**Human Reproduction Open, Vol.00, No.0, pp. 1–7, 2020**
doi:10.1093/hropen/hoaa056

human reproduction open

ORIGINAL ARTICLE

# SARS-Cov-2 viral and serological screening of staff in 31 European fertility units

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*Submitted on July 31, 2020; resubmitted on September 28, 2020; editorial decision on October 14, 2020*

**STUDY QUESTION:** What is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral presence and seroconversion in staff members in European fertility units prior to recommencement of clinical activity?

**SUMMARY ANSWER:** A large proportion of fertility clinic staff remain susceptible to SARS-CoV-2 with no evidence of seroconversion, indicating that continued comprehensive risk mitigation strategies are essential.

**WHAT IS KNOWN ALREADY:** In response to the coronavirus disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2, routine fertility treatment was temporarily stopped in several European countries. The SARS-CoV-2 prevalence and seroconversion in fertility clinic staff, who are at potentially lower risk than routine healthcare workers, are unknown.

**STUDY DESIGN, SIZE, DURATION:** This cross-sectional study included 554 staff in 16 European IVF clinics, 13 ultrasound clinics, one diagnostic laboratory and one head office in four European countries (Austria, Denmark, Germany and the UK) between 15 April and 30 June 2020.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** There were 554 staff members returning for resumption of clinical activity. Paired nucleic acid amplification tests of oropharyngeal swabs for SARS-CoV-2 and serological testing for SARS-CoV-2 IgG were performed.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Of the 554 staff members tested, 0.19% (95% CI 0.03, 1.10%) had evidence of SARS-CoV-2 as detected by RT-PCR. In contrast, 23 staff members, i.e. 4.15% (95% CI 2.78, 6.15%), had antibodies against SARS-CoV-2, with a wide range of antibody titres. There was no evidence of differences in seroconversion between countries with estimates ranging from 2.78% (95% CI 0.77, 9.58) in Austria to 6.75% (95% CI 4.46, 10.1) for the UK. There was no strong evidence of clustering within the clinics, with 21 of the 30 facilities having no staff members affected (prevalence estimates ranging from 0% to 35%), and one clinic having seven staff members affected (35% (95% CI 18.1%, 56.7%)). The single staff member who tested positive for SARS-CoV-2 virus was in the pre-symptomatic phase and was isolated, with no contacts having evidence of infection on repeat testing.

**LIMITATIONS, REASONS FOR CAUTION:** This was a cross-sectional study prior to resumption of clinical activity, with repeat testing not undertaken.

**WIDER IMPLICATIONS OF THE FINDINGS:** The low prevalence of seroconversion of fertility clinic staff highlights the need for continued comprehensive risk mitigation strategies and engagement with national endeavours to identify and isolate new cases and their contacts as we embark on the resumption of fertility services.

**STUDY FUNDING/COMPETING INTEREST(S):** The Fertility Partnership funded the study. S.M.N. reports personal fees from Access Fertility, personal fees from Merck, personal fees from Ferring, grants and personal fees from Roche Diagnostics, personal fees from The Fertility Partnership and personal fees from Modern Fertility, outside the submitted work. T.C. reports personal fees from

Merck and personal fees from Ferring, outside the submitted work. G.T. reports personal fees from Merck, personal fees from Ferring and personal fees from Roche Diagnostics, outside the submitted work. S.E. and P.S.G. report no conflicts of interest.

**TRIAL REGISTRATION NUMBER:** N/A.

**Key words:** SARS-CoV-2 / COVID-19 / antibody tests / seroprevalence / fertility clinics

## WHAT DOES THIS MEAN FOR PATIENTS?

This study looks at how many staff from IVF clinics in Austria, Denmark, Germany and the UK have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus which causes coronavirus disease 2019 (COVID-19). Each staff member was tested with both the gold standard test to identify active infection and antibody tests to identify those who had had infection in the past. We showed that overall, only 4% of staff members had been infected with the virus, highlighting that standalone IVF unit staff have had a lower rate of infection than hospital-based healthcare workers. We also conclude that there is an urgent continued need to follow national guidance to reduce viral transmission as a large proportion of staff remain at risk of infection.

# Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhu *et al.*, 2020), has affected millions of people worldwide igniting an unprecedented effort to decrease transmission and reduce morbidity and mortality (Wu and McGoogan, 2020). Following national public health recommendations, the two principal reproductive medicine professional bodies, the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE), recommended the suspension of initiation of new treatment cycles in the week commencing 16 March 2020. In response to this guidance, several national authorities within Europe including the UK, Denmark, Austria and Germany quickly instigated compulsory temporary cessation of non-elective fertility treatments (HFEA, 2020).

