6. The British Medical Journal: covid 19: lack of capacity led to halting of community testing in March, admits deputy chief medical officer. 2020. https://www.bmj.com/content/369/bmj.m1845 (accessed April 23, 2021).
7. Public Health England COVID-19: guidance for maintaining services within health and care settings. *Infect Control Prevent Recommend* 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/954690/Infection_Prevention_and_Control_Guidance_January_2021.pdf (accessed April 23, 2021).
8. Office for National Statistics. 2019 Mid-year Population Estimates. June 2020. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland (accessed April 23, 2021).
9. Lauer S., Grantz K., Bi Q., et al. The Incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Int Med* 2020;**172**:577–82.
10. World Health Organisation COVID-19 symptoms list. 2021. https://www.who.int/health-topics/coronavirus#tab=tab_3 (accessed April 23, 2021).

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Rapid antigen test for SARS-CoV-2 and primary health care

Dear Editor,

We have carefully read the article published by Buliete et al. in your prestigious journal.[1] This is, in our opinion, an excellent article about the usefulness of rapid antigen detection tests (RADTs) in the diagnosis of SARS-CoV-2 infection. Its strengths are that it is a real-life, primary care study, its careful design and the large and calculated sample size, congratulations. However, there are some issues that we believe should be highlighted and others that should be nuanced based on their results, especially with regard to policy implications.

Firstly, we believe that the high specificity found in both, symptomatic and asymptomatic patients, close to 100%, has not been sufficiently highlighted. This near absence of false positives, as the authors comment, has been noted in other published articles. This finding is consistent with two recently published papers by our research group in two different contexts: population screening[2] and an outbreak in a nursing home.[3] As the authors conclude, this means that a positive test is a source of infection, but in both symptomatic and asymptomatic patients, so confirmatory tests are unnecessary. Based on the internal validity provided by the manufacturer, other authors recommend confirmatory testing in screening cases because of the expected high false positive rate.[4] It is well known that if the expected prevalence is higher than 1 - Specificity the positive predictive value will be very low and even all positives could be false positives.[5] However, if the prevalence is close to 100% the positive predictive value will be very high even with pre-test probabilities below 5%, which is the WHO recommended limit for the use of RADTs.[6]

With regard to nuance, we were surprised that the authors praise the reliability of the negative results in symptomatic subjects and question those of asymptomatic subjects with similar results and with confidence intervals that overlap widely. In both cases we believe that a negative test does not rule out the presence of infection. Even in those cases where the reason for the request for testing is unknown, the pre-test probability is high, 7.8%,[1] and therefore a clear scenario of maintaining caution, the same in the case of close contacts, the quarantine situation should be maintained for the stipulated time regardless of the result of the test not only for antigen, but even for PCR.[7,8] On the contrary, in a low pre-test probability scenario of less than 5%, as may be the case in population-based screening, the negative predictive value is very high and the presence of infection can be reasonably ruled out.[2]

In any case, we would like to congratulate the COVID-19 Primary Care Research Group for its interesting work and just remind that diagnostic tests are not to be read but must be interpreted in their context.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Bulilete O., Lorente P., Leiva A., Carandell E., Oliver A., Rojo E., et al. Panbio™ rapid antigen test for SARS-CoV-2 has acceptable accuracy in symptomatic patients in primary health care. *J Infect* 2021;**82**(3):391–8.
2. Fernández-Vázquez J.P., Reguero S., Sánchez-Antolín G., Martín-Sánchez V. Population-based screening for acute SARS-CoV-2 infection using rapid antigen testing and the 5% pre-test probability. Is the specifity our problem?. EIMC (accepted to publication).
3. Diez-Flecha C., Rivero Rodríguez A.M., Fernández-Villa T., Fernández García P., Ferreira de Jesús J.L., Sánchez Antolín G. et al. [Internal validity of a rapid test for COVID-19 antigens in a nursing home]. SEMERGEN 2021 (accepted to publication)
4. Peeling R.W., Olliaro P.L., Boeras D.I., et al. Scaling up COVID-19 rapid antigen tests: promises and challenges. *Lancet Infect Dis* 2021 S1473-3099(21)00048-7.
5. Rogan W.J., Gladen B.. Estimating prevalence from the results of a screening test. *Am J Epidemiol* 1978;**107**:71–6.
6. World Health Organization. *Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays*. World Health Organization; 2020. [Internet]Available from: *https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays* .
7. Centers for Disease Control and Prevention – CDC. *When to Quarantine. Stay home if you might have been exposed to COVID-19*. Centers for Disease Control and Prevention – CDC; 2021. [Internet]Available from: *https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html* .
8. Salathé M., Althaus C.L., Neher R., Stringhini S., Hodcroft E., Fellay J., et al. COVID-19 epidemic in Switzerland: on the importance of testing, contact tracing and isolation. *Swiss Med Wkly* 2020;**150**:1112.

