# Updated Report

## Post-market validation of a further three serological assays for COVID-19

## –

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**Report prepared for:**

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# Executive Summary

Here, we present results of our post-market validation of a further three serological assays for the detection of SARS-CoV-2 antibodies and comparison with findings for assays already reported. Testing was undertaken on a cohort of stored serum prior to the COVID-19 outbreak in Australia, and on samples of serum collected from patients with SARS-CoV-2 infection confirmed by molecular testing.

Our findings suggest that overall sensitivities of these three point-of-care tests (PoCT) tested are below that reported by the manufacturer in the instructions for use (IFU). The Genbody COVID-19 IgM/IgG and Innovita 2019-nCoV Ab Test sensitivity on initial testing were significantly lower than that reported by the manufacturer and lower than the previous assays tested in this ongoing post-market validation. The Wantai SARS-CoV-2 Ab Rapid test results were lower than those reported in the IFU, but in keeping with previously reported results for other assays.

Overall, our findings continue to support a recent position statements by the Public Health Laboratory Network (PHLN) and the Royal College of Pathologists Australasia (RCPA) that serological assays have limited, if any, role in the diagnosis of acute COVID-19 infection. The role of PoCT in population-level serosurveys remains to be seen in the context of other emerging serological tests for SARS-CoV-2.

## 1. Introduction

This work continues the post-market validation work first reported on 28th April and 2nd June 2020. Following the Initial laboratory responses and release of the viral whole genome sequence by Chinese investigators in early January 2020, there was initially a rapid development of serological assays for COVID-19.[1–3] The most publicised serological tests for COVID-19 have been lateral flow immunoassays, also known as serological point of care tests

(PoCT). The urgent need for diagnostic testing has meant that many test kits have had an expedited assessment from the Australian Therapeutic Goods Administration (TGA). As such, robust post-market validation of COVID-19 diagnostic kits that are listed on the Australian Register of Therapeutic Goods (ARTG) is essential.

Here, we present findings from a post-market validation study of three further serological PoCT (all listed on the ARTG), to supplement the reports dated 28th April 2020 and 2nd June 2020, to bring the total to eight PoCT and one ELISA.

## 2. Methods

### 2.1    Establishment of patient cohorts and serum samples

In order to test sensitivity and specificity of the included lateral flow assays, a testing panel was developed consisting of the following three patient cohorts:

***Sensitivity analysis***

1. Serum from patients with SARS-CoV-2 detected by RT-PCR from upper and / or lower respiratory tract specimens.

***Specificity analysis***

2. Serum from patients with infections with the potential for cross-reactivity in serological assays, namely (i) patients with respiratory viral infections, including seasonal coronavirus infections and (ii) patients with other acute infections (e.g. dengue; CMV; EBV).
3. Serum from a representative sample of the Victorian population collected in 2018 and 2019 ('pre-pandemic controls').

All serum samples were obtained from a tertiary hospital (Royal Melbourne Hospital, RMH) or the state reference laboratory for virology (Victorian Infectious Diseases Reference Laboratory, VIDRL). Serum samples were aliquoted into 100uL aliquots for processing and storage at time of entry into the study. Serum panel 1 was used in the initial validation of serological assays (previous reports) and for the Genbody COVID-19 IgM/IgG, Innovita and lot 1 (JNB20200301) of the Wantai SARS-CoV-2 Ab Rapid Test post-market validation (Table 1), serum panel 2 was utilised for lot 2 (JNB20200405) of the Wantai assay as part of a planned transition to a smaller, more sustainable serum panel for this ongoing post-market validation work.