With the initial stabilization of the pandemic in Europe, resumption of clinical activity was proposed by ESHRE on 23 April 2020, with guidance on risk reduction strategies related to minimizing exposure to SARS-CoV-2/COVID-19-positive patients or staff during treatment (ESHRE, 2020). Central to these recommendations was a staff triage questionnaire to be undertaken 2 weeks before beginning clinical activities, with subsequent stratification to either no further testing required, a nucleic acid amplification test (NAAT) for SARS-CoV-2 or an antibody test (ESHRE, 2020; La Marca *et al.*, 2020). Although easily deployed across a range of clinical settings with variable support infrastructure, the proposed pathway does not account for the temporal dynamics of viral infection or seroconversion and would not detect asymptomatic infected staff, pre-symptomatic staff in the early phases of the infection or staff with previous asymptomatic exposure (Bai *et al.*, 2020; Gandhi *et al.*, 2020). In contrast, NAAT testing to identify asymptomatic or pre-symptomatic staff and overcome inadequacies in symptom-based screening has been proposed for prioritized healthcare settings (Arons *et al.*, 2020; Gandhi *et al.*, 2020).

The current study aimed to estimate the prevalence of active SARS-CoV-2 infection and seroconversion using paired NAAT and serological testing in all staff members in 30 fertility units and a head office across four countries before the resumption of routine clinical activity.

# Materials and methods

In the immediate 2 weeks prior to each clinic became fully operational, all staff members recommencing work at the Fertility Partnership, including clinical and head office staff, were offered voluntary participation in a screening system of paired oropharyngeal swab testing and blood draws for serological testing for SARS-CoV-2. These sites included 16 European IVF clinics, 13 ultrasound clinics, one diagnostic laboratory and one head office in four European countries (Austria, Denmark, Germany and the UK). Specifically, there were three IVF clinics in Austria; Klagenfurt, Vienna and Wels, two IVF clinics in Denmark; Aarhus and Copenhagen, three IVF clinics in Germany; Berlin, Düsseldorf and Wiesbaden, a head office with staff split between Berlin and Frankfurt and a diagnostic laboratory in Düsseldorf, with the remainder of the 21 locations spread throughout the UK. The testing time frame varied for each facility, reflecting their different reopening times per national legislation, but all were between 15 April and 30 June 2020. No staff were symptomatic at the time of testing, or had previously had a positive test, although a history of previous symptoms not an exclusion criterion for participation.

## NAAT testing

The genesig® Real-Time PCR Coronavirus (COVID-19) CE IVD Assay was used for the RT-PCR for SAR-CoV-2 in line with the manufacturer's instructions. Nucleic acid extraction was performed using the GXT NA Extraction Kit in combination with the GenoXtract®, with amplification using the FluoroCycler® XT. Independent clinical performance evaluation of the genesig® COVID-19 assay was undertaken by the National Infection Service (Public Health England, Colindale, UK) who confirmed the specificity of this assay using upper or lower respiratory clinical samples from current patients and known SARS-CoV-2 positive material. Public

Health England confirmed that the assay showed >98% specificity to the SARS-CoV-2 virus in clinical samples.

## Antibody testing

Detection of SARS-CoV-2 antibodies was performed by the Abbott Diagnostics SARS-CoV-2 IgG assay on an Abbott Architect i2000 according to the manufacturer's instructions. This qualitative assay detects IgG binding to an undisclosed epitope of the SARS-CoV-2 nucleocapsid protein. The amount of IgG antibodies to SARS-CoV-2 in each sample is determined by comparing its chemiluminescent relative light unit (RLU) to the calibrator RLU (index S/C). Using an index S/C threshold of 1.4, the manufacturer reported a sensitivity of 86.4% 7 days after symptom onset and 100% after 14 days, and a specificity of 99.6%, using RT-PCR as the gold standard. These figures were corroborated by a validation study using a set of samples from patients who tested positive for SARS-CoV-2 by RT-PCR and in samples obtained in 2018–2019, thus before the epidemic (sensitivity of 100% 17 days after symptom onset and a specificity of 99.9%) (Bryan *et al.*, 2020). A further verification study by the National Centre for Microbiology (Spain) used samples obtained before 8 December 2019 and showed a sensitivity of 89.7% in serum samples from RT-PCR-positive patients 14 days after symptom onset and a specificity of 100% (Pollán *et al.*, 2020).

