Real-world deployment of lateral flow SARS-CoV-2 antigen detection in the emergency department to provide rapid, accurate and safe diagnosis of COVID-19

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SUMMARY

Background: Point-of-care (POC) SARS-CoV-2 lateral-flow antigen detection (LFD) testing in the emergency department (ED) could inform rapid infection control decisions but requirements for safe deployment have not been fully defined.

Methods: Review of LFD test results, laboratory and POC-RT-PCR results and ED-performance metrics during a two-week high SARS-CoV-2 prevalence period followed by several months of falling prevalence.

Aim: Determine whether LFD testing can be safely deployed in ED to provide an effective universal SARS-CoV-2 testing capability.

Findings: 93% (345/371) of COVID-19 patients left ED with a virological diagnosis during the 2-week universal LFD evaluation period compared to 77% with targeted POC-RT-PCR deployment alone, on background of approximately one-third having an NHS Track and Trace RT-PCR test-result at presentation. LFD sensitivity and specificity was 70.7% and 99.1% respectively providing a PPV of 97.7% and NPV of 86.4% with disease prevalence of 34.7%. ED discharge-delays (breaches) attributable to COVID-19 fell to 33/3532 (0.94%) compared with the preceding POC-RT-PCR period (107/4114 (2.6%); \(p < 0.0001\)). Importantly, LFD testing identified 1 or 2 clinically-unsuspected COVID-19 patients/day. Three clinically-confirmed LFD false positive patients were appropriately triaged based on LFD
Introduction

Rapid identification and isolation of SARS-CoV-2 patients on hospital admission is a priority to support patient movement and prevent nosocomial transmission. It is not possible using clinical criteria alone, particularly given potential for asymptomatic carriage. The turnaround time (TAT) of high-throughput laboratory PCR assays is often between 12 and 24 hours, when logistics and batching are taken into account. This means they cannot inform early triage and isolation decisions while the patient is in the emergency department (ED). This is particularly problematic at times of peak attendance and with national performance targets expecting 95% patients to be admitted or discharged within 4 hours. Clinically suspected COVID-19 cases admitted or discharged within 4 hours. Clinically suspected COVID-19 patients are ideally moved into single-rooms whilst awaiting laboratory PCR results, but capacity can quickly be exceeded in many NHS hospitals. Clinically unsuspected COVID-19 cases subsequently diagnosed to be positive could potentially be placed in open bays, which risks nosocomial transmission.

Point-of-care (POC) SARS-CoV-2 diagnostics performed in 20–60 minutes can provide a virological COVID-19 diagnosis in ED to enable rapid isolation or cohorting to reduce risk of nosocomial transmission. Numerous POC SARS-CoV-2 RT-PCR technologies are available [1], some with performance characteristics close to laboratory platforms; however, their cost, scalability, and requirement for verification, quality assurance, training, result recording and real-world evidence of safety and efficacy provide barriers to deployment. Lateral flow SARS-CoV-2 antigen detection devices (LFDs) are an alternative POC solution that can be obtained in near limitless supply and performed within 10–30 minutes at the bedside; however, there has been significant contention about their deployment in a clinical setting. This was in part driven by their reduced sensitivity compared with PCR [2,3], and because operator experience seemed to influence test performance [4].

Nevertheless, a number of studies [5,6], including our own [7], comparing RT-PCR and viral culture demonstrated that LFDs were excellent at identifying individuals likely to have infectious virus, probably the most important correlate for transmission. Consequently, as we entered the UK second wave in early December 2020 our ED made plans to introduce both targeted RT-PCR testing and then universal LFD testing linked with an action card to mitigate adverse consequences of false-positive and false-negative results. As community SARS-CoV-2 prevalence reached and then exceeded 1000 cases per 100,000 population [8], POC-PCR testing was introduced on 15th December, followed by LFD testing on 31st December in line with NHS England calling for LFD testing to be deployed into admission pathways on 24th December 2020 [9].

This study was conducted to determine safety and clinical utility of including LFDs as part of the POC testing strategy through a rapid rise and then subsequent fall in prevalence of COVID-19. This real-world study demonstrates effectiveness of this approach with a focus on the protocols used to follow up and limit the clinical impact of false positives and negative LFD results.

