 otherwise healthy individuals with specimens sent for immunity screening) were pooled
143 to create the negative control. Reproducibility was assessed by running replicates of 3
144 in triplicate for all EIAs. Precision was determined with quality control (QC) material
145 provided by the manufacturer (positive and negative controls), which was run singly
146 each day of testing (Abbott, DiaSorin), or in triplicate for each day of testing (Affinity,
147 BioRad and Euroimmun). As no QC material was provided for the Roche assay, the
148 pooled positive and pooled negative controls were used as positive and negative
149 controls.

150

151 *Sample collection:*

152 Negative samples were retrieved from bio-banked sera stored at the Public Health
153 Laboratory (Alberta Precision Laboratories) in Alberta collected before November 1,
154 2019. To develop a panel of positive sera from patients with COVID-19, serum samples
155 were collected from hospitalized patients confirmed to be positive for SARS-CoV-2 on
156 nasopharyngeal swab or endotracheal aspirate testing by rRT-PCR. Samples were
157 collected, spun down (3000 RPM for 10 min), aliquoted into single-use aliquots, and
158 frozen at -80 °C until the time of testing.

159

160 Eleven COVID-19 positive patients had serum collected at multiple time periods,
161 however, only one sample per patient was used per time interval to calculate assay
162 sensitivity. When more than one serum sample from the same individual was within the
163 same time interval, only the most recently collected serum sample was included.

164

165 To evaluate cross-reactivity of the EIA serology tests with other respiratory viruses,
166 convalescent sera (either retrieved from stored sera or prospectively collected) were
167 used (note: cross-reactivity panel was not assessed on the POCTs). The sera were
168 from patients who had tested negative for COVID-19 by in-house rRT-PCR, but positive
169 for other viruses as follows (with number of sera used indicated): influenza A (n=5),
170 influenza B (n=5), respiratory syncytial virus (RSVA, n=6; RSVB, n=1),
171 rhinovirus/enterovirus (n=6), human metapneumovirus (hMPV; n=5), parainfluenza virus
172 (PIV-1 and PIV-4; n=4), coronavirus (CoV)-229E (n=6), CoV-NL63 (n=11), CoV-OC43
173 (n=7), or CoV-HKU1 (n=7). One patient was positive for multiple viruses (RSVA and
174 enterovirus/rhinovirus). All non-COVID-19 respiratory virus testing was done using the

175 Luminex Respiratory Pathogen Panel (RPP; NxTAG® Respiratory Pathogen Panel,

176 Luminex, Austin, TX, USA).

177

178 *Chart review*

179 To obtain baseline demographic variables and outcomes for the patients with confirmed

180 SARS-CoV-2 infection, a retrospective chart review of each patient's electronic medical

181 record was performed by two study team members using the provincial electronic

182 medical record (Epic Systems Corporation, Verona, WI, USA). All symptoms listed

183 were at presentation to hospital, and death was attributed to COVID-19 if within 30 days

184 of symptom onset. Basic summary statistics (proportions, median, range) were

185 calculated using Microsoft Excel.

186

187 *Determining the date of symptom onset*

188 The date of symptom onset for each case of laboratory confirmed COVID-19 was

189 determined via history taking using a standardized history intake form by a member

190 from the Alberta Health Services Communicable Diseases Team (Public Health). All

191 serum samples were stratified by this date to determine the number of days between

192 collection of serum and time of symptom onset.

193

194 *Ethics*

195 This study received ethics approval from both the University of Calgary and University

196 of Alberta Health Research Ethics Boards. Certification approval numbers are REB20-

197 0516 and Pro00099818, respectively.

198

199

200 **Results**

201

202 *Population demographics*

203 Serum from twenty-eight patients who tested positive for SARS-CoV-2 by rRT-PCR
204 were used in this study. The mean age of patients was 70.1 (range 34-102 years), with
205 a majority being male (57%; Table 2). Seven percent of patients were ambulatory,
206 while most were hospitalized (93%), and 35% were admitted to the intensive care unit
207 (ICU). Of those who were hospitalized, 27% required mechanical ventilation and 92%
208 developed COVID-19-associated pneumonia. The most common co-morbidities in the
209 cohort were: hypertension (64%), dyslipidemia (57%), and hypothyroidism (36%). All
210 dates of symptom onset were reported earlier than the date of diagnostic sample
211 collection (mean 16 days (range 2 to 48 days)). The date of symptom onset to date of
212 hospitalization ranged from 0-19 days with a mean of 5 days post symptom onset.
213 Recent travel was reported in 14% of all cases, with the United States being the most
214 frequent location of travel (Table 2).