## Ethical approval

Approval for the study was provided by The Fertility Partnership Ethics Committee.

## Statistical analysis

All analyses were conducted using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). We estimated the proportion of staff with positive NAAT testing and we estimated seroprevalence as the proportion of individuals who had a positive result in the immunoassay. All data analyses used in this study were conducted in R version 4.0.0. Due to the nature of the outcomes, we used the 'DescTools' package (version 0.99.36) (Signorell *et al.*, 2020). The *BinomCI()* function was used to calculate the lower and upper limits of the 95% CI for a proportion for the overall population, geographical locations and individual clinics (Wilson, 1927).

# Results

There were 554 staff members tested, of whom 513 (92.6%) had an interpretable NAAT result and 554 (100%) had a valid SARS-CoV-2 serological result. This differential reflected that two sites in Austria and Germany did not performed NAAT testing on 5.6% and 7.7%, respectively of the staff members, while the UK had 100% compliance. Of the 513 staff members who underwent NAAT testing, only one tested positive for SARS-CoV-2, giving an overall prevalence of 0.19% (95% CI 0.03 to 1.10%) (Fig. 1). This individual was initially asymptomatic at the time of testing, with the development of mild COVID-19 symptoms, fatigue, headache and increased respiratory rate, over the next 5 days.

For the serological testing, 23 staff members of the 554 tested had evidence of antibodies, with an overall prevalence of 4.15% (95% CI 2.78 to 6.15%) (Fig. 1). Of these, approximately one-third had no recollection of symptoms since January 2020. Assessment of the geographical distribution of SARS-CoV-2 seroconversion did not demonstrate any statistical difference between countries (Table 1, Fig. 2). Similarly, there was no strong evidence of clustering within the clinics, with 21 of the 31 facilities (70%) having no staff members with evidence of antibodies (prevalence estimates ranging from 0% to 35%), and one clinic having seven staff members having evidence of seroconversion (35% (95% CI 18.1% to 56.7%) (Fig. 2). IgG antibody titres

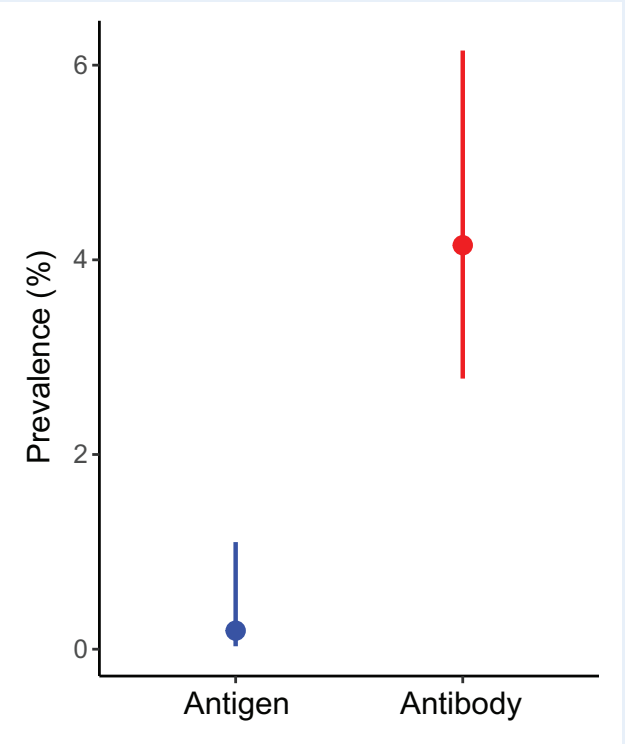


**Figure 1. Overall SARS-CoV-2 virus and antibody prevalence for whole group**. Prevalence estimates and 95% CIs for staff being tested for SARS-CoV-2 by NAAT (n = 513) and antibodies to SARS-CoV-2 (n = 554).

**Table 1 Seroprevalence per country.**

| Country | IgG positive (n) | Antibody tests performed (n) | Prevalence % (95% CI) |
|---|---|---|---|
| Austria | 2 | 72 | 2.78 (0.77–9.58) |
| Denmark | 1 | 34 | 2.94 (0.52–14.91 |
| Germany | 4 | 137 | 2.92 (1.14–7.27) |
| UK | 21 | 311 | 6.75 (4.46–10.1) |

Prevalence estimates and 95% CIs for each country for staff with antibodies to SARS-CoV-2 (n = 544).