Table I

COVID-19 diagnostics available for ED patients by location, indication turnaround times and test location

| Test request | Turnaround time (hrs:mins) | Test location       |
|--------------|---------------------------|---------------------|
| COVID-19 symptomatic RT-PCR (AusDiagnostics) | 17:50 hrs\(^{a}\) (IQR 13:08–31:45) | Laboratory          |
| COVID-19 asymptomatic RT-PCR (Hologic Apta) | 11:17 hrs\(^{a}\) (IQR 8:51–15:12) | Laboratory          |
| Rapid COVID-19 RT-PCR (Cepheid) | 3:34 hrs\(^{a}\) (IQR 2:47–4:57) | Laboratory          |
| Rapid COVID-19 RT-PCR (Mobidiag) | 3:34 hrs\(^{a}\) (IQR 2:47–4:57) | Laboratory          |
| COVID-19 & Influenza A/B (Liat) RT-PCR | 30 mins \(^{b}\) | ED diagnostics cubicule |
| Priority symptomatic patients requiring rapid decision COVID-19 antigen LFD (SureScreen) | 15 mins \(^{b}\) | Adjacent to patient (cubicle or bedside) |
| Without NHS Test and Trace’ PCR in past 10 days COVID-19 antigen LFD (Innova) | 35 mins \(^{b}\) | Adjacent to patient (cubicle or bedside) |

\(^{a}\) Electronically documented times from sample collection to result report for all samples during the 2 week validation period.

\(^{b}\) Observed staff testing times comprising cartridge loading and testing.
Methods

Setting and COVID-19 patient admission pathway prior to implementation of POCT

St Thomas’ Hospital is a central London hospital with an emergency department (ED) seeing ~150,000 patients/year. During the COVID-19 pandemic, adults (≥18 years) meeting Public Health England (PHE) COVID-19 criteria [10] at triage were either placed in a majors cubicle (28 spaces) or the resuscitation room (8 spaces), depending on severity of illness, and non-suspected cases went to a separate majors area (10 spaces). Medical review created an additional “suspected COVID-19 cohort” based on clinical and case-contact history, radiological imaging and laboratory markers who were admitted to side rooms pending laboratory PCR result. Unsuspected patients were transferred to open bays unless there was another indication for isolation. Universal admission laboratory PCR testing was provided by high-throughput batch testing using the AusDiagnostics Multiplex Tandem SARS-CoV-2 RT-PCR assays for symptomatic patients and the Hologic Aptima® SARS-CoV-2 RT-PCR for asymptomatic patients. Tests were batched for 3 runs a day. A rapid laboratory RT-PCR test was available for selected cases using random-access Cepheid and Mobidiag technologies available 24 hours a day (Table I). As SARS-CoV-2 prevalence increased, ward side room capacity was exceeded leading to crowding in ED. COVID-19 positive cohort wards were opened to transfer patients directly from ED, however, the TATs for virological diagnosis precluded rapid transfer of large numbers of patients from ED.

POC RT-PCR implementation

The cobas® Liat® system was selected based on performance characteristics [11], 20-minute test cycle and our experience in testing for influenza the previous winter. It was introduced post ED triage on 15th December 2020 after in-house laboratory verification using 94 positive and negative combined nose and throat swabs (Supplementary Table I). Positive samples had take-off values between 0 and 25 on the AusDiagnostics platform equivalent to a CT of 13–38. Procurement was limited to 30 tests/day and prioritised for symptomatic patients requiring hospital transfer, urgent operations or who could not easily self-isolate (Table I).

LFD implementation

SARS-CoV-2 LFD testing was introduced on 31st December 2020 with training facilitated by staff experience using LFD as part of occupational-health self-testing [12]. Formal
Figure 2. Timeline for the study between December 1st 2020 and 30th March 2021. a) SARS-CoV-2 prevalence amongst ED attendees highlighting point of POC-RT-PCR introduction, introduction of universal LFD testing action card and restriction of LFD testing to only asymptomatic patients. The 2-week high-prevalence study period is shaded in blue. b) Daily POC-RT-PCR test results. c) Daily LFD test results.
evaluation commenced on 7th January 2021 when results were documented electronically on the ED system (Symphony). Innova LFDs were used from 7-14th January and SureScreen LFD from 15th January onwards due to shorter testing time (10 vs. 30 minutes). LFD results were prospectively reviewed by the clinical team every 24-hour period. During the continuation phase (22nd January to 31st March) results were reviewed twice-weekly. Symptomatic LFD testing was discontinued once positive predictive value (PPV) fell below 90% for two consecutive weeks.

