Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Optimising the initial investigation of suspected cases of SARS-CoV-2 reinfection

Reply to

Testing Dilemmas: Post negative, positive SARS-CoV-2 RT-PCR – is it a reinfection?

Travel Med Infect Dis. 2020 May–June; 35: 101743.

Alvarez-Moreno and Rodriguez-Morales provide timely, considered observations to optimise strategies for investigation of potential reinfection among recovered cases of Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) [1]. This is particularly important given more recent recognition of variants of concern, including speculation of spike protein mutations that may confer a degree of immune escape [2].

Alvarez-Moreno and Rodriguez-Morales highlight the limitations of RNA polymerase chain reaction (PCR) for inferring infection with viable virus in such cases, particularly following observations on the limited capacity to isolate virus after eight days of symptoms, despite prolonged periods of RNA shedding [3]. They conclude by urgently calling for multi-faceted investigative case reports in order to assist the development of diagnostic pathways in this situation.

We therefore report the management of one such case involving a 25 year-old female healthcare worker working in a high-acuity intensive care setting who tested positive on April 19, 2020 for SARS-CoV-2 antibodies as part of a serological staff screening programme implemented in April at the referring hospital [4]. The patient reported a new onset cough two weeks prior to testing that had since resolved and testing demonstrated the presence of SARS-CoV-2 specific IgG antibodies (Encode SARS-CoV-2 CE marked split IgM/IgG One Step Rapid Test Device) [4]. The patient re-presented to the symptomatic staff testing programme on the June 16, 2020 with new onset symptoms of cough, headache and fluctuating fevers over the preceding five days. There was a strong clinical suspicion of COVID-19 infection and PCR testing was positive for SARS-CoV-2 (AusDiagnostics, Australia). Case investigation was completed by the clinical infection team at the referring hospital, with support from the national reference laboratory (Public Health England). Further investigation included retrieval of the 16 June nasopharyngeal swab sample for retesting for both SARS-CoV-2 and a full respiratory panel for common respiratory pathogens. The patient was recalled once symptom free and nasopharyngeal swabbing was repeated. Repeat serological testing was also carried out.

On review of the initial swab from June 16, 2020, only the ORF1ab target was detected towards the lower limit of detection (with a second stage cycle threshold of 24.65) and a negative second target (ORF 8). Repeat testing of this original sample was negative for SARS CoV-2 but the full viral respiratory panel was strongly positive for rhinovirus/enterovirus. Repeat PCR testing on July 09, 2020, 24 July and August 17, 2020 as part of staff screening requirements were also negative. Repeat antibody testing with the Abbott IgG anti-nucleocapsid chemiluminescent microparticle immunoassay was reactive (Binding ratio 3.46). In this case, it was concluded that rhinovirus/enterovirus was the cause of the new symptoms with the initial positive SARS-CoV-2 PCR result either a false positive result or some low-level remnant RNA from past infection.

While we agree with Alvarez-Moreno and Rodriguez-Morales in that confirmation of reinfection may require demonstration of inoculation of isolated virus on cell lines or demonstration of molecularly distinct viruses following evidence of clearance, we would add further detail to their strategy [1]. We highlight that this is limited by the requirement for a dedicated containment level 3 laboratory and experience in cell maintenance, inoculation and viral culture. Since publication, the COVID-19 Genomics UK (COG-UK) consortium initiative have identified a variant of concern (B 1.1.7) that now predominates throughout the UK and is in part characterised by S gene target failure [2]. Despite the COG-UK undertaking the largest such initiative in the world at present, and with a turnaround time that can be sufficient to impact clinical management, real-time throughput remains challenging. Identifying the development of S gene target failure in such cases, for example, could help highlight samples for sequencing. Recognition of such test characteristics could help to maximise this limited resource in the context of consideration for possible reinfection going forward. Additionally, we demonstrate how early investigation of suspected cases of SARS-CoV-2 reinfection can be undertaken in order to rule out reinfection locally. Where concordance between PCR-positive infection and detection of anti-nucleocapsid antibodies is incomplete [4], additional serological testing with anti-spike protein immunoassays could add further value. Review and retesting of initial PCR samples should be undertaken in order to assess the possibility of a false positive result. Resampling of nasopharyngeal swabs could provide further support where doubt remains but must be considered in the clinical context. Serological testing may increase confidence in alternative diagnoses but should be interpreted with caution. This is particularly the case where serological assays are limited to non-neutralizing nucleocapsid targets. Additionally, it is unclear how emerging reports of antibody decline in the early convalescent period may affect interpretation going forward [5].