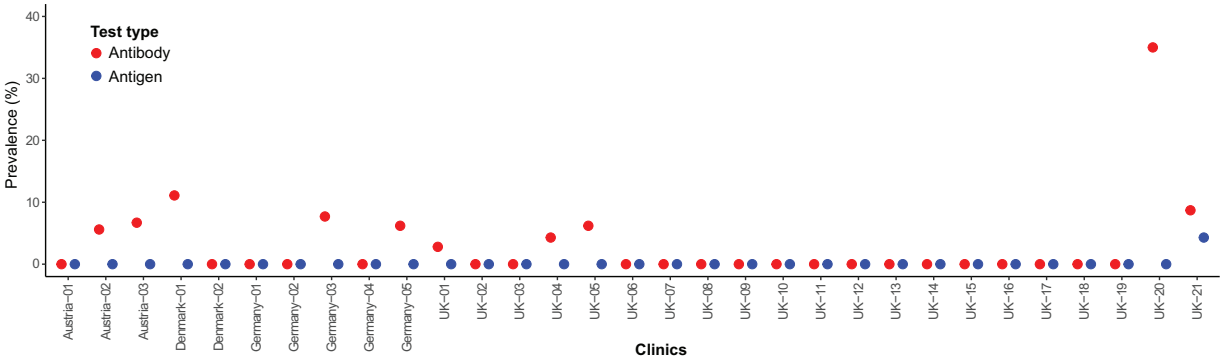


**Figure 2. SARS-CoV-2 virus and antibody prevalence per geographical site**. Prevalence estimates for staff being tested for SARS-CoV-2 by NAAT (n = 513) and antibodies to SARS-CoV-2 (n = 554) across four countries and 31 sites.

were highly variable for all staff members tested (Fig. 3), and four staff members were just below the diagnostic threshold for the assay.

## Discussion

The findings from this seroprevalence study for SARS-CoV-2 indicate that the prevalence of IgG antibodies against this coronavirus is around 4% of staff working in European fertility units, with substantial variability in antibody titres. As the study was designed to evaluate the multidisciplinary workforce across four countries, we were able to show the equivalent prevalence for both patient-facing and non-clinical staff, across different clinical settings and multiple geographies. The use of paired NAAT and serological testing facilitated the identification of a pre-symptomatic SARS-CoV-2 infected staff member that would have been missed if we had been solely reliant on questionnaire triage.

Our low prevalence of positive tests for SARS-CoV-2 is consistent with contemporaneous UK community estimates, which had observed a decline in private-residential households testing positive for SARS-CoV-2 from 0.32% (95% credible interval (CrI) 0.19% to 0.52%) on 26 April to 0.08% (95% CrI 0.05% to 0.12%) on 28 June (Pouwels *et al.*, 2020). Other studies have reported similar low estimates of the prevalence of SARS-CoV-2 in the general population, with a study from Vo in Italy reporting an initial infection prevalence of 2.6% (95% CI 2.1 to 3.3%) and 1.2% (95% CI 0.8 to 1.8%) 14 days later (Lavezzo *et al.*, 2020). In Iceland, in a study of 2283 participants, 13 testing positive (0.6%; 95% CI 0.3% to 1.0%) (Gudbjartsson *et al.*, 2020). During the period of the study, the incidence of SARS-CoV-2 was highly variable across the different countries reflecting both differences in spread but also the different reporting and testing structures. During the period of 15 April to 30 June 2020, the peak of daily cases was 162 cases per day for Austria, 235 cases per day for Denmark, Germany 3609 cases per day for Germany and 6201 cases per day for the UK. Prevalence figures for all countries were not available for the time period, but a prevalence study undertaken within the UK during 27 April to 10 May assessing 10 705 participants estimated that 0.27% (95% CI 0.17–0.41%) of the community population were infected. Our incidence estimate of 0.19% (95% CI 0.03–1.10%) for SARS-CoV-2 infection would be consistent with this. With respect to the residual risk of infectivity, it has been estimated that it is low if patients are beyond day 10 of symptoms and have less than 100 000 viral RNA copies per ml of sputum, however, national policies may differ in the period of isolation required after the onset of symptoms and the frequency of retesting and threshold for determining a negative PCR result.