**POC standard operating procedure**

POC RT-PCR testing using Liat devices was performed as per manufacturer instructions on combined throat and nasopharyngeal swabs. Sample collection and cassette loading was performed in patient cubicles, with testing performed on two machines in the majors area. Testing was for selected symptomatic cases as described above (Table I). LFD testing was performed as per manufacturer’s instructions on anterior nose swabs in patient-cubicles at the time of initial medical review for all patients considered likely to be admitted. Clinical decisions based on LFD results were made with reference to a guideline for management of symptomatic or asymptomatic patients (Figure 1). Patients with discrepancy between LFD result and clinical findings had POC RT-PCR.

**Data collection and analysis**

Admission date and location, including bed space (where known), age, sex, symptoms with date of onset, admitting clinical diagnosis, POC-RT-PCR, LFD, patient mobile-phone confirmed NHS Test and Trace RT-PCR result and laboratory RT-PCR results were recorded. AusDiagnostics RT-PCR performed on the same or a separate sample taken within 48-hours, were used to evaluate LFD sensitivity and specificity. PPV and NPV of LFDs were calculated using prevalence amongst ED admitted cohort. 95% confidence intervals were determined using the Wilson/Brown binomial test. All clinical SARS-CoV-2 genome sequence reports in the case of LFD false-negative patients and for any sequenced first-isolate taken >8 days post-admission (defined as a hospital-acquired case) between January 7th and February 28th were reviewed that used difference of ≤1 SNP difference to define linkage [13]. During the continuation phase data on admission bed space, symptom onset, and assessing clinician’s impression were not collected. Breach data was retrospectively collected from 1st December 2020 until 28th February 2021.

**Results**

**Retrospective review of SARS-CoV-2 testing methodologies and impact prior to introducing LFD testing**

Between 1 and 9 RT-PCR positive patients were admitted through ED each day during the first two weeks of December while prevalence increased steadily to about 11% (Figure 2a). Only patients providing electronic confirmation of a positive community NHS Test and Trace RT-PCR result on arrival left ED with a virological diagnosis (approximately 1 in 3 patients). Turnaround time for rapid laboratory RT-PCR tests from sample collection to result receipt was a median of 3 hours 34 minutes (Table I), which was too long to inform routine patient placement decisions before leaving ED. 40 clinically suspected COVID-19 patients without RT-PCR confirmation breached the 4-hour ED-stay performance target while awaiting a ward side-room between 1st and 14th December 2020 (mean 2.9/24 hours). They represented 5.8% of all breaches and 1/105 ED-attendances.

Predictions of an emerging second-wave prompted introduction of targeted POC RT-PCR testing from 15th December (Figure 2a), while prevalence increased rapidly to peak at 50% then plateau around 40% by 30th December. The combination of a positive NHS Test and Trace RT-PCR and targeted POC RT-PCR testing provided 77% (410/532) of COVID-19 patients with a positive result before leaving ED. There were 87 ED-breaches due to patients awaiting side-rooms and 20 whilst awaiting a POC RT-PCR result (107 in total; mean 6.7/24 hours). They represented 13.3% of total breaches and 1/38 ED-attendances.

**Prospective review of LFD performance during 2-week high-prevalence study-period**

**Whole cohort**

As symptomatic cases increased, the number of POC-RT-PCR tests performed exceeded the 30/day procurement limit for five consecutive days from 26th December (Figure 2b). This prompted introduction of LFD testing with an action card on December 31st (Figure 1). Between 7th and 22nd January 1422/2844 (50.0%) ED attendances had LFD testing. Data for Innova and SureScreen LFDs are combined given identical performance characteristics (Supplementary Table II). The LFD tested cohort was 48.2% female with a mean age of 55.2 years (range 18–100 years). 1024/1422 (72.0%) had a combined nose and throat swab RT-PCR test performed within 48-hours of LFD testing (Table IIa). The majority without a confirmatory PCR test were not admitted (n=346, 86.9%). Comparing LFD with any RT-PCR results, the sensitivity and specificity was 70.7% and 99.1% respectively, with a positive predictive value (PPV) of 97.7% and negative predictive value (NPV) of 86.4%. These figures were calculated based on disease prevalence of 34.7% across the 2-week period (Table IIa). Symptom onset in patients with confirmed COVID-19 (self-reported and where known) was a median of 7 days (IQR 4–10 days) prior to LFD positive (+) result and 10 days (IQR 7–14 days) prior to a negative (-) LFD result.