215

216 *Performance characteristics of EIA assays*

217 In total, 46 samples from 28 different patients testing positive for SARS-CoV-2 by rRT-
218 PCR and 50 negative samples from serum samples stored prior to November 1, 2019,
219 were run on each assay. Overall, the positivity rate for each assay increased over time
220 (Table 3). With the exception of the Affinity assay (100% detection), all assays

221 performed poorly prior to seven days post symptom onset (range 40-60%; data not
222 shown). However, this improved over time, and all assays had at least 80% sensitivity
223 (range 80-100%) after 21 days (Table 3). The earliest time to detection was seen when
224 assays had a combination of IgG with either IgM or IgA. For example, Affinity IgM and
225 IgG assays had sensitivities of 76% and 62% respectively when considered individually
226 at 0-14 days post symptom onset, however when combined (with either IgM or IgG
227 positive in a sample), the overall sensitivity increased to 90% (Table 3). Notably, sera
228 collected 46 and 48 days after symptom onset were still detectable for IgM with both
229 BioRad and Affinity Assays, and IgA with the Euroimmun assay.

230

231 Only the Affinity IgM assay was able to detect antibodies with >95% sensitivity before
232 21 days post symptom onset. After 21 days post symptom onset, four assays (Abbott,
233 Affinity, BioRad, and Euroimmun) achieved >95% sensitivity – all four had 100% overall
234 sensitivity (Table 3). However, due to the relatively small sample size, confidence
235 intervals show a substantial overlap between time periods. All assays, with the
236 exception of the Euroimmun IgA assay had specificities >95% for samples collected
237 from patients pre-November 1, 2019 (Table 3).

238

239 *Precision and reproducibility studies*

240 Reproducibility for the EIAs was excellent; all assays showed 100% concordance for all
241 samples. Likewise, precision of the assays was high, with all assays having 100%
242 qualitative agreement for positive and negative controls.

243

244 *Performance characteristics of POCTs*

245 The same validation panel used for the EIA assays was used for all POCTs, with the
246 exception of one specimen (collected day 13 post symptom onset), as the volume of
247 serum was exhausted following evaluation of the EIA assays. As with the EIA assays,
248 performance of the POCTs was poor <7 days post onset with sensitivities ranging from
249 40-60% (data not shown). The performance of the assays increased over time, and all
250 POCTs had >75% sensitivity after 14 days post onset and >90% sensitivity after 21
251 days (Table 4). However, only 4 assays had overall sensitivities that would be
252 acceptable for use in a clinical laboratory (>95%) after 21 days post symptom onset
253 (Table 4). Of note, IgM was poorly detected by a number of POCT assays; Getein
254 detected IgM in only 1 of 42 positive specimens, while Biolidics detected IgM in 10-12%
255 of positive samples. The highest sensitivities for IgM detection among the POCT
256 assays were consistently reported for BTNX, Deep Blue and Genrui; these kits had
257 statistically significantly higher overall (i.e. all-time points calculation) IgM sensitivities as
258 compared to Getein ($p<0.001$ for all), Biolidics ($P\leq 0.004$ for all) and Innovita ($p\leq 0.009$
259 for all) (Table 4).

260

261 Reading the lateral flow assays was often challenging; many kits frequently produced
262 only very faint lines. Because package inserts did not indicate appropriate density of
263 bands to call a positive, for this study, any visualization of a band for either IgM or IgG
264 was considered positive. This approach may have over-called the sensitivity of the
265 lateral flow assays. Of the total reported positives, equivocal bands were observed in
266 9% (3 of 32) of positive samples for Biolidics, 9% (3 of 32) for BTNX, 15% (5 of 33) for

267 Deep Blue, 0% (0 of 33) for Genrui, 4% (1 of 26) for Getein GP BioTech, and 37% (11
268 of 29) for Innovita.

269

270 *Cross-reactivity studies with EIA assays*

271 An additional 62 serum samples were used to assess cross-reactivity with other
272 respiratory viruses on EIA assays. Of those, 15 sera were collected prior to the first
273 case of SARS-CoV-2 diagnosis in Alberta, and 47 were collected after the first case of
274 SARS-CoV-2 was detected in Alberta. All samples collected after the first case were
275 confirmed to be from patients who tested negative for SARS-CoV-2 by rRT-PCR on
276 nasopharyngeal swab testing. Time of RPP positive to serum collection ranged from 11
277 to 135 days (mean 45 days) from the date of the original RPP result.