The proportion of asymptomatic infections in different studies has varied greatly ranging from 4% to 41%, potentially reflecting differences in the follow-up of asymptomatic cases and populations studied (Buitrago-Garcia *et al.*, 2020; Byambasuren *et al.*, 2020). Our observed frequency of ~33% asymptomatic cases is similar; however, we acknowledge the limitations of symptom recall may have had on accurate ascertainment. Onward secondary infection transmission from asymptomatic cases ranges from none to 2.2%, as compared to symptomatic cases where transmission rates range between 0.8% and 15.4% (Byambasuren *et al.*, 2020). That the virus was detectable before the onset of symptoms further highlights the disadvantages of relying solely on questionnaire triage. An intermediate contribution of pre-symptomatic and asymptomatic infections to overall SARS-CoV-2 transmission means that a combination of prevention measures, including enhanced hand and respiratory hygiene, testing, tracing, isolate strategies and physical distancing, will continue to be required (Arons *et al.*, 2020; Gandhi *et al.*, 2020).

Several large scale serological surveys of SARS-CoV-2 have been performed (Adams *et al.*; Bryan *et al.*, 2020; Garcia-Basteiro *et al.*, 2020; Pollán *et al.*, 2020; Salje *et al.*, 2020; Snoeck *et al.*, 2020; Sood *et al.*, 2020; Steensels *et al.*, 2020; Stringhini *et al.*, 2020; Valenti *et al.*, 2020) or are ongoing (Bobrovitz *et al.*, 2020), with several including data on health-care workers (Garcia-Basteiro *et al.*, 2020; Korth *et al.*, 2020; Pollán *et al.*, 2020; Shields *et al.*, 2020; Steensels *et al.*, 2020; TosaTo *et al.*, 2020). To date, these studies have been heterogeneous in the population studied, their sampling, methodological rigour and use of a range of non-validated antibody tests with low sensitivity or specificity, or have not reported the performance characteristics of the chosen assay (Bobrovitz *et al.*, 2020). Despite these limitations, seroprevalence estimates for health-care workers have ranged from 5.2% to 24.4%, approximately twice that of the general population and

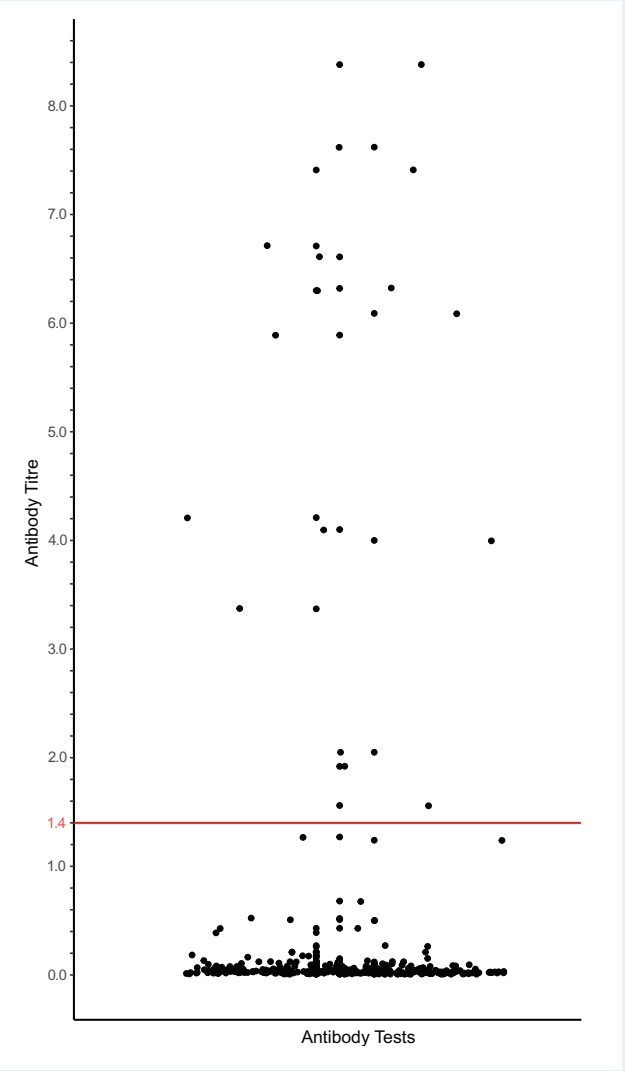


**Figure 3. SARS-CoV-2 antibody titres**. Antibody titre as determined by Abbott Diagnostics SARS-CoV-2 IgG assay for staff (n = 554). The red line indicates the diagnostic threshold, 1.4, above which tests are determined as positive.