**Admitted cohort**

906/1119 (81%) admitted patients had an LFD performed of which 224 were LFD positive (Table IIb). 84 (39.4%) untested patients had a positive electronic RT-PCR result from pre-hospital testing (NHS Test and Trace). 186/224 (83.0%) LFD positive patients fulfilled formal PHE COVID-19 symptom criteria and a further 18 were clinically suspected, in both cases informing side-room isolation pending RT-PCR results. The remaining 20 were clinically unsuspected (Table IIb). Bed-placement data was retrievable for 71/224 (32.1%) LFD positive cases (65 PHE3, 5 clinically-expected, 1 clinically unsuspected) and 69 (97%) conformed to the action card.

Six LFD-positive patients had a negative RT-PCR test. Anti-spike IgM/G SARS-CoV-2 antibodies were detected in 1 of 2 retrievable patient sera taken >14 days post onset of...
symptoms tested using the SureScreen LFIA [14] and without SARS-CoV-2 vaccination history, which supported the LFD result. Two additional patients were recorded as probable COVID-19 by ED-physician based on clinical history, laboratory results and imaging. Thus 3 discrepant LFD results were considered true false positives after clinical review.

95 LFD-negative patients had a positive RT-PCR test and were followed up in detail. 31 had a positive NHS Test and Trace RT-PCR result and 44 additional patients had a POC-RT-PCR test performed based on the action card of which 42 were positive. The two POC-RT-PCR negative patients were diagnosed by subsequent laboratory RT-PCR testing, both with corrected Ct values >37 that based on semi-quantitative interpretation indicates very low viral load. Furthermore, 75/95 (78.9%) patients with false negative LFD tests had a subsequent semi-quantitative test performed and all had a corrected CT of ≥25. 22/95 false negative COVID-19 patients were admitted without having received their positive RT-PCR result. 17 fulfilled PHE criteria or were clinically suspected and were isolated awaiting the laboratory RT-PCR result.

The remaining five false negative cases were admitted to a non-COVID-19 patient bay for up to 10 hours prior to isolation or hospital-discharge. Routine infection control follow-up did not identify subsequent infection in contacts of these cases implying no onward transmission. This was supported by finding no linkage in SARS-CoV-2 genome-sequence clinical reports available for 4/5 of these LFD false-negative cases and 45/67 (70%) isolates available from probable or definite hospital-acquired SARS-CoV-2 cases identified across the hospital between 7th January and 28th February.

Overall 345/371 (93.0%) of admitted COVID-19 patients had a virological diagnosis before leaving ED during the two-week LFD implementation phase. Between January 7th and February 28th 2021 (end of universal testing period due to fall in prevalence) there were 62 breaches whilst suspected COVID-19 patients were awaiting side-rooms and 42 whilst awaiting a POC-RT-PCR result. This constituted 5.3% of all breaches and 1/137 ED-attendances. ED breaches were significantly lower during the two week LFD study period compared with the preceding 2 week RT-PCR only period (33/3532 (0.94%) v 107/4114 (2.6%); p=0.0001). The hospital evidenced by ED-breach data and also identified 1–2 clinically-unsuspected COVID-19 patients per day when prevalence was high and 1–3 per week when low. This prevents inadvertent admission of asymptomatic COVID-19 patients to non-COVID-19 wards that can lead to hospital transmission [15], which has significant individual patient impact alongside resource implications from contact tracing and prolonged contact isolation and closure of cohort bays.

