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Correspondence

A simple rule for interpreting COVID-19 antibody test results, by seroprevalence and vaccination status

Dear editor,

A positive COVID-19 antibody (serological) test result supposedly indicates immunity, safety for business travel, and no need for further vaccination. False positive results, however, will mislead important decisions.

Risk of false positive results is not only determined by specificity/sensitivity but also by prevalence.[1] Prevalence of COVID-19 antibody is estimated by seroprevalence surveys using a serological test. Nevertheless, since the serological test itself is not perfect, the seroprevalence can be substantially different from the true prevalence.

Theoretically, the (unadjusted) seroprevalence should be no less than one minus specificity and no larger than sensitivity. If one knows exact sensitivity and specificity, it is feasible to calculate the true prevalence by adjusting seroprevalence with sensitivity and specificity. However, sensitivity and specificity information provided by the manufacturers can be over-optimistic, because the United States Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for COVID-19 serological test does not require the demonstration of a lack of cross-reactions with common cold coronaviruses (e.g. HKU1, NL63, OC43, 229E).[2,3]

If the exact sensitivity and specificity of a test are uncertain, it is still possible to estimate sensitivity, specificity, and prevalence using one of latent class model-based numerical methods.[4] But this approach is cumbersome, and not suitable for practical use.

To develop a simple and accurate rule for correct interpretation of COVID-19 serological test results, we solve for the probability that a positive result is false (false discovery rate, FDR), in terms of crude (unadjusted) seroprevalence, for EUA authorized COVID-19 serological tests (≥95% specificity and ≥90% sensitivity):3 (Supplementary Appendix):

$$FDR = 1 - \frac{SE \cdot (SeroPrev + SP - 1)}{SeroPrev \cdot (SE + SP - 1)}$$

SeroPrev, crude (unadjusted) seroprevalence; SE, sensitivity; SP, specificity (SE and SP values are assumed error-free, without bias).

Fig. 1 shows that, when the crude (unadjusted) seroprevalence is higher than 9.5%, an EUA authorized COVID-19 serological test offers clinically meaningful positive test results (more likely to be true positive than to be false positive). Confirmation with a second test (orthogonal testing algorithm) will further improve the PPV.[1] However, when crude seroprevalence is between 2.0% and 9.5%, the chance of a false positive result varies from less than 10% (when specificity is 99% and sensitivity is 99%) to nearly 100% (when specificity is 95% and sensitivity is 90%). In such seroprevalence range, interpretation of serological test results highly depends on the specificity of test kits used. For settings with a crude seroprevalence lower than 2.0%, serological testing using a test kit with a specificity of less than 99% are not advisable due to a nearly 100% false positive rate. On the other hand, since authorized COVID-19 vaccines are expected to yield a protective antibody response in ≥ 70% vaccinees,[5] the risk of false positive result will be less than 1.7% for an EUA antibody test (Fig. 1).

Our results show that, for an unvaccinated person from settings with seroprevalence less than 9.5% and without a

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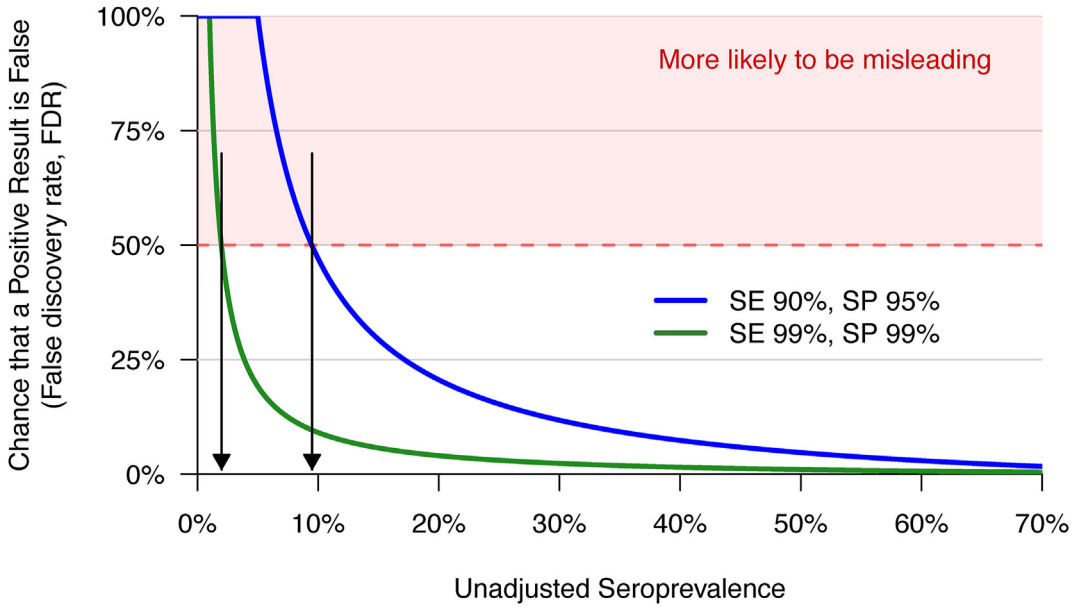

Figure 1. Chance that a positive result of FDA EUA authorized COVID-19 serological test is false, by unadjusted seroprevalence. The blue line shows the relationship when specificity (SP) is 95% and sensitivity (SE) is 99%. The green line shows the relationship when SP is 99% and SE is 99%. Right arrow marks the seroprevalence threshold (9.5%) for a >50% false discovery rate when the test just meets the minimum EUA requirement (an SP of 95% plus an SE of 90%); while left arrow marks the 50% false discovery rate threshold (2.0%) for a test with SP 99% and SE 99%. The relationship when SP is 99% and SE is 90% is nearly identical to the relationship when SP is 99% and SE is 99%.

history of PCR-confirmed COVID-19, a positive COVID-19 antibody test result must be interpreted skeptically. In contrast, for vaccinated persons, current available EUA COVID-19 antibody tests provide highly accurate results on whether the immunization is successful.

Author contributions

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Declaration of competing interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.02.008.

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