278 Overall, all assays performed well, with only a few samples showing cross-reactivity.

279 Most notably, the BioRad IgM assay showed cross-reactivity with hMPV on a serum
280 collected 31 days after the RPP, and to PIV-4 on serum from 120 days post RPP, while
281 the BioRad IgG assay showed cross-reactivity with rhinovirus/enterovirus (collected 48
282 days post RPP), and CoV-229E (collected 14 days post RPP). DiaSorin showed cross-
283 reactivity with PIV-4 collected 54 days post RPP. The Euroimmun IgA assay showed
284 cross-reactivity to two CoV-NL63 (collected 37 and 46 days post RPP from different
285 patients), two CoV-OC43 (collected 15 and 49 days post RPP from different patients),
286 CoV-229E (collected 13 days post RPP), and PIV-4 (collected 54 days post RPP), while
287 the IgG assay showed cross-reactivity against PIV-4 (collected 54 days post RPP). The
288 Affinity IgM assay showed cross-reactivity to PIV-4 (collected 120 days post RPP).

289 Abbott, Roche and the Affinity IgG assay did not show any cross reactivity against other

290 respiratory viruses (Table 5). Overall, PIV-4 and CoV-229E were most cross reactive
291 across assays, with additional cross-reactivity noted for CoV-NL63 and CoV-OC43 in
292 one assay (Table 5).

293

294 *Time course of antibody development*

295 To evaluate the progression of antibody development, eleven patients in our study had
296 serial serum samples collected (Table 6). Samples ranged from 5 to 29 days post
297 symptom onset, and patients had between 2 and 6 samples collected overtime.
298 Overall, Abbott detected 63.6% (7 of 11 patients) of the earliest sample drawn from a
299 patient, Affinity detected 100%, BioRad 72.7%, Euroimmun 45.5%, DiaSorin 36.4%, and
300 Roche 63.6% (Table 6). Interestingly, despite four different samples collected from
301 patient 6 (ranging from 18-29 days post symptom onset), antibodies were never
302 detected by the Roche assay. Likewise, patient 7 antibodies were not detected by the
303 DiaSorin, however collection of the two samples was at days 6 and 8, which is relatively
304 early during the course of infection (Table 6). Once a patient was positive by an assay,
305 all sera from subsequent collection days were also positive; and in no instances did a
306 patient go from positive to negative for this timeframe.

307

308 **Discussion**

309

310 We conducted a head-to-head comparison of fourteen different serology assays for
311 detection of SARS-CoV-2 antibodies, in 161 different samples from 143 patients. We
312 found Abbott, Affinity, and BioRad to have the highest clinical sensitivity and specificity

313 compared to the other EIAs. Despite the relatively small panel size, and the wide
314 statistical confidence intervals, we believe these data are very useful and informative for
315 evaluation, comparison and validation purposes. Most EIAs and POCTs performed well
316 after 21 days post symptom onset, however, and most importantly, no single assay was
317 sensitive enough to detect antibodies <7 days post symptom onset. Even assays with
318 IgM or IgA components were unable to detect antibodies reliably before 14 days from
319 time of symptom onset (Tables 3 and 4). Furthermore, many of the assays did not
320 perform at a level that is considered acceptable for laboratory diagnostics (>95%
321 sensitivity and specificity). The use of these assays for diagnostic testing is therefore
322 not recommended.

323

324 It is worth noting that these performance characteristics were determined using a cohort
325 of COVID-19 positive patients which represented mostly hospitalized patients with high
326 mortality rates. Preliminary studies have suggested that more severe infection may
327 have higher seroconversion rates and antibodies may develop earlier when compared
328 to those with mild infection⁸. Therefore, our study data may artificially improve
329 performance characteristics of the assays. Further studies should be done for mostly
330 non-hospitalized COVID-19-positive patients to ensure findings remain consistent
331 across all cohorts.