substantially higher than the 4% reported here (Garcia-Basteiro *et al.*, 2020; Pollán *et al.*, 2020; Steensels *et al.*, 2020; TosaTo *et al.*, 2020). This may reflect the standalone nature of fertility centres, i.e. the private healthcare setting, that most staff were sequestered at home due to government restrictions rather than redeployed to routine clinical care, and that they were not involved in the direct care of COVID-19 patients. In Spain, health-care workers comprise 24% of all confirmed COVID-19 cases (Pollán *et al.*, 2020), and in the UK a cross-sectional study of 554 National Health Service (NHS) health-care workers identified that 24.4% had seroconverted (Shields *et al.*, 2020).

We observed substantial variability in IgG titres, despite all staff only having mild symptoms and none requiring hospitalization. Previous studies have suggested that high antibody titres may positively correlate with disease severity (Zhao *et al.*, 2020), however, the non-standardization of antibody titres makes cross-study comparisons difficult. IgG also lasts longer than IgM or IgA (Theel *et al.*, 2020; To *et al.*, 2020) and in the absence of longitudinal testing, we were unable to determine whether those individuals with levels just below the 1.4 threshold were in the early phases of seroconversion or had exhibited a weak antibody response or were true negatives.

Our study has several strengths including the use of paired NAAT and serological testing, the inclusion of all staff groups and the range of geographical settings. However, we acknowledge several limitations including, due to the voluntary participation, there was incomplete NAAT testing for all staff members, although >95% staff had serology testing. Additionally, the diagnostic performance of NAAT testing is largely influenced by viral load, sample site and method of specimen collection, all of which can contribute to a false-negative result (La Marca *et al.*, 2020). Of these, viral load and sampling sites are the most variable, with the viral load in oropharyngeal swabs at its highest at the time of symptom onset and decreasing monotonically thereafter (To *et al.*, 2020; Zou *et al.*, 2020). That testing was performed by individuals trained in oropharyngeal swab techniques and during follow-up, no additional staff members became symptomatic would suggest initial case detection was complete. We recognize that some individuals may not develop antibodies to SARS-CoV-2, however, seroconversion has recently been reported to be as high as 99% for patients if follow-up is extended beyond 15 days from symptom onset (Wajnberg *et al.*, 2020). In keeping with this, a recent systematic review and meta-analysis of antibody test performance, derived from 54 study cohorts with 15 976 samples, reported antibody tests had a sensitivity of 30.1% (95% CI 21.4 to 40.7) for 1 to 7 days, 72.2% (95% CI 63.5 to 79.5) for 8 to 14 days and 91.4% (95% CI 87.0 to 94.4) for 15 to 21 days after the onset of symptoms (Deeks *et al.*, 2020). The motivation for participation was not ascertained and may have reflected altruistic or personal concerns, or suspicion regarding previous symptoms. Finally, to protect staff anonymity, we had limited details on the job description or medical history, but both patient-facing and head office staff were included.

Our study provides estimates of SARS-CoV-2 spread within staff of fertility units in European countries. Despite the prominent impact of COVID-19 in the UK and other European countries, the low prevalence of seroconversion of staff highlights the need for continued comprehensive risk mitigation strategies and engagement with evolving national endeavours and guidance to reduce viral transmission and to identify and isolate new cases and their contacts as we embark on the resumption of fertility services.

## Data availability

The data underlying this article cannot be shared publicly due to privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

## Acknowledgements

We acknowledge all staff who participated in the study.

## Authors' roles

S.M.N., T.C. and G.T. conceived the idea, S.M.N. wrote the first draft of the manuscript, P.S.G. performed the statistical analyses,

S.E. completed the assays, and all authors contributed and approved the final version of the manuscript.

## Funding

The Fertility Partnership funded the study but had no role in the study design, the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

## Conflict of interest

No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. S.M.N. reports personal fees from Access Fertility, personal fees from Merck, personal fees from Ferring, grants and personal fees from Roche Diagnostics, personal fees from The Fertility Partnership and personal fees from Modern Fertility, outside the submitted work. T.C. reports personal fees from Merck and personal fees from Ferring, outside the submitted work. G.T. reports personal fees from Merck, personal fees from Ferring and personal fees from Roche Diagnostics, outside the submitted work. S.E. and P.S.G. report no conflicts of interest.

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