Journal of Assisted Reproduction and Genetics (2021) 38:539–541
https://doi.org/10.1007/s10815-020-02024-w

LETTER TO EDITOR

Letter to editor

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Received: 18 November 2020 / Accepted: 25 November 2020 / Published online: 7 January 2021
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Dear Sir

As we face rapidly accelerating increases in COVID-19 across much of Europe and the USA, with no apparent end to the initial waves of the global pandemic in these regions, we were dismayed at the suggestion that our intent was to be divisive [1]. Rather, our objective was to emphasise the need for greater global collaboration [2], particularly at a time when the science is uncertain, complex, incomplete and contested. As scientists, we should acknowledge uncertainty, debate the interpretation of the emerging evidence and encourage scientific discourse and rigour regarding the relative merits of any specific guidance, especially if disparate approaches are being recommended.

With respect to the comments raised. Timing and context are of critical importance when undertaking diagnostic evaluation of serological testing, in as much as they influence pre-test probability i.e. prevalence rates and the likelihood that an individual has COVID-19 based on symptoms. Figure 1 shows two different COVID-19 serological testing scenarios with a pre-test probability of 5% and the 10-fold higher 50% [3]. In the current context where background prevalence estimates remain low [4], the likelihood of a false positive is high, while as prevalence rates increase, the risk of a false negative will increase substantially. When combined with the temporal dynamics of the humoral response [5], serological testing may have limited utility in informing acute care decisions in fertility treatment provision. The CDC have recommended that serologic testing by itself should not be used to establish the presence or absence of SARS-CoV-2 infection or reinfection [6]. With elucidation of the role of serological testing, there is increasing scientific convergence on the principal indications [3, 6, 7]:

1. As a method to support diagnosis of acute COVID-19 illness for patients who present late (9–14 days after symptom onset) in conjunction with classic viral detection methods.
2. In a research context to monitor the quality and longevity of the immune response in patients with previously confirmed COVID-19 disease or potentially to monitor response to vaccination.
3. For seroprevalence surveys for research and public health monitoring.

The recent iteration of the ESHRE guidance continues to recommend testing, with an extension of testing to asymptomatic individuals including all staff and patients in high-risk areas (≥ 120 cases per 100,000—currently most of Europe), considered a "minimal action" [8]. Given the inherent logistical issues delivering this level of testing and the public health implications on a finite resource, this statement would appear aspirational rather than obligatory. Although many country-specific public health guidance has subsequently discounted this recommendation, non-compliance with professional body guidance may have profound as yet unrecognised regulatory implications.

In the haste to describe our analyses as "quite superficial" and suggest "non-critical reading" of the documents, the authors appear to have overlooked that our original figure incorporated the suggested repeat triage questionnaires and the section of our manuscript highlighting the issues regarding availability of testing. The suggestion