332

333 As the time course for antibody development has not yet been fully determined for
334 SARS-CoV-2, it is important to compare equivalent start points when analyzing and
335 comparing these data. The sensitivity of serology assays decreases significantly when

336 time of symptom onset rather than time from first PCR positive result is used as the start
337 of infection. In our study, time of PCR positivity was 5.3 days after date of symptom
338 onset on average (range 0-19 days). This time difference has the potential to
339 significantly skew the data. If time of first PCR positive result was used as the start-
340 point for this study, all EIAs and POCTs would perform better earlier in the disease
341 course compared to when the time from symptom onset is used. However, using a
342 positive PCR result to define the start of the infection would be an inaccurate reflection
343 of the development of antibody in an individual. Therefore, whenever possible, studies
344 should strive to include performance data in relation to date of onset, to allow true
345 comparison of SARS-CoV-2 testing data.

346

347 Cross-reactivity with other respiratory viruses was observed with PIV-4, hMPV,
348 rhinovirus/enterovirus, and most importantly CoV-229E, CoV-NL63 and CoV-OC43
349 infection in some of the commercial EIA assays. To date, only small panels assessing
350 cross-reactivity have been performed, and very little cross-reactivity with coronaviruses
351 other than SARS-CoV-1 has been shown⁹. Our larger convalescent sera panel
352 suggests that cross-reactivity with other respiratory viruses may influence SARS-CoV-2
353 serology results, particularly following a recent respiratory infection (within 13-49 days
354 post RPP). As the majority of individuals have been exposed to endemic coronaviruses
355 229E, NL63, OC43, and HKU1 during their lifetime,¹⁰ the cross reactivity of these
356 viruses in particular should be evaluated. In our hands, two different assays showed
357 cross-reactivity against CoV-229E (Euroimmun IgA and BioRad IgG), and one assay
358 (Euroimmun IgA) showed cross-reactivity to two different patient samples positive for

359 CoV-NL63, and an additional two different patient samples positive for CoV-OC43
360 (Table 5). An additional study found a single patient sample to be cross-reactive
361 against coronavirus-OC43, and although the sample number tested was small ($n=5$)⁶,
362 these results are consistent with what we observed in our panel. The potential cross-
363 reactivity of the endemic coronaviruses with SARS-CoV-2 is a significant drawback.
364 Cross-reactivity to other coronaviruses should therefore be considered when
365 interpreting serological results, particularly when determining SARS-CoV-2 prevalence
366 of infection.

367

368 We assessed the ability of EIAs and POCTs to detect antibodies against SARS-CoV-2
369 in human sera, however no correlation with neutralizing antibodies was performed.
370 While a few neutralizing antibody studies have been completed, and show some
371 antibodies are protective (namely against the receptor-binding domain (RBD) of the
372 spike domain),¹¹ the assays that we have evaluated in this study detect total, and not
373 specifically neutralizing, antibodies. Additionally, not all assays target the same
374 antigen-specific antibodies, and therefore the kinetics of detection may not be
375 equivalent between assays (Table 1). As antigen presentation and trafficking will vary
376 between different epitopes, variability between assays is expected. We therefore
377 caution the use of these serology results as indicators of immunity, and recommend
378 further studies be done to measure appropriate immunity markers. This will be
379 particularly important for the POCT assays as the antigens used are often not described
380 (Table 1). Additionally, because SARS-CoV-2 is a recently emerged virus, there is little
381 data on the longevity of immunity following infection. Here we found that both IgM, IgA

382 and IgG were detected in samples >45 days post symptom onset, suggesting that
383 antibodies are detectable for extended periods, however, more extensive long-term
384 evaluations on the level and duration of immunity following infection are needed.
385
386 While the use of serology assays in clinical testing is currently under debate, some
387 recommendations as to the appropriate use of these assays is beginning to emerge.
388 The American Society for Microbiology (ASM) and the WHO recently published similar
389 recommendations against using serology testing for diagnosis of acute infection^{12,13}. A
390 natural delay is seen from the time a patient is exposed to the virus to the time the
391 patient starts creating antibodies against the virus. Therefore, regardless of the
392 sensitivity of the assay, there will always be a delay between infection and the
393 development of antibodies. Recent studies suggest that most patients seroconvert
394 between 7 and 14 days, with IgM and IgA detected as early as 3 and 4 days post
395 symptom onset respectively.⁹ However, we found that detection of antibodies earlier
396 than 14 days was unreliable but performance for all serology assays improved overtime.
397 To this end, both the Centers for Disease Control¹⁴ and the Public Health Agency of
398 Canada¹⁵ have also recommended against using serology assays as an aid in the
399 diagnosis of acute infection. However, serology assays will be helpful in understanding
400 the prevalence of SARS-CoV-2 infection in the population, understanding the timeline of
401 antibody development in different patient populations, and the longevity of the antibody
402 response.
403

