Letter to the Editor – ACCEPTED MANUSCRIPT

Title:
Diagnostic accuracy and utility of SARS-CoV-2 antigen lateral flow assays in medical admissions with possible COVID-19

Authors:
Hamish Houston\textsuperscript{a}, Ankur Gupta-Wright\textsuperscript{b,c,d}, Edward Toke-Bjolgerud\textsuperscript{a}, James Biggin-Lamming\textsuperscript{a}, Laurence John\textsuperscript{a}.

Author affiliations:
\begin{itemize}
\item[a] Northwick Park Hospital, London North West University Healthcare NHS Trust, Harrow, United Kingdom
\item[b] Institute for Global Health, University College London, London, United Kingdom
\item[c] Clinical Research Department, London School of Hygiene & Tropical Medicine, London, United Kingdom
\item[d] Ealing Hospital, London North West University Healthcare NHS Trust, London, United Kingdom
\end{itemize}

Corresponding Author:
Dr Ankur Gupta-Wright
Institute for Global Health
University College London
Mortimer Market, off Caper Street
London
WC1E 6JB
United Kingdom
07764607560
a.gupta-wright@ucl.ac.uk / ankurgw@outlook.com
Dear Editor,

The scale-up of SARS-CoV-2 antigen lateral flow assays (LFAs) has caused much controversy, with concerns about lower sensitivity in asymptomatic individuals and when assays are performed by operators without healthcare training.\textsuperscript{1,2} The proposed benefits of SARS-CoV-2 antigen LFAs are high specificity, fast turnaround times for results (under 30 minutes) and ease of scalability.\textsuperscript{3} These assays are of potential utility for rapidly identifying SARS-CoV-2 in patients who fit the COVID-19 case definition and require hospital admission as prompt isolation prevents nosocomial transmission. Isolation rooms are often limited and capacity easily overwhelmed, necessitating the cohorting of patients with proven COVID-19. Even using rapid platforms, SARS-CoV-2 RT-PCR turnaround times are often too slow to inform patient placement from emergency departments (EDs).\textsuperscript{4} SARS-CoV-2 LFAs could help improve flow of patients from the ED into ‘COVID-19 positive’ cohorts and reduce pressure on limited hospital isolation rooms. However, little data exists on their diagnostic accuracy in this setting.

We therefore evaluated diagnostic accuracy of the Innova SARS-CoV-2 Antigen Rapid Qualitative Test (Lotus Global Company, London, UK) compared to SARS-CoV-2 RT-PCR from nasopharyngeal swabs (NPS) in adult admissions who met the COVID-19 case definition at a busy acute hospital in the UK.\textsuperscript{5} The Innova LFA was performed as per the manufacturer’s instructions by appropriately trained health-care assistants in the ED. A second NPS was simultaneously sent for SARS-CoV-2 RT-PCR. Between the 17\textsuperscript{th} November 2020 and 31\textsuperscript{st} December 2020, 728 patients presenting to the ED met the COVID-19 case definition and had valid Innova LFA and RT-PCR results. Baseline characteristics are shown in Table 1A. 55·1\% were male and median age was 67·5 years. 264 patients tested positive by Innova LFA. Those testing positive were younger (median age 65 vs 71, p=0.038), more unwell (NEWS of 5 vs 3, p<0.001) and more often febrile on arrival (Temperature >38°C in
41.9% vs 15.8%, p<0.001) than those with negative LFA results. Overall, admission SARS-CoV-2 RT-PCR was positive in 38.5% (280/728).