**Table 1: Panel 1 - Number and type of samples included in initial post-market validation of serological PoCT assays.**

| Cohort | Characteristics | Purpose of samples | Total (samples / patients) |
| --- | --- | --- | --- |
| 1 | SARS-CoV-2 RT PCR-positive patients | Sensitivity analysis | 137/91 |
| 2 | Other non-COVID-19 infections | Specificity analysis | 36/36 |
| 3 | Pre-pandemic controls | Specificity analysis | 56/56 |

**Table 2: Panel 2 - Number and type of samples included in ongoing post-market validation of serological PoCT assays.**

| Cohort | Characteristics | Purpose of samples | Total (samples / patients) |
| --- | --- | --- | --- |
| 1 | SARS-CoV-2 RT PCR-positive patients | Sensitivity analysis | 50/49 |
| 2 | Other non-COVID-19 infections | Specificity analysis | 30/30 |
| 3 | Pre-pandemic controls | Specificity analysis | 70/70 |

## 2.2. Test descriptions

### 2.2.1 Point of care lateral flow serological assays

Eight lateral flow serological assays in total have been assessed, two were described in detail in report date 28th April, three were described in an updated report on the 2nd June, three are additionally described here. Common features are that:

i. they are single use immunochromatographic lateral flow tests, for the detection of IgM and/or IgG in serum, plasma or whole blood

ii. the specific SARS-CoV-2 recombinant antigen(s) incorporated into the assay are not described in the IFU

iii. IFUs indicate that test results should not be used as the sole basis for clinical management decisions, requiring interpretation alongside clinical features and other diagnostic (molecular) assays

Immunochromatographic assays involve detection of anti-SARS-CoV-2 IgM or IgG antibodies through binding to immobilised recombinant antigen attached to colloidal gold, followed by detection of the conjugates by an anti-human IgM or IgG antibody. A control line is also incorporated, which measures adequacy of fluid flow along the test strip. Reported manufacturer reported characteristics are summarised in Table 3 and include details for assays described in previous reports. In general, with respect to the generation of reported performance characteristics limited information was supplied regarding:

i. where validation samples were sourced from

ii. whether plasma, serum, whole blood or a combination of these were used for validation

iii. what proportion of patients included were confirmed by a result from RT-PCR

iv. what the time frame was for collection of samples post the onset of clinical symptoms.

**Table 3: Reported performance characteristics of included serological assays according to manufacturer's instructions for use**

| Assay | Sensitivity | Specificity |
|---|---|---|
| Genbody COVID-19 IgM/IgG | Overall IgM or IgG positive: 89.3% ≥ 7 days from symptom onset IgM or IgG: 88% | IgM or IgG 95.9% |
| Innovita 2019-nCoV Ab Test | 85.0% (95% CI: 62.11, 96.79%)@ 87.3% (95% CI: 80.4, 92%)^ | 97.4% (95% CI: 91.04, 99.69%)@ 100.0% (95% CI: 94.2, 100%) |
| Wantai SARS-CoV-2 Ab Rapid Test | 94.70% (95%CI: 89.38, 97.84%) | 98.89% (96.80, 99.77%) |

@ RT-PCR confirmed positive cases; ^ Composite clinical end point

### 2.2.3 RT-PCR

Patients with confirmed COVID-19 infection had SARS-CoV-2 detected using the Coronavirus Typing assay (AusDiagnostics, Mascot, NSW). This is a two-step, hemi-nested multiplex tandem PCR, with seven coronavirus RNA targets plus a proprietary artificial sequence as an internal control. In addition, all positive samples had SARS-CoV-2 detected at VIDRL where testing was first conducted using an in-house assay for the SARS-CoV-2 RdRp gene. If positive, subsequent testing for the SARS-CoV-2 E gene was performed, using previously published primers.[4]

### 2.2.4 MICRONEUTRALISATION ASSAY

The microneutralisation assay is an in-house assay performed in the Subbarao laboratory, based in the Doherty Institute, University of Melbourne. SARS-CoV-2 virus, initially isolated from a clinical specimen from a patient in Melbourne, Australia,[5] is propagated in Vero cells, before being incubated with dilutions of test sera. This solution is subsequently inoculated onto a monolayer of Vero cells. Cell cultures are reviewed at five days, with cytopathic effect scored and compared between test and control wells. The ability of test sera to inhibit viral invasion and replication is reported as a titre, calculated by the Reed and Muench method,

with titles above 40 considered positive. The assay has been validated against an initial panel of serum from SARS-CoV-2 PCR confirmed patients and a representative serum cohort from 2016 with the assay cut-off of 40 determined by a receiver operating curve (ROC) analysis.