404 Here, we present a comprehensive serology panel consisting of sera from known
405 COVID-19 positive patients and known negatives. We have evaluated six different
406 commercial EIA platforms and eight POCT with the same serum panel to give an
407 accurate comparison across all platforms. Based on our results, serology assays
408 should not be used for the diagnosis of acute infections, but rather in carefully designed
409 serosurveys to facilitate understanding of seroprevalence in a population and to identify
410 previous exposure to the virus.

411

412 *Acknowledgements:*

413 We would like to thank the staff of the Public Health Laboratory for their help with
414 specimen logistics. We would also like to thank the following manufacturers for
415 supplying kits for analysis: Abbott, Affinity, BioRad, DiaSorin, Euroimmun, Roche,
416 BTNX, Biolidics, Deep Blue, Genrui, Getein BioTech, and Innovita.

417

418 **Table 1:** Description of serology assays used in this study

419

Company	Detection of Antibody Class	Type of Assay	Volume and Estimated TAT	Assay Target	Approvals	Notes
Abbott	IgG	CMIA	High throughput 45 min per sample	Recombinant antigen nucleocapsid protein	FDA EUA granted April 26, 2020 HC Approved May 14, 2020	A clean of the instrument before and after running SARS-CoV-2 samples is required (~40 min total)
Affinity	IgM and IgG	ELISA	Mid volume 4 hours per 96-well plate	Recombinant antigens of the RBD and spike protein	CE Marked	Package insert recommends testing each sample in duplicate
BioRad	IgM and IgG	ELISA	Mid volume 4 hours per 96-well plate	Antibodies recognizing recombinant nucleocapsid proteins and peptides	Submitted to HC	Package insert recommends testing each sample in duplicate
Diasorin	IgG	CLIA	High throughput 40 min per sample	IgG antibodies directed against the S1 and S2 domains of the spike protein	FDA EUA granted April 24, 2020 HC Approved May 12, 2020	

Eurolmmun	IgA and IgG	ELISA	Mid volume 4 hours per 96- well plate	Recombinant S1 domain of the structural protein	FDA EUA granted May 4, 2020 CE Marked	Package insert recommends testing each sample in duplicate
Roche	IgG	ECLIA	High throughput 45 min per sample	Recombinant protein representing the nucleocapsid antigen	FDA EUA granted May 2, 2020	
BTNX	IgM and IgG	Lateral flow	POCT 15 min per sample	Target unspecified		
Biolidics	IgM and IgG	Lateral flow	POCT 15 min per sample	Recombinant protein, target unspecified		
Deep Blue	IgM and IgG	Lateral flow	POCT 15 min per sample	Target unspecified	Removed from FDA EUA	
Genrui	IgM and IgG	Lateral flow	POCT 15 min per sample	Target unspecified		
Getein BioTech	IgM and IgG	Lateral flow	POCT 15 min per sample	Recombinant nucleocapsid and spike proteins		

Innovita	IgM and IgG	Lateral flow	POCT 15 min per sample	Target unspecified		
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420 **Table 2:** Demographic and clinical variables of patients with confirmed SARS-CoV-2 infection (COVID-19) (n=28).

421

Variable		Value
Age (yrs)	Mean	70.1
	Median	73
	Range	34-102
Female (n (%))		12 (43)
Type of specimen used in diagnosis	Nasopharyngeal (n (%))	27 (96)
	Endotracheal suction (n (%))	1 (4)
Hospitalized (n (%))		26 (93)
Duration of hospitalization (days)	Range	4-51
	Mean	17
	Median	11