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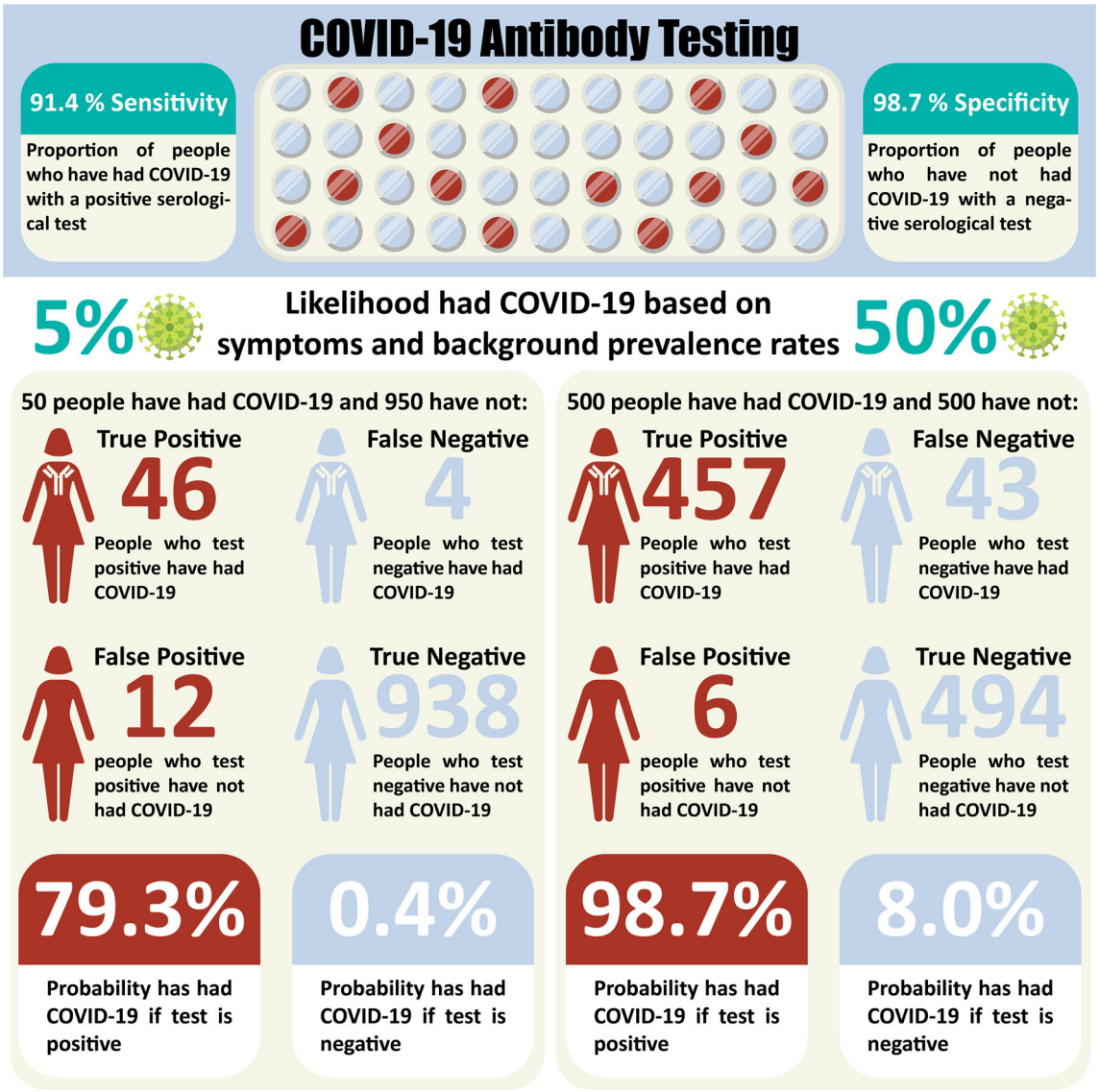

Fig. 1 Interpreting COVID-19 antibody tests. The implications of pre-test probabilities of 5% and 50% on the interpretation of COVID-19 antibody test if 1000 people were tested. The Cochrane review identified a mean sensitivity of 91.4% and mean specificity of 98.7% and these are here used for illustrative purposes. For the 5% pre-test probability, e.g. a patient with no symptoms but answers yes to a triage question, should the test have a lower sensitivity, particularly if the peak incidence and therefore likely time of infection is > 35 days ago, this would proportionally increase the false-negative and false-positive rate substantially. For example, for 57% specificity, the false-negative rate is 2.1% and the false-positive rate would be 21%. In contrast, if the pre-test probability is 50%, e.g. patient has atypical symptoms for several weeks, a positive test is compelling due to the low false-positive result, but the false-negative rate is still high at 8%. Antibody tests have high specificity, but sensitivity is variable and depends on the time since symptom onset

that we were trying to discredit the two major societies is similarly inaccurate. Rather, our analyses supported the ASRM guidance, which continues to recognise the limitations of testing, and wished to particularly highlight the discordance with the non-referenced ESHRE pathway incorporating serological testing within the treatment care algorithm and discuss the clinical implications of this critical difference. As a scientific community, rather than demonise opposing views, we should be encouraged to debate alternative theories in an open and respectful manner and resolve these by doing great research.

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