Compared to SARS-CoV-2 RT-PCR as the reference standard, the Innova LFA had sensitivity of 86.4% (242/280, 95% Confidence Interval [CI] 81.9-90.0) and specificity of 95.1% (426/448, 95%CI 92.6-96.7) (Table 1B). 22/448 (4.9%) patients with a negative SARS-CoV-2 RT-PCR on admission had a positive LFA. 8 of these 22 patients reported a positive COVID-19 test result up to 14 days prior to admission and 5/22 subsequently had a positive PCR result within 5 days of admission. 13/22 had chest radiograph features consistent with ‘classic/probable COVID-19’ as reported by a radiologist. Only 5/22 patients had no PCR or radiological evidence of COVID-19. 1/5 patients reported a confirmed household contact and only 2/5 left hospital with a diagnosis other than COVID-19. This suggests the lower than expected specificity of Innova LFA is likely to be a result of an imperfect reference standard, and specificity would be higher if using a clinical and RT-PCR based composite reference standard.6

38 patients had negative Innova LFAs but positive PCR results. 20/38 had cycle threshold (Ct) values available, with median Ct values of 29 (IQR 27-35). Innova LFA results were available a median 3.2 hours after arrival (IQR 2.0-4.3, n=681) compared to 13.8 hours (IQR 9.9-18.2, n=679) for RT-PCR. 57.1% (n=35) had chest radiographs which were reported as typical for COVID-19. Of those with symptom duration recorded, 77.3% (17/22) were symptomatic for at least 7 days prior to attending the ED.

Accounting for the inadequacy of a single SARS-CoV-2 RT-PCR as a reference standard, we found the Innova SARS-CoV-2 Antigen Rapid Qualitative Test had good specificity in patients with symptoms of COVID-19 presenting to hospital. Sensitivity in this setting was high (86.4%) when compared to pre-clinical evaluation studies.1 Furthermore, results were mostly available within a few hours of
presentation, allowing transfer of patients to COVID-19 cohort areas and reducing demand for isolation rooms whilst awaiting PCR results. Placing patients in the ‘right bed’ first-time is also likely to reduce delays in care and increase efficiency, and allows isolation rooms to be prioritised for individuals requiring admission with suspected COVID-19 but negative LFA results. Of the 38 patients with COVID-19 (based on SARS-CoV-2 RT-PCR) who were ‘missed’ by the Innova LFA, median Ct values were reasonably high, and correspond to viral loads associated with lower sensitivity in previous studies. However, sensitivity of the Innova LFA appears lower than some other SARS-CoV-2 viral antigen LFAs. Importantly, individuals requiring admission with suspected COVID-19 should not be moved out of isolation on the basis of a negative SARS-CoV-2 viral antigen LFA results.

In summary, the Innova LFA can be used to rapidly identify COVID-19 cases amongst hospital admissions meeting the COVID-19 case definition with good diagnostic accuracy, and rapidly identify patients that can be allocated to COVID-19 cohort areas. Based on these data, this application of COVID-19 LFAs has now been recommended by NHS England.
Declarations:

Funding: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sector. The manufacturer (Lotus Global Company, London, UK) had no role in the study conception, design, data analysis or manuscript preparation.

Approval: The study was approved by the London North West University Hospitals Trust Research and Development Committee, and given the SARS-CoV-2 antigen lateral flow assay was implemented as part of routine clinical care and this was a retrospective review using routinely collected clinical data, they deemed formal ethical approval was not required.

Acknowledgements: We would like to acknowledge to all the clinical staff at Northwick Park Hospital who cared for the patients involved in this study, particularly the point-of-care team within the emergency department.

Conflicts of interest: The authors declare that they have no competing interests.
References


2. Deeks, JJ. Operation Moonshot proposals are scientifically unsound. BMJ 2020;370:m3699. doi: https://doi.org/10.1136/bmj.m3699