## 2.3    Testing protocol

Testing of the lateral flow assays was performed in the Clinical Trials Research Laboratory in the Department of Pathology RMH, by three laboratory research technicians, all of whom had undergone previous training in the use of lateral flow assays. Testing was performed exactly as per the IFU. Test panel 1 (Table 1) was undertaken in duplicate for the Genbody SARS-CoV-2 IgM/IgG Antibody Rapid Test and Innovita 2019-nCoV Ab Test, with a third test undertaken for discordant results, with the following caveats: i) two RT-PCR and one negative control sample were excluded from testing in the Genbody SARS-CoV-2 IgM/IgG Antibody Rapid Test assay as results were discordant and insufficient test kits remained to test in triplicate, ii) two RT-PCR positive samples were tested only once in the Genbody as there was insufficient sample to repeat, iii) four sera from RT-PCR patients were only tested a single time in the Innovita due to insufficient sera for replicates, iv) three sera from cohort 2 and all samples from cohort 3 were only tested a single time in the Innovita due to a combination of insufficient sera and insufficient test kits. The majority result (i.e. 2/3) was taken as the final result, any faint line present at test termination was considered a positive result.

Subsequent lot numbers 20200404 and 20200405 for the Innovita 2019-nCoV Ab Test distributed by AM Diagnostics were tested for lot to lot variation in a dilution series of 3 high positive samples (with microneutralisation titres 1016, 905 and 1280; positive titre is any titre above 40). Doubling dilutions were undertaken from neat samples to 1/256 dilution, for a total of 10 test sera per sample (neat, ½, ¼, 1/8, 1/16, 1/32, 1/64, 1/128, 1/256 and normal saline control). The last dilution at which the test kit detected antibody is reported here. Test

strips were read in duplicate, a third read was undertaken if the first two were discordant, with the third read taken as the final result.

For the Wantai SARS-CoV-2 Ab Rapid test (lots JNB20200301 and JNB20200405), each serum sample was tested in serum panel 2 (Table 2). Test strips for test panel 2 were read in duplicate, a third read was undertaken if the first two were discordant, with the third read taken as the final result.

All testing was undertaken in a blinded manner with results collated by an independent investigator at the conclusion.

## 2.4 Statistical analysis

Statistical analysis was carried out using GraphPad Prism (version 8.4.2). Binomial 95% confidence intervals (CI) were calculated for all proportions.

- Sensitivity of the serological assays was calculated as the number of positive results for each component of the test, divided by the number of samples from patients with confirmed COVID-19 as determined by RT-PCR.
- Specificity was calculated as the number of negative results for each component of the test, divided by the number of samples from patients without confirmed COVID-19 as determined by RT-PCR and clinical end point (Cohort 2 and 3).

## 2.5 Ethics

Ethical approval for this project was obtained from the RMH Human Research Ethics Committee (RMH HREC QA2020052). This ethics approval allows for prospective serum collection following discharge from hospital, thus enabling longitudinal assessment of the

performance of serological assays. Patients recruited into this project also provided specimens to assess the performance of plasma samples.

## 3. Results

### 3.1 Comparison of serological PoCT with RT-PCR

Serum samples included in the analysis included panel 1 (Table 1) for the Genbody COVID-19 IgM/IgG and Innovita 2019-nCoV Ab Test, and panel 2 (Table 2) for the Wantai SARS-CoV-2 Ab Rapid Test, missing samples were due to a combination of insufficient sample volume in and/or insufficient test kits to repeat on alternative or replacement serum samples. Sensitivity findings are reported in Tables 4 to 6; lot to lot variation in sensitivity for subsequent Innovita 2019-nCoV Ab Test lots are reported in Table 7.