LFD testing was introduced with an ED action card that limited adverse clinical consequences from the many expected false-negative results and few false-positive results each day during the high prevalence period. The 95 false-negative LFD results were exclusively in samples with low viral loads (CT ≥25) and most already had a recent NHS Test and Trace result or had subsequent POC RT-PCR tests in ED informed by the action card. Consequently, only 5 patients were inappropriately placed on a COVID-19 negative ward over the 2-weeks. All were moved within 10 hours following laboratory PCR results and no onward transmission was identified by either hospital

Review of LFD testing following the intensive study-period through to a low prevalence baseline

82 false negative LFD results were identified between 22nd January (end of the 2-week intensive study period) and 31st March. All had corrected CT values ≥25 where semi-quantitative testing was performed. PPV of LFD-positive results fell and NPV rose from mid-February as SARS-CoV-2 prevalence amongst ED attendees dropped below 5% (Supplementary Figure 1). This prompted restriction of LFD testing to clinically unsuspected asymptomatic patients only from 1st March 2021, which identified between 1 and 3 cases each week.

Discussion

This study demonstrates the diagnostic, infection control and operational benefit of introducing universal SARS-CoV-2 LFD testing alongside laboratory and targeted POC-RT-PCR testing during periods of both high (up to 50%) and then low (<5%) prevalence. It enabled a virological-diagnosis of COVID-19 for 93% of patients while in ED, compared with 77% during the preceding two weeks, when a combination of community NHS Test and Trace results and targeted POC RT-PCR testing was available. This improved the efficient flow of patients into the hospital evidenced by ED-breach data and also identified 1–2 clinically-unsuspected COVID-19 patients per day when prevalence was high and 1–3 per week when low. This prevents inadvertent admission of asymptomatic COVID-19 patients to non-COVID-19 wards that can lead to hospital transmission [15], which has significant individual patient impact alongside resource implications from contact tracing and prolonged contact isolation and closure of cohort bays.

LFD testing was introduced with an ED action card that limited adverse clinical consequences from the many expected false-negative results and few false-positive results each day during the high prevalence period. The 95 false-negative LFD results were exclusively in samples with low viral loads (CT ≥25) and most already had a recent NHS Test and Trace result or had subsequent POC RT-PCR tests in ED informed by the action card. Consequently, only 5 patients were inappropriately placed on a COVID-19 negative ward over the 2-weeks. All were moved within 10 hours following laboratory PCR results and no onward transmission was identified by either hospital

Table II

| LFD test results during the two-week high prevalence study period | a) Data informing calculation of performance characteristics based on LFD testing of all ED attendees b) Characteristics of the admitted patient cohort who were reviewed to determine clinical impact including review of false positive and false negative LFD results |
|---|---|
| Total attendances | 2844 |
| Total LFD | 1422 |
| LFD positive (LFD+) | 288 |
| LFD negative (LFD-) | 1134 |
| Total with PCR performed | 1024 |
| True positive (LFD+/PCR+) | 251 |
| False positive (LFD+/PCR-) | 6 |
| True negative (LFD-/PCR-) | 663 |
| False negative (LFD-/PCR+) | 104 |
| Sensitivity | 70.7% (65.8–75.2) |
| Specificity | 99.1% (98.1–99.6) |
| Positive predictive value (PPV)a | 97.7% (95.0–98.9) |
| Negative predictive value (NPV)a | 86.4% (84.4–88.2) |

| Total admissions | 1119 |
| Total with LFD performed | 906 |
| True negative (LFD-/PCR-) | 682 |
| False negative (LFD+/PCR+) | 95 |
| True positive (LFD+/PCR+) | 224 |
| PHE3+ | 186 |
| PHE3- but COVID-19 suspected | 18 |
| PHE3- and clinically unexpected | 20 |
| False positive (LFD+/PCR+)b | 6 |

a PPV and NPV calculated based on ED-attendee prevalence during the two week period of 34.7%.
b Only 3 cases were considered true false positive cases after clinical and serological review.
contact tracing combined with reviewing genome sequence results of isolates from available probable and definite hospital-acquired cases, important given potential for cryptic linkage between wards [13]. In addition, only three genuine false-positive results were identified from 906 tests during the high prevalence period. All were asymptomatic and clinically unsuspected of having COVID-19 thus were isolated pending a confirmatory RT-PCR result. Together, this real-world evidence demonstrates safe deployment of universal LFDs in ED to inform admission placement decisions.