Time from symptom onset to hospitalization (days)	Range	-29 to 19*
	Mean	5
	Median	5
Of those hospitalized (n=26):		
ICU admission required in those hospitalized (n (%))		9 (35)
Need for mechanical ventilation in those hospitalized (n (%))		7 (27)
Pulmonary embolism (n (%))		1 (4)
Development of COVID-19 pneumonia (n (%))	Yes	26 (92)
	No	1 (4)
	Unknown	1 (4)
Development of acute	Yes	13 (46)

respiratory distress syndrome (n (%))		
	No	14 (50)
	Unknown	1 (4)
Died (n (%))		9 (32)
Receipt of investigational treatments (n (%))		8 (29)
	HCQ alone	3 (37)
	HCQ + AZT	2 (25)
	LPV/R	1 (13)
	HCQ + LPV/r	2 (25)
Viral co-pathogen (n (%))	Coronavirus-NL63	1 (4)
Symptoms at presentation (n (%))	Fever	17 (61)
	Cough	24 (86)
	Dyspnea	26 (93)

	Myalgias	10 (36)
	Abdominal pain	6 (21)
	Diarrhea	4 (14)
	Sore throat	2 (7)
	Chest pain	10 (36)
	Malaise	18 (64)
	Anorexia	9 (32)
Comorbidities (n (%))	Hypertension	18 (64)
	Diabetes mellitus	7 (25)
		Median HBA1c – 7.2% Range HBA1c – 4.2-10.9%
	COPD	4 (14)
	Coronary artery disease	4 (14)

	Valvular disease	2 (7)
	Obesity (BMI >30 kg/m ²)	4 (14)
	Chronic renal disease (%)	7 (25)
	Hypothyroid (%)	9 (36)
	Asthma	6 (24)
	Congestive heart failure	7 (25)
	Atrial fibrillation	4 (14)
	Dyslipidemia	16 (57)
	Cancer	4 (14)
	HIV	0
Exposures:		
Travel-related	Yes (%)	4 (14)
	No (%)	23 (82)
	Unknown (%)	1 (4)
Location of travel (n=7) (of those who travelled)	United States (%)	2 (50)

	United Arab Emirates (%)	1 (25)
	Within Canada (%)	1 (25)
Contact with traveller	Yes (%)	6 (21)
	No (%)	21 (75)
	Unknown (%)	1 (4)
Related to outbreak in long term care/continuing care facility (%)		9 (32)

422 *Negative due to one health-care acquired case of COVID-19 which occurred 29 days post hospital admission. If this
423 case is removed, the range is 0-19 days.

424

425 *Abbreviations:*

426 HCQ – hydroxychloroquine

427 AZT – azithromycin

428 LPV/r – lopinavir/ritonavir

429 COPD – chronic obstructive pulmonary disease

430 BMI – body mass index (kg/m²)

431 HIV – human immunodeficiency virus
432 HBA1c – glycated hemoglobin (reported for diabetic patients only)
433
434
435

436 **Table 3.** Performance of six SARS-CoV-2 EIAs by date of serum collection relative to date of symptom onset
437

Assay		Positive Samples																				All time points						Negative Samples (serum collected pre Nov 2019)					
		0-14 days								15-21 days								>21 days															
		Neg	Equ	Pos	Sens ¹	CI ²	Neg	Equ	Pos	Sens	Sens ¹	CI ²	Neg	Equ	Pos	Sens	Sens ¹	CI ²	Neg	Equ	Pos	Sens ¹	CI ²	n ³	Neg	Equ	Pos	Spec	Spec ⁴	CI ²			
Abbott	IgG	6	0	15	71	71	48-89	2	0	9	82	82	48-98	0	0	10	100	100	69-100	8	0	34	81	81	66-91	42	49	0	1	98	98	89-100	
Affinity	IgM	5	0	16	76	76	53-92	0	0	11	100	100	72-100	0	0	8	100	100	63-100	5	0	35	88	88	73-96	40	47	0	0	100	100	92-100	
	IgG	8	0	13	62	62	38-82	3	1	7	64	73	31-89	1	0	7	88	88	47-100	12	1	27	68	70	51-81	40	47	0	0	100	100	92-100	
Overall	IgM/IgG	2	0	19	90	90	70-99	0	0	11	100	100	72-100	0	0	8	100	100	63-100	2	0	38	95	95	83-99	40	47	0	0	100	100	92-100	
BioRad	IgM	9	0	12	57	57	34-78	4	1	6	55	64	23-83	5	0	5	50	50	19-81	18	1	23	55	57	39-70	42	49	1	0	98	100	89-100	
	IgG	4	0	17	81	81	58-95	1	2	8	73	91	39-94	0	0	10	100	100	69-100	5	2	35	83	88	69-93	42	50	0	0	100	100	93-100	
Overall	IgM/IgG	4	0	17	81	81	58-95	1	0	10	91	91	59-100	0	0	10	100	100	69-100	5	0	37	88	88	74-96	42	50	0	0	100	100	93-100	
Diasorin	IgG	11	1	9	43	48	22-66	3	0	8	73	73	39-94	1	0	9	90	90	55-100	15	1	26	62	64	46-76	42	48	1	1	96	98	86-100	
Euroimmun	IgA	7	0	14	67	67	43-85	2	0	9	82	82	48-98	0	1	7	88	100	47-100	9	1	30	75	78	59-87	40	46	4	0	92	100	81-98	
	IgG	11	0	10	48	48	26-70	3	0	8	73	73	39-94	1	0	7	88	88	47-100	15	0	25	63	63	46-77	40	50	0	0	100	100	93-100	
Overall	IgA/IgG	5	0	16	76	76	53-92	2	0	9	82	82	48-98	0	0	8	100	100	63-100	7	0	33	83	83	67-93	40	50	0	0	100	100	93-100	
Roche	Total AB	7	0	14	67	67	43-85	3	0	8	73	73	39-94	2	0	8	80	80	44-97	12	0	30	71	71	55-84	42	50	0	0	100	100	93-100	