### A – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LFA Negative</th>
<th>LFA Positive</th>
<th>Total</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>464</td>
<td>264</td>
<td>728</td>
<td></td>
</tr>
<tr>
<td>Age on arrival (years) median (IQR)</td>
<td>71 (53-5, 83) (n=464)</td>
<td>65 (49-5, 80) (n=264)</td>
<td>67-5 (52, 82) (n=728)</td>
<td>0.038</td>
</tr>
<tr>
<td>Age over 65 years, n (%), 95%CI</td>
<td>260 (56-0%, 51-5 - 60-6)</td>
<td>125 (47-3%, 41-3 - 53-4)</td>
<td>385 (52-9%, 49-3 - 56-5)</td>
<td>0.024</td>
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<td>Female Sex, n (%)</td>
<td>211 (45-5%, 40-9 - 50-0)</td>
<td>116 (43-9%, 38-0 - 49-9)</td>
<td>327 (44-9%, 41-3 - 48-5)</td>
<td>0.69</td>
</tr>
<tr>
<td>Male Sex, n (%)</td>
<td>253 (54-5%, 50-0 - 59-1)</td>
<td>148 (56-1%, 50-1 - 62-0)</td>
<td>401 (55-1%, 51-5 - 59-7)</td>
<td></td>
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<tr>
<td>NEWS, median (IQR)</td>
<td>3 (1, 6) (n=422)</td>
<td>5 (3, 7) (n=230)</td>
<td>4 (2, 6) (n=652)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse, median (IQR)</td>
<td>94 (82, 111) (n=426)</td>
<td>96 (84, 108) (n=229)</td>
<td>95 (82, 110) (n=655)</td>
<td>0.66</td>
</tr>
<tr>
<td>Systolic BP, median (IQR)</td>
<td>136 (120, 151) (n=421)</td>
<td>135·5 (122·5, 149) (n=228)</td>
<td>136 (121, 151) (n=649)</td>
<td>0.93</td>
</tr>
<tr>
<td>Diastolic BP, median (IQR)</td>
<td>78 (68, 88) (n=421)</td>
<td>80 (71, 89) (n=228)</td>
<td>79 (70, 88) (n=649)</td>
<td>0.10</td>
</tr>
<tr>
<td>Respiratory rate, median (IQR)</td>
<td>20 (18, 27) (n=425)</td>
<td>24 (20, 32) (n=228)</td>
<td>22 (18, 28) (n=653)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Required Supplemental Oxygen, n (%), 95%CI</td>
<td>72 (16-9%, 13-3 - 20-4)</td>
<td>69 (29-9%, 24-0 - 35-8)</td>
<td>141 (21-4%, 18-3 - 24-6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature &gt;38°C, n (%), 95%CI</td>
<td>67 (15-8%, 12-3 - 19-2)</td>
<td>96 (41-9%, 35-5 - 48-3)</td>
<td>163 (24-9%, 21-6 - 28-2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### B – Diagnostic Performance

<table>
<thead>
<tr>
<th></th>
<th>LFA Negative</th>
<th>LFA Positive</th>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>464</td>
<td>264</td>
<td>728</td>
<td></td>
</tr>
<tr>
<td>SARS-CoV2 RNA Detectable on RT-PCR, n (%)</td>
<td>38</td>
<td>242</td>
<td>280</td>
<td>Sensitivity = 86-4% (95%CI 81·9-90·0)</td>
</tr>
<tr>
<td>SARS-CoV2 RNA Undetectable on RT-PCR, n (%)</td>
<td>426</td>
<td>22</td>
<td>448</td>
<td>Specificity = 95-1% (95%CI 92·6-96·7)</td>
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</table>

**Table 1 footnotes:**

**A** - Baseline characteristics and SARS-CoV-2 RT-PCR results for patients testing positive and negative by the Innova Lateral Flow Antigen (LFA) Assay. For observations on arrival, 9·6 to 10·9% of data were missing. Pair-wise comparisons were performed using chi-squared tests for proportions, t-tests for means and Wilcoxon rank sum for median. *P*-values are shown for the comparison between the LFA positive and LFA negative groups. IQR=Inter-quartile range, CI=Confidence Interval, NEWS=National Early Warning Score, SpO2=Oxygen Saturations.

**B** - Diagnostic performance of the Innova Lateral Flow Antigen (LFA) Assay compared to a single SARS-CoV-2 RT-PCR from nasopharyngeal swab on admission. PPV = Positive Predictive Value, NPV = Negative Predictive Value, CI = confidence interval.