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Impact of COVID-19 vaccination program on seroprevalence in blood donors in England, 2021

Dear Editor,

We read with interest in this journal the letter of Tré-Hardy et al.[1] which contrasts serological responses following mRNA vaccination in individuals with and without prior infection; good responses were seen in all study participants. England introduced a mass vaccination programme against COVID-19 on 8th December 2020 primarily based on age, starting with those over 80 years of age, along with health and social care workers.[2] Since the beginning of the programme to 7th March 2021 over 19 million individuals in England have been vaccinated with at least one dose of vaccine: either Pfizer BioNTech (from 8th December) or AstraZeneca (from 4th January).[3] We describe the impact of vaccination rollout on antibody prevalence in blood donors in England.

As part of COVID-19 infection monitoring, Public Health England, in collaboration with the National Health Service Blood and Transplant Service has arranged regular collections of plasma from English blood donors to be sent for COVID serology testing; results are reported weekly.[4] Approximately 250 samples per week are collected from each of seven NHS regions. We present seropositivity estimates from 23rd November 2020 onward, which covers the period of vaccine rollout and the peak of England's B.1.1.7-variant dominated epidemic wave.

The vaccination status of donors is not available but parallel testing using a nucleoprotein (Roche N) and a spike (Roche S) assay allows us to monitor trends in natural infection transmission and vaccine-induced seropositivity. Nucleoprotein assays (Roche N) only detect antibodies post natural infection, whereas spike assays (Roche S) detect both post natural infection and vaccine-induced antibodies. Antibody responses to both targets reflect infection/vaccination occurring 2–3 weeks previously given the time taken to generate a SARS-CoV2 antibody response.[5] We have shown strong agreement between serological responses using these two assays following natural infection that was sustained 6 months post infection.[6]

Seropositivity estimates are calculated on a 4-week rolling basis and are population weighted by NHS region, age group and sex. Estimates are not adjusted for assay sensitivity and specificity, which are estimated to be in excess of 97% and 99.8% respectively.[7, 8] Additionally, estimates are compared against vaccine uptake, which is calculated using the National Immunisation Management System (NIMS), a new national vaccine register to facilitate management of the vaccination programme in England.

7720 samples were available during the most recent 4-week period 22nd February-21st March 2021, of which 3224/7720 were Roche S positive and 1111/7717 were Roche N positive. Overall population weighted seropositivity amongst blood donors was 46.4% (95% CI 45.4% - 47.5%) using the Roche S assay. This compares with all-England seropositivity of 54.7%3 (95% CrI 49.3% - 60.5%) from the UK Office of National Statistics (ONS) Infection Survey for the period 18th February – 14th March, based on a single spike target based assay.[9] Roche N seropositivity was considerably lower at 14.5% (95% CI 13.7% - 15.4%).

Based on Roche S assay results, seroprevalence has been clearly increasing across all age groups from survey weeks 7th December 2020 – 3rd January 2021 (Fig. 1). For the most recent 4-week period, the population weighted seroprevalence was highest in the age 70–84 group at 93.5% (95% CI 90.9% - 95.4%). In parallel, the Roche N assay, a marker for natural infection, showed not only the lowest seroprevalence in the age 70–84 group for the same period at 4.7% (95% CI 3.1% - 7.1%), but this also stabilised over successive four week intervals; for example over the period 1st-31st January 2021 seropositivity was 5.2% (95% CI 3.1% - 8.5%). Seropositivity based on Roche N was highest in the youngest donor cohort and continues to increase, suggesting transmission was ongoing.

Cumulative first dose vaccine uptake was 91.6% to the week ending 21st February, which roughly corresponds with the most recent 4-week period given 2–3 weeks for antibody response (Fig. 2). The increase in S positive N negative outcomes accelerated from survey weeks 11th January – 7th February 2021 following a rise in uptake. Note that age 70+ uptake in Fig. 2 is weighted by the 70+ donor age distribution, which tails off with age.

The vaccine uptake of 8.7% to the week ending 7th February in those 18–59y is lower than S positive N negative seroprevalence in younger blood donors, suggesting that health and social care workers are over-represented in the latter group.

Since vaccine rollout commenced Roche S seropositivity has increasingly risen above Roche N seropositivity and clearly shows trends in vaccine-induced antibodies, especially within the 70–84 age group who were amongst the first to be targeted for vaccination. Second dose coverage is less an 1% amongst the oldest donor age group, hence we observe a robust antibody response following a single vaccine dose. Meanwhile Roche N seropositivity in this age group has remained stable, suggestive of vaccine impact. This adds to a growing body of evidence suggestive of vaccine impact in the UK population.[10]

Ethics

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient information for national surveillance of communicable diseases. Specific ethical approval was not required for this surveillance work.

Author's contributions

HW, SE, IH, SR, KB and GA wrote the manuscript, with input from MR. GA, KB and MR contributed to conceptualization, funding acquisition and project administration. HW performed statistical analysis. EC, AL, CT, CC collated vaccine uptake statistics. EL, IH,