438

439

440 ¹Sensitivity if equivocal is considered positive441 ²Confidence intervals (CI) are calculated for sensitivity and specificity where equivocals are considered negative442 ³Two invalid samples were observed for Affinity and for Euroimmun (total n = 40)443 ⁴Specificity if equivocal is considered positive

444

445 **Table 4:** Performance of six SARS-CoV-2 lateral flow assays (POCT) by date of serum collection relative to date of
446 symptom onset

Assay		Positive Samples																				Negative Samples (serum collected pre Nov 2019)										
		0-14 days						15-21 days						>21 days						All time points												
		Neg	Equ	Pos	Sens	Sens ¹	CI ²	Neg	Equ	Pos	Sens	Sens ¹	CI ²	Neg	Equ	Pos	Sens	Sens ¹	CI ²	Neg	Equ	Pos	Sens	Sens ¹	CI ²	n ³	Neg	Equ	Pos	Spec	Spec ⁴	CI ²
BTNX	IgM	7	5	8	40	65	19-64	3	1	6	60	70	26-88	0	4	6	60	100	26-88	10	10	20	50	75	34-66	40	50	0	0	100	100	93-100
	IgG	8	1	11	55	60	32-77	3	0	7	70	70	35-93	1	0	9	90	90	55-100	12	1	27	68	70	51-81	40	50	0	0	100	100	93-100
	Overall	6	1	13	65	70	41-85	2	0	8	80	80	44-97	0	1	9	90	100	55-100	8	2	30	75	80	59-87	40	50	0	0	100	100	93-100
Biolidics	IgM	14	2	4	20	30	6-44	8	0	2	20	20	3-56	6	3	1	10	40	0-45	28	5	7	18	30	7-33	40	48	1	1	96	98	86-100
	IgG	6	1	13	65	70	41-85	2	0	8	80	80	44-97	0	0	10	100	100	69-100	8	1	31	78	80	62-89	40	50	0	0	100	100	93-100
	Overall	6	1	13	65	70	41-85	2	0	8	80	80	44-97	0	0	10	100	100	69-100	8	1	31	78	80	62-89	40	50	0	0	100	100	93-100
Deep Blue	IgM	5	4	11	55	75	32-77	3	1	6	60	70	26-88	0	0	10	100	100	69-100	8	5	27	68	80	51-81	40	49	1	0	98	100	89-100
	IgG	11	3	6	30	45	12-54	3	1	6	60	70	26-88	1	0	9	90	90	55-100	15	4	21	53	63	36-68	40	50	0	0	100	100	93-100
	Overall	5	4	11	55	75	32-77	2	1	7	70	80	35-93	0	0	10	100	100	69-100	7	5	28	70	83	53-83	40	50	0	0	100	100	93-100
Genui	IgM	6	0	14	70	70	46-88	2	0	8	80	80	44-97	0	0	10	100	100	69-100	8	0	32	80	80	64-91	40	48	2	0	96	100	86-100
	IgG	10	0	10	50	50	27-73	3	0	7	70	70	35-93	1	0	9	90	90	55-100	14	0	26	65	65	48-79	40	50	0	0	100	100	93-100
	Overall	6	0	14	70	70	46-88	2	0	8	80	80	44-97	0	0	10	100	100	69-100	8	0	32	80	80	64-91	40	50	0	0	100	100	93-100
Getein BioTech	IgM	19	0	0	0	0	0-18	9	0	1	10	10	0-45	10	0	0	0	0	0-31	38	0	1	3	3	0-13	39	50	0	0	100	100	93-100
	IgG	11	0	8	42	42	20-67	3	0	7	70	70	35-93	0	0	10	100	100	69-100	14	0	25	64	64	47-79	39	50	0	0	100	100	93-100
	Overall	11	0	8	42	42	20-67	3	0	7	70	70	35-93	0	0	10	100	100	69-100	14	0	25	64	64	47-79	39	50	0	0	100	100	93-100
Innovita	IgM	9	8	3	15	55	3-38	5	2	3	30	50	7-65	5	3	2	20	50	3-56	19	13	8	20	53	9-36	40	50	0	0	100	100	93-100
	IgG	12	4	4	20	40	6-44	3	1	6	60	70	26-88	1	3	6	60	90	26-88	16	8	16	40	60	25-57	40	50	0	0	100	100	93-100
	Overall	8	7	5	25	60	9-49	2	1	7	70	80	35-93	1	3	6	60	90	26-88	11	11	18	45	73	29-62	40	50	0	0	100	100	93-100

