

Investigation of SARS-CoV-2 suspected cases of reinfection among hospital staff members in the greater Paris area

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Highlights:

After one year, among 236 hospital staff members (HSMs) tested positive for SARS-CoV-2, we observed 5 cases of suspected reinfection in our teaching hospital in France. No probable reinfection was retained considering PCR Cycle Threshold and clinical context. Focus should concern COVID-free HSMs still not vaccinated rather than the ones previously infected.

Introduction:

It has been more than a year since the COVID-19 pandemic began, and numerous publications supported the high risk of infection among healthcare workers (HCWs) [1–3]. In a previous study we described the risk factors of infection among hospital staff members (HSMs) during the first wave of the epidemic in France [3], which

enabled us to implement targeted prevention measures during the second wave to preserve workforces.

Recently, HCWs have expressed concerns about the possibility and frequency of reinfections. This parallels the gaps in knowledge regarding the strength and durability of the immune response to SARS-CoV-2 infection.

Moreover, the emergence of a new SARS-CoV-2 variant lineage B.1.1.7 in United Kingdom (UK) [4] raised questions about the potential of reinfection. So far, there were limited cases of reinfection reported due to the wild-type strain in the literature. Moreover, most of the cases were asymptomatic or presented with mild symptoms (75%) rather than moderate or severe [5]. Of note, no viral genome sequencing was routinely performed at that time.

Lumley *et al.* [6] showed that among 1,265 HCWs positive for anti-spike IgG, only 2 (0.11%) had a positive PCR testing and were considered as reinfected while being asymptomatic in the ensuing 6 months.

Recently, Letizia *et al.* [7] studied 2,436 marine recruits aged from 18 to 20 years-old during quarantine, and reported that among 189 seropositive participants, 19 (10.1%) had at least one positive PCR test for SARS-CoV-2 during the six-week follow-up. Interestingly, reinfection was associated with the lower baseline neutralizing spike protein IgG titers ($p < 0.0001$).

Some worries began to get raised among HCWs after Zucman *et al.* [8] had reported a case of severe reinfection with the South-African SARS-CoV-2 variant in a 58-year old immunocompetent male requiring admission in intensive care unit (ICU) in France. However, conclusions cannot be drawn from a single case.

The aim of the present work is to describe the risk of reinfection among HSMs after one year of early prevention measures and a surveillance system of COVID-19 were

implemented, and evaluate the presence of variance strains amongst recent infections.

Methods:

Setting

Raymond Poincaré Hospital, a 386-bed (Assistance Publique - Hôpitaux de Paris) hospital located in the surrounding of Paris, is a second line center in epidemic risk management appointed as one of the referral centers for the management of COVID-19 patients by the French Health Ministry. As previously described the center has an area of expertise in COVID-19 with dedicated wards in infectious diseases and ICU and a consultation for the screening of SARS-CoV-2 for the HSMs [3]. Initially in March 2020, only symptomatic HSMs had access to COVID-19 diagnosis and later on starting from July 2020 onwards, SARS-CoV-2 screening was extended to contact-cases.

From March to June 2020, SARS-CoV-2 screening from nasopharyngeal samples was achieved by a non-commercial RT-PCR targeting RdRp gene. Since June 2020, SARS-CoV-2 RNA has been detected by using three distinct commercial assays, namely Alinity-m SARS-CoV-2 AMP Kit® (Abbott Diagnostics GmbH, Wiesbaden, Germany) targeting RdRp and N genes, Xpert® Xpress SARS-CoV-2 (Cepheid, Sunnyvale, USA) targeting E and N genes, or BioFire® Respiratory Panel 2.1 plus (bioMérieux, Marcy-Etoile, France), targeting S and M genes. Since January 2021, screening of the UK variant lineage B.1.1.7 was systematically performed, using TaqPath™ COVID-19 RT-PCR Kit (Thermo Fisher, Bleiswijk, Netherlands).

Data collection

Data on the date of positive PCR testing, symptoms presented during the COVID-19 infection and date of onset of symptoms, age, affiliation department (COVID-19 ward) and professional category (i.e. nurses, physicians, support staff, administrative employees).