We suggest that while a multi-tiered approach is required for a robust investigation of potential cases of reinfection, including SARS-CoV-2 sequencing, this should in the first instance include local testing (where available) looking for S-gene drop out, alternative viral pathogens, and testing for SARS-CoV-2 serological markers, as described in recent guidance [6]. Organisation of provision for cell line cultures where required is best delivered at a national level according to defined protocols, such as those developed through PHE's SIREN (Sarscov2 Immunity & REinfection EvaluatioN) study.

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Authors' contributions

SJCP, NM and LSPM conducted the initial investigation. RJ carried out serological testing. PR carried out PCR testing and analysis of results. CB provided clinical and laboratory advice. SJCP, CB and LSPM drafted the initial response. All authors reviewed the manuscript and contributed comments to its development. All authors agreed with the final draft for submission.

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Ethical approval and consent to participate

Informed consent was sought and provided by the patient prior to submission.

Availability of data and materials

The data analysed during the current study and further details on the assays are available from the corresponding author (SJCP; scott.pallett@nhs.net) on reasonable request, as long as this meets local ethical and research governance criteria.

Declaration of competing interest

LSPM has consulted for/received speaker fees from bioMerieux (2013–2021), DNAelectronics (2015–18), Dairy Crest (2017–2018), Profile Pharma (2018), Umovis Lab (2020–2021), Eumedica (2016–2018), and Pfizer (2018–2021), received research grants from the National Institute for Health Research (2013–2019), and CW+ Charity (2018–2021). NM has received speaker fees from Beyer (2016) and Pfizer (2019) and received educational support from Eumedica (2016) and Baxter (2017). RJ has received honoraria, speaker fees, travel support and/or research grant funding from Gilead, ViiV Healthcare, BMS, Abbvie, Janssen and Merck. SJCP has received a research grant from the Scientific Exploration Society. All other authors have no conflicts of interest to declare.

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Scott JC. Pallett*
Centre of Defence Pathology, Royal Centre for Defence Medicine, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, B15 2WB, UK
Chelsea and Westminster Hospital NHS Foundation Trust, 369 Fulham Road, London, SW10 9NH, UK

Colin S. Brown
National Infection Service, Public Health England Colindale, 61 Colindale Ave, London, NW9 5EQ, UK

Nabeela Mughal
Chelsea and Westminster Hospital NHS Foundation Trust, 369 Fulham Road, London, SW10 9NH, UK
North West London Pathology, Fulham Palace Road, London, W6 8RF, UK

Rachael Jones
Chelsea and Westminster Hospital NHS Foundation Trust, 369 Fulham Road, London, SW10 9NH, UK

Paul Randell
North West London Pathology, Fulham Palace Road, London, W6 8RF, UK

Luke SP. Moore
Chelsea and Westminster Hospital NHS Foundation Trust, 369 Fulham Road, London, SW10 9NH, UK
North West London Pathology, Fulham Palace Road, London, W6 8RF, UK
Imperial College London, NIHR Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Du Cane Road, London, W12 0NN, UK

* Centre of Defence Pathology, Royal Centre for Defence Medicine, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, B15 2WB, UK.
E-mail address: scott.pallett@nhs.net (S.JC. Pallett).