



Statement from RCPATH's Immunology Specialty Advisory Committee on COVID-19 / SARS CoV2 antibody evaluation

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The Immunology SAC are aware of the many national and local initiatives currently undertaken to establish commercial and locally produced antibody tests for COVID-19 and the proliferation of rapidly developed commercial assays.¹

The SAC wish to ensure that assay evaluations are robust and fit for purpose.^{2,3}

The SAC recommend that there is a national and networked effort to harmonise and eventually standardise evaluation methodologies to ensure comparable utility and enable selection of the correct tests for the clinical outcomes desired.

The SAC recommend that evaluations must define the clinical function that the test will be used to support; the performance characteristics (predictive values, sensitivity and specificity) for back up diagnostic testing, testing of staff to enable safe early return to work, and evaluation of the extent of immunity and spread in the population will be very different.⁴

The biological variability of antibody response kinetics will make the assessment of true performance in diagnostic settings difficult without convalescent sera (IgG production will be expected delayed for a week or so after infection, IgM will be produced sooner, but lower limits of detection will need to be optimised for sensitivity).^{4,5,6}

Evaluations must be fit for purpose, if we are to avoid using the wrong tests for the wrong purpose.

Diagnostic testing

These samples will have high pre-test probability of disease, but in early days after infection false negatives are inevitable. Assays need acceptable PPV and NPV at early stage to ensure cohort separation in hospitals. IgG assessment alone unlikely to be sufficient.

Screening for absence of infection and return to work

Variable pre-test probability of infection is expected in different localities (currently 10–20% in some centres).

There are two scenarios:

- **Ruling out COVID disease in key workers to supplement or replace PCR testing** (if capacity not available) and therefore enabling them to return to work early. Use in this scenario will require high NPVs evaluated at a similar pre-test probability as seen in key workers locally.
- **Confirmation of previous infection with possible immunity and therefore able to return to work.** This requires a high PPV; with the caveat that we don't yet know if having detectable antibody reliably equates to protection from re-infection.

In this context it is important that we have a national / international network looking at the association of antibody status and virus neutralising protection.

Population screening for exposure (contact tracing and epidemiological surveillance).

- A low pre-test probability is assumed at present. Acceptable performance criteria need to be defined nationally, but high false positivity or negativity will impair epidemiological assessment.
- The performance criterion should be established and shared between evaluating laboratories to ensure comparability across the UK.
- PPV and NPV should be assessed on sample sets which mimic the lowest pre-test probability expected, as many perfectly usable assays in high probability populations become useless in low probability scenarios and this is the most challenging scenario for a test. Predicted efficacy in high prevalence populations may be derived from this data.

Harmonisation and standardisation

Harmonisation and eventual standardisation of assays will be required.

A common pooled antibody calibrant should be prepared promptly and used to harmonise detection across multiple assays in multiple centres allowing rapid access to testing across the country.

To achieve harmonisation and standardisation, a national network of diagnostic laboratories should be formed to collect and pool sera and plasma from antibody positive patients as soon as possible. Use of multiple centres of expertise and sample collection will supplement and amplify the benefits of large central provision, increase evaluation of all possible diagnostic options for each usage scenario and enhance security of testing availability. This would enable harmonised reporting against a single reference and improve speed of evaluation and collection of relevant data.

All assays should be validated/verified against these performance criteria for the relevant clinical use intended (preferably the lowest expected pre-test probabilities of COVID-19 infection prevalence) and using sample sets that are relevant to the scenario in question.

Thresholds for diagnosis should be optimised by ROC curve analysis cognoscent of the Reference Change Values (RCV) incorporating the inter-assay variability (CV) to determine the minimal measurable difference in serial samples that can be used to determine serological conversion .1,2,3

Harmonisation is essential and an EQA scheme is required as soon as practicable.

Assay performance data should be shared with the Medicines and Healthcare Regulatory Agency (MHRA).

References

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