Definitions: suspected and probable cases of COVID-19 reinfection

Suspected cases of reinfection were based on CDC criteria issued in October 2020

[9]:

- a subsequent RT-PCR positive to SARS-CoV-2 more than 45 days after the initial presentation if the second test is accompanied by compatible symptoms or epidemiological exposure,
- a subsequent RT-PCR positive to SARS-CoV-2 more than 90 days after the initial presentation if the second test is performed among an asymptomatic HSM with a close contact with a person known to have a laboratory-confirmed COVID-19.

Thereafter, “probable reinfection”, defined by clinical context (symptoms, risk exposure) plus a Cycle Threshold (Ct) < 37 and the absence of other diagnosis, was assessed by an infectious disease specialist and a microbiologist.

Statistical analysis

HSMs were classified depending on the date of their positive PCR testing, according to time periods. The first wave happened from 03/01/2020 to 06/11/2020 while the second wave spread out from 08/10/2020 until now 03/01/2021.

Participants’ characteristics were described as median (interquartile range, IQR) and numbers (proportions) for continuous and categorical variables respectively.

Statistical analyses were carried out using the *R* studio open source software.

Ethics

This post-hoc study is part of our previous work approved by the Ethical Review Committee of the University Paris-Saclay (Poletis) (CER-Paris-Saclay-2020-048).

Results:

During the whole study period, 2,111 SARS-CoV-2 PCR tests were performed. During the first wave, the PCR positivity rate was 26.9% (n=71/264) and 8.9% (n=165/1,847) during the second wave. Overall, 236 HSMs had a positive SARS-CoV-2 PCR (Figure 1). Characteristics from HSMs are detailed in Table 1 (Supplementary data).

During the second wave, we noted 5/236 cases (2.1%) of suspected reinfection: 2 asymptomatic individuals tested as contact-cases (cases #3 and #4), and 3 symptomatic. According to definitions no probable reinfection was retained. Cases #2 and #5 were considered as false positives whereas cases #1, #3 and #4 were almost certainly cases of persistent viral carriage (Figure 1).

Discussion:

While we observed a substantial number of infections in the first year of the pandemic, the PCR positivity rate among HSMs seemed to be higher in the first wave despite the fact that France operated 2 lockdowns (from March to May and from November to December 2020) followed by a curfew. Also, it should be reminded that different testing practices were applied between the 2 waves which explain why we might have underestimated the number of asymptomatic HSMs during the first wave

of the epidemic (2.8%) in comparison to the second wave where asymptomatic were tested.

Interestingly, we retained no probable case of reinfection over a one-year period. This is concordant with the relatively low number of reinfections estimated at around 0.3% after 90 days among a large series of individuals previously seropositive to SARS-CoV-2 [10]. In our study, we only reported a few HSMs infected by the UK variant. None of them were suspected cases of reinfection. This may be partly explained by the scarcity of the UK variant in France at the time of the study. This is all the more true, for the other variants of concerns, not routinely detected.

One major limitation of this work is that we certainly missed some COVID-19 cases in HSMs, tested outside the hospital, and thus cases of reinfection. However, in our center the occupational health service is actively involved in the monitoring of COVID-19 in HSMs.

To our knowledge this is the first study where each suspected case of reinfection was carefully reviewed using clinical context and Ct in order to support or rule out the diagnosis of reinfection. Indeed, differencing persistent viral shedding from true new infection is not straightforward as highlighted by Falahi *et al.* [11]. This supports the use of Ct values as suggested by the CDC guidelines [9]. For instance, one of the HSMs with a suspicion of reinfection had a transient positive PCR for SARS-CoV-2 almost one year after the first episode (positive PCR followed by a negative one within 2 days), and had a positive PCR for *Metapneumovirus* following an exposure to an infected child. Interestingly, she had recently given birth. The specificity of the immune response during pregnancy may have resulted in variations from the usual course of COVID-19 [12].

Another limitation could be that we did not use any viral genomic data. Indeed, performing genomic analysis would have been useful if we had identified probable cases of reinfection in order to confirm them.

