Serology and PCR: Optimising COVID-19 Episode Identification

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> Accurately identifying distinct COVID-19 illness episodes proved a persistent challenge throughout the pandemic, complicating the evaluation of vaccine efficacy and therapeutic interventions. The variability in diagnostic tool performance, influenced by factors like testing timing and vaccination status, necessitated a more integrated approach. The BRACE trial investigators developed an algorithm to classify COVID-19 episodes by combining serology, PCR, and rapid antigen test (RAT) results.1

KEY TAKEAWAYS

- The Pivot: A new algorithm integrates serology with PCR and RAT results to improve COVID-19 episode identification, especially in vaccinated populations.
- The Data: The algorithm demonstrated improved accuracy in classifying episodes compared to relying solely on PCR/RAT, particularly for asymptomatic or mild infections.
- The Action: Clinicians should consider serological data alongside PCR and RAT results for a more comprehensive understanding of COVID-19 infection history, especially when evaluating vaccine responses or post-infection immunity.

The COVID-19 pandemic highlighted the need for precise episode identification to assess the effectiveness of vaccines and treatments. Standard diagnostic tools, such as PCR and rapid antigen tests, often presented limitations. These limitations included the transient nature of viral shedding, the impact of vaccination on viral load kinetics, and the varying sensitivity and specificity of tests at different stages of infection. Serology, which detects antibodies, offers a longer window for identifying past infection but does not confirm active disease. The BRACE trial, a large-scale randomised controlled trial investigating the BCG vaccine's effect on COVID-19, provided a unique dataset to develop and validate an optimised algorithm for episode classification.1

Investigators in the BRACE trial enrolled healthcare workers in Australia, Brazil, and Spain, randomising them to receive either the BCG vaccine or placebo. The trial collected extensive longitudinal data, including regular PCR and RAT results, as well as serological samples at baseline and various follow-up points. This comprehensive data collection allowed for a detailed examination of how different diagnostic markers evolved over time in both vaccinated and unvaccinated individuals, and across varying severities of COVID-19. The primary objective of this specific analysis was not to report on the BCG vaccine itself, but to leverage the rich diagnostic data to refine the definition of a COVID-19 episode.1

Defining a COVID-19 Episode

The BRACE trial's approach to episode identification moved beyond simple positive test results. The investigators aimed to distinguish between new infections, persistent viral shedding, and reinfections. They defined a COVID-19 episode as a period of illness or asymptomatic infection confirmed by diagnostic testing. The algorithm integrated PCR, RAT, and serology, considering the timing of tests relative to symptom onset, vaccination status, and previous infection history. This multi-modal strategy was particularly important given the evolving understanding of SARS-CoV-2 immunology and the widespread vaccination campaigns.1

A key component of the algorithm involved the interpretation of serological data. Anti-spike (S) antibody levels were used to indicate prior vaccination or infection, while anti-nucleocapsid (N) antibodies were primarily indicative of natural infection, as most vaccines did not induce anti-N responses. The algorithm established thresholds and kinetics for these antibodies to differentiate between vaccine-induced immunity and infection-induced immunity, and to identify seroconversion following an infection. This distinction became increasingly vital as vaccination rates climbed, making it harder to interpret positive PCR tests without additional context.1

The algorithm classified an episode as a new infection if there was a positive PCR or RAT, accompanied by seroconversion (a significant rise in antibody levels) or a sustained high antibody titre in the absence of recent vaccination. For individuals with prior vaccination, the presence of anti-N antibodies was a strong indicator of infection, even with mild or asymptomatic cases that might otherwise be missed by PCR or RAT alone due to infrequent testing or low viral loads. The algorithm also accounted for the duration of viral shedding, typically considering a new positive PCR after 90 days as a potential reinfection, unless serological evidence strongly suggested otherwise.1

The Role of Serology in Classification

Serology played a critical role in identifying episodes that PCR or RAT alone might misclassify or miss entirely. For instance, individuals with asymptomatic infections often do not present for testing, but seroconversion can reveal these past events. The algorithm used a four-fold rise in anti-S or anti-N antibody levels from baseline as a marker of seroconversion, indicating a recent infection. This was particularly useful in vaccinated individuals where anti-S antibodies were already present due to vaccination, making the detection of anti-N antibodies or a significant boost in anti-S levels essential for identifying breakthrough infections.1

The investigators found that relying solely on PCR or RAT could lead to an underestimation of COVID-19 incidence, especially in populations with high vaccination rates or those with mild symptoms. Serology helped to capture these missed infections, providing a more accurate picture of the true burden of disease. This enhanced accuracy is vital for epidemiological studies and for understanding population-level immunity. The impact of public health measures, for example, relies on accurate incidence data.1

But the interpretation of serology was not without its complexities. Cross-reactivity with other coronaviruses, waning antibody levels over time, and the variability in individual immune responses all presented challenges. The BRACE algorithm addressed these by incorporating longitudinal serological data, allowing for the tracking of antibody trajectories rather than relying on single time-point measurements. This longitudinal perspective provided a more robust basis for inferring infection status.1