447

448 ¹Sensitivity if equivocal is considered positive449 ²Confidence intervals (CI) are calculated for sensitivity and specificity where equivocals are considered negative450 ³Control failure on one Getein BioTech sample was reported (n=19 for 0-14 day time frame)451 ⁴Specificity if equivocal is considered positive

452

453 **Table 5:** Cross-reactivity of high- to mid-volume serological EIA assays with sera from patients infected for other
 454 respiratory viruses by antibody class

Virus	Abbott G		Affinity M		Affinity G		BioRad M		BioRad G		DiaSorin G		Euroimmun A		Euroimmun G		Roche G	
	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos
Influenza A	5	0	5	0	5	0	4	0	5	0	5	0	5	0	5	0	5	0
Influenza B	5	0	5	0	5	0	5	0	5	0	5	0	5	0	5	0	5	0
RSV A	6	0	6	0	6	0	6	0	6	0	6	0	6	0	6	0	6	0
RSV B	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
Rhino/Entero	6	0	6	0	6	0	6	0	5	1	6	0	6	0	6	0	6	0
hMPV	5	0	5	0	4	1	4	1	4	1	4	0	5	0	5	0	5	0
PIV	4	0	3	1	4	0	3	1	4	0	3	1	3	1	3	1	4	0
Coronavirus 229E	6	0	6	0	6	0	5	0	5	1	6	0	5	1	6	0	6	0
Coronavirus NL63	11	0	11	0	11	0	11	0	11	0	11	0	9	2	11	0	11	0
Coronavirus OC43	7	0	7	0	7	0	7	0	7	0	7	0	5	2	7	0	7	0
Coronavirus HKU1	7	0	7	0	7	0	7	0	7	0	7	0	7	0	7	0	7	0

455
 456

457 **Table 6:** Blood collection over time for SARS-CoV-2 positive PCR patients from time of symptom onset to serum
 458 collection date tested by EIA platform

459

	Days from symptom onset to serum specimen collection ^{1,2}																													
	<7 days						7-14 days							15-21 days							>21 days									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Patient 1												AF/E								AB/B/D/R										
Patient 2							AB/AF/B/D/E/R																							
Patient 3					AB/AF/B/R							D/E																		
Patient 4									AB/AF/B/R				E			D														
Patient 5									AB/AF/B/R			D/E																		
Patient 6																		AF/E			B		AB						D	
Patient 7						AF/R		AB/B/E																						
Patient 8					AB/AF/B/D/E/R																									
Patient 9													AF/B/D/E									AB/R								
Patient 10					AB/AF/B/D/E/R																									
Patient 11						AB/AF/B						D/E/R																		

460

461

462 ¹Day of sample collection is indicated with a grey box with black outline

463 ²The earliest detection of antibodies by an assay is indicated by: AB, Abbott; AF, Affinity; B, BioRad; D, DiaSorin; E,

464 Euroimmun; R, Roche

465

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