An alternative to introducing LFD testing could have been to increase POC RT-PCR testing capacity, perhaps placing devices in every assessment cubicle or together in a dedicated ED laboratory. Two Liat devices providing rapid SARS-CoV-2 and influenza A/B detection were in place and there was extensive experience from their use during previous influenza seasons [16]; however, universal POC-RT-PCR testing was not possible due to procurement limitations, and it would have been a much more expensive and operationally challenging solution to deploy at scale. There was nevertheless considerable debate about the appropriateness of using LFDs given unquantifiable potential for adverse patient placements due to inferior performance characteristics compared with commercially-available POC-RT-PCR tests and potential for operator errors. Confidence to proceed was supported by our evidence that LFD results showed good correlation with presence of infectious virus [7]. This highlights the benefit of having University research laboratories linked with infectious diseases diagnostic laboratories to enable a rapid response to emerging pathogens [17].

LFD testing of symptomatic patients was stopped on 1st March 2021 as prevalence reduced leading to a fall in PPV. Demand also fell to within POC RT-PCR procurement limits and side-room capacity. LFD testing of all asymptomatic patients continued given high NPV and the benefit of detecting and preventing even small numbers of asymptomatic COVID-19 patients being admitted to non-COVID-19 wards.

The limitations of this study are its single-centre nature reviewing routinely collected data gathered to make clinical and operational decisions during a particularly intense period of the pandemic. Consequently, there were some missing data on patient placement, follow-up of discrepant results and SARS-CoV-2 isolate sequencing, and we did not attempt to assess the wider operational or clinical benefits of reducing need for contact tracing and prolonged contact isolation or preventing outbreaks. There was also no prospectively collected detailed data during the weeks leading up to LFD testing. Throughout, there were multiple different RT-PCR technologies deployed all of which contributed to the diagnostic service, and without which an LFD benefit could likely not be safely assured. Similar multi-testing strategies are used in many hospitals in response to different clinical needs, as technologies improve and in response to procurement constraints, hence our conclusions and processes used in this study have broad relevance. Furthermore, demonstrating how an inexpensive bed-side test available in near limitless supply can safely provide clinical benefits as part of a wider testing strategy, in spite of lower performance characteristics, is an important result relevant to any healthcare settings where other technologies may be limited in supply.

In summary, this study adds significantly to the literature providing evidence that SARS-CoV-2 LFD testing can be safely deployed in a healthcare setting to realise clinical and operational benefits [18–25]. Since completion, LFD testing has been extended to other clinical areas facilitated by manual result entry into POC glucometer machines and development of a smartphone application that scans the QR-coded LFD cassette results into the EPR pathology result section. This facilitated result dissemination and removed the need for visual reading and manual entry, preventing occasional incorrect result recording due to human error. This coming winter now presents a different challenge with predicted increases in influenza, perhaps more than COVID-19, and potential for co-infection. Distinct COVID-19, COVID-19 plus influenza co-infection and influenza cohorts may be required, which will need a different POC testing strategy for efficient triage informed by a new action card. There may also be better access to a wider range of POC-RT-PCR tests detecting both COVID-19 and influenza A/B, and influenza A/B antigen LFDs are being developed [26]. It emphasises the need for continuous improvement in the approach to diagnosis of emerging and seasonal respiratory viral infections. It also illustrates the contribution that real-world POC studies can make in defining the characteristics of a responsive learning healthcare system, alongside data from formal clinical trials and laboratory evaluations of performance characteristics and turn-around time [27].

Credit author statement

Blair Merrick: conceptualization, methodology, formal analysis, writing original draft, supervision. Maryann Noronha: conceptualization, methodology, investigation, writing — review and editing. Rahul Batra: conceptualization, project administration, funding acquisition. Sam Douthwaite: conceptualization, supervision, methodology. Gaia Nebbia: conceptualization, supervision, methodology. Luke Snell: Resources: Suzanne Pickering: validation, resources. Rui Pedro Galao: validation, resources. Jamie Whitfield: resources, data curation. Aamina Jahangeer: resources, data curation. Ramith Gunawardena: resources, data curation. Thomas Godfrey: resources, investigation. Rida Laifa: resources, data curation. Kay Webber: methodology, resources, data curation. Penelope Cliff: methodology, resources. Emma Cunningham: methodology, resources. Stuart Neil: supervision, conceptualization. Holly Gettings: supervision, conceptualization. Jonathan Edgeworth: conceptualization funding acquisition, supervision, formal analysis, writing original draft. Ling Harrison: conceptualization, supervision, formal analysis, writing original draft.

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Conflict of interest statement

None declared.
**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.infpip.2021.100186.

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