Impact on Episode Identification

The BRACE algorithm demonstrated improved accuracy in identifying COVID-19 episodes compared to methods relying solely on PCR or RAT. While specific quantitative metrics like sensitivity and specificity for the algorithm itself were not explicitly detailed in the abstract, the authors highlighted its utility in optimising episode identification. This optimisation meant fewer missed infections and a clearer distinction between new infections and persistent viral RNA detection. The algorithm's ability to integrate different diagnostic modalities provided a more comprehensive understanding of infection dynamics.1

The algorithm was particularly effective in scenarios where PCR results were ambiguous or where individuals had received multiple vaccine doses. For example, a positive PCR in a highly vaccinated individual might be difficult to interpret without serological evidence of a new infection. The algorithm's structured approach helped to resolve such ambiguities, leading to more confident episode classifications. This is particularly relevant when considering the coadministration of COVID-19 and flu shots, where immune responses can be complex.1

The investigators also considered the timing of tests. A positive PCR within 90 days of a previous positive test was generally considered part of the same episode, unless there was clear serological evidence of reinfection (e.g., a significant rise in anti-N antibodies after they had waned). This temporal component prevented overcounting episodes due to prolonged viral shedding, a common issue with PCR testing. The algorithm's design reflects a pragmatic approach to real-world diagnostic challenges, moving beyond simplistic definitions of infection.1

Limitations and Future Directions

The BRACE trial's algorithm provides a valuable framework, but it does have limitations. The algorithm's reliance on regular serological sampling, while ideal for a research setting, may not be feasible in routine clinical practice due to cost and logistical constraints. The generalizability of the specific antibody thresholds and kinetics derived from the BRACE cohort, primarily healthcare workers, to broader populations with different demographic profiles and comorbidities also requires further validation. The algorithm was developed during a period when specific variants dominated; its performance against future variants with altered immunogenicity might need re-evaluation.1

The algorithm also assumes the availability of both anti-S and anti-N antibody testing, which may not be universally accessible. In settings where only anti-S antibodies are measured, differentiating vaccine-induced immunity from infection-induced immunity becomes more challenging. Still, the underlying principle of integrating multiple diagnostic markers remains sound. The Oxford Handbook of Infectious Diseases and Microbiology provides a comprehensive overview of diagnostic strategies for various pathogens, highlighting the evolving nature of such approaches.

The BRACE trial's work offers a template for optimising episode identification for other respiratory viruses where diagnostic ambiguity can complicate research and public health efforts. The methodology could be adapted to future pandemics, ensuring more accurate data collection for vaccine and therapeutic trials. The emphasis on longitudinal data and the integration of serology with molecular tests represents a significant step forward in infectious disease diagnostics.1

The algorithm's development within a large, well-characterised cohort like BRACE lends it considerable credibility. The detailed collection of vaccination status, symptom data, and repeated diagnostic testing allowed for a robust evaluation of the algorithm's performance. This level of data granularity is often absent in observational studies, making the BRACE insights particularly valuable. The investigators' careful consideration of factors like waning immunity and the impact of booster doses on antibody responses further strengthens the algorithm's clinical relevance.1

The trial was not powered to detect differences in specific clinical outcomes based on the algorithm's classifications, and that gap matters. While the algorithm improves episode identification, its direct impact on patient management or clinical decision-making was not the primary focus of this analysis. Future research could explore how such refined episode definitions correlate with long-term health outcomes or the risk of post-acute sequelae of COVID-19. The BRACE trial's contribution lies in providing a more accurate lens through which to view the epidemiology of SARS-CoV-2 infection, a foundational step for all subsequent clinical research.1

CLINICAL IMPLICATIONS

The BRACE trial's algorithm for COVID-19 episode identification offers a more precise tool than relying solely on PCR or rapid antigen tests. For clinicians, this means a more accurate understanding of a patient's true infection history, particularly in the context of multiple vaccine doses and prior infections. It moves beyond the simplistic 'positive test equals infection' paradigm, which often failed to capture the full picture.

This refined approach has direct implications for interpreting antibody tests in clinical practice. When assessing a patient's immune status or investigating potential reinfections, serological data, especially anti-N antibodies, provides important context that PCR alone cannot. It helps differentiate between vaccine-induced immunity and natural infection, a distinction that can inform discussions about future vaccination strategies or risk assessment.

For public health, the algorithm provides a more robust method for tracking disease incidence and vaccine effectiveness. Underestimating infection rates due to missed asymptomatic cases or ambiguous PCR results skews epidemiological models. Adopting such an integrated diagnostic strategy could lead to more accurate data, which in turn supports better policy decisions and resource allocation during future outbreaks.

The challenge remains in translating this research-grade algorithm into routine clinical workflows. The logistical and cost implications of widespread longitudinal serological testing are substantial. However, the principle of combining diagnostic modalities to overcome individual test limitations is sound and should guide the development of future diagnostic strategies for emerging infectious diseases.

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REFERENCES

1. 1. McDonald E, Pittet LF, Bonten M. Optimising COVID-19 episode identification using serology and PCR/rapid antigen testing: insights from the BRACE trial. BMC Infect Dis 2026.

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