In the context of a current low observed risk of reinfection, efforts should be placed on careful monitoring of infections in HCWs and ensuring high coverage of COVID-19 vaccination. This is particularly relevant in a context of a long lasting second wave in Europe where HCWs are precious workforces for the cure of patients suffering from severe form of COVID-19. Therefore, vaccine hesitancy should be addressed, to limit the spread of new infections among HCWs and the risk of nosocomial infections among hospitalized patients in non-COVID wards.

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Contributors' Statement:

BD, PDT, CL, ED and SG conceptualized and designed the manuscript, coordinated and supervised data collection, drafted the initial manuscript, and reviewed the manuscript. SG and BD were in charge of the figure and the table. BD, CL, PDT, ED, SG, MDR, ASM, DA, EG and CL reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure legends

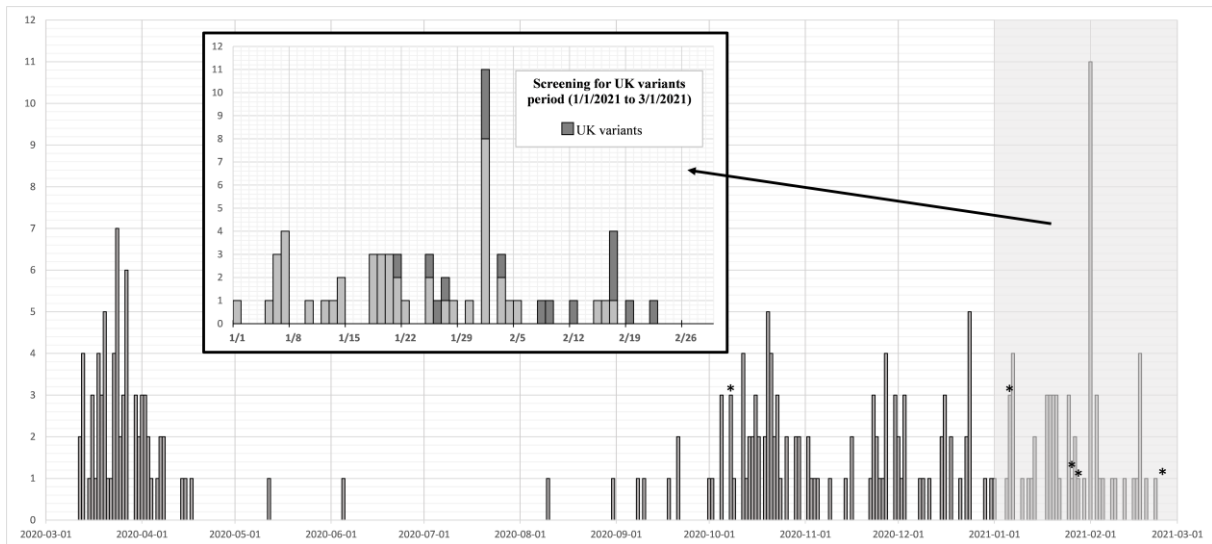


Figure 1: Epidemic curve of cases according to date of PCR testing. Focus on the period from January 1 to March 1, 2021 where screening for UK variants was implemented.

* Stars represent the 5 cases suspected of reinfection with a subsequent PCR positive for SARS-CoV-2. The peak on 02/01 corresponds to cases detected during a mass testing carried out for a cluster investigation.

Case #1: 35 years-old male tested positive on 03/18/20, retested asymptomatic as a contact-case on 10/8/20 positive at 41 Ct (Cepheid)

Case #2: 49 years-old female tested positive on 03/30/20, retested for symptoms (headache) on 1/4/21 positive at 41 Ct (Alinity) and retested negative again 72 hours later

Case #3: 24 years-old female tested positive on 12/15/20, retested as paucisymptomatic on 1/26/21 positive at 37 Ct (Cepheid)

Case #4: 30 years-old female tested positive on 10/12/20, retested asymptomatic as a contact-case on 1/28/21 positive at 38 Ct (Cepheid)

Case #5: 31 years-old female tested positive on 03/23/20, retested for symptoms (mild rhinitis with anosmia for 7 days) on 2/24/21 positive at 41 Ct (Alinity), and

retested negative again 48 hours later with a positive PCR for
Metapneumovirus (BioFire)

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