**Table 4: Comparison of the Genbody COVID-19 IgM/IgG with RT-PCR for 91 patients with confirmed COVID-19 infection, stratified by days post-symptom onset.**

| Days post-symptom onset | Samples (n) | IgM detected (%) [95% CI] | IgG detected (%) [95% CI] | IgM or IgG (%) [95% CI] |
|---|---|---|---|---|
| 0-3 | 23 | 0 (0.0) [0.0, 14.8] | 0 (0.0) [0.0, 14.8] | 0 (0.0) [0.0, 14.8] |
| 4-8 | 26 | 4 (15.4) [4.4, 34.9] | 5 (19.2) [6.6, 39.4] | 5 (19.2) [6.6, 39.4] |
| 9-14 | 21 | 5 (23.8) [8.2, 47.2] | 9 (42.9) [21.8, 66.0] | 9 (42.9) [21.8, 66.0] |
| 15-20 | 8 | 6 (75.0) [34.9, 96.8] | 6 (75.0) [34.9, 96.8] | 6 (75.0) [34.9, 96.8] |
| 21-30 | 27 | 6 (22.2) [8.6, 42.3] | 14 (51.9) [32.0, 71.3] | 14 (51.9) [32.0, 71.3] |
| >30 | 30 | 4 (13.3) [3.8, 30.7] | 18 (60.0) [40.6, 77.3] | 18 (60.0) [40.6, 77.3] |
| **Total** | **135** | **25 (18.5) [12.4, 26.1]** | **52 (38.5) [30.3, 47.3]** | **52 (38.5) [30.3, 47.3]** |

CI = Confidence interval (Clopper-Pearson)

**Table 5: Comparison of the Innovita 2019-nCoV Ab Test with RT-PCR for 91 patients with confirmed COVID-19 infection, stratified by days post-symptom onset.**

| Days post-symptom onset | Samples (n) | IgM detected (%) [95% CI] | IgG detected (%) [95% CI] | IgM or IgG (%) [95% CI] |
|---|---|---|---|---|
| 0-3 | 23 | 0 (0.0) [0.0, 14.8] | 0 (0.0) [0.0, 14.8] | 0 (0.0) [0.0, 14.8] |
| 4-8 | 28 | 6 (21.4) [8.3, 41.0] | 5 (17.9) [6.1, 36.9] | 7 (25.0) [10.7, 44.9] |
| 9-14 | 21 | 9 (42.9) [21.8, 66.0] | 7 (33.3) [14.6, 57.0] | 10 (47.6) [25.7, 70.2] |
| 15-20 | 8 | 6 (75.0) [34.9, 96.8] | 6 (75.0) [34.9, 96.8] | 6 (75.0) [34.9, 96.8] |
| 21-30 | 27 | 13 (50.0) [28.7, 68.1] | 13 (50.0) [28.7, 68.1] | 14 (53.8) [32.0, 71.3] |
| >30 | 30 | 9 (30.0) [14.7, 49.4] | 15 (50.0) [31.3, 68.7] | 17 (56.7) [37.4, 74.5] |
| **Total** | **137** | **43 (31.4) [23.7, 39.9]** | **46 (33.6) [25.7, 42.1]** | **54 (39.4) [31.2, 48.1]** |

CI = Confidence interval (Clopper-Pearson)

**Table 6: Comparison of the Wantai SARS-CoV-2 Ab Rapid Test with RT-PCR for patients with confirmed COVID-19 infection, stratified by days post-symptom onset.**

| Days post-symptom onset | Samples (n) | Positive Test Result (%) [95% CI] |
|---|---|---|
| 0-3 | 0 | 0 |
| 4-8 | 6 | 4 (66.7) [22.3, 95.7] |
| 9-14 | 6 | 5 (83.3) [35.9, 99.6] |
| 15-20 | 6 | 6 (100) [54.1, 100] |
| 21-30 | 16 | 13 (81.3) [54.4, 96.0] |
| >30 | 16 | 13 (81.3) [54.4, 96.0] |
| **Total** | **50** | **41 (82.0) [68.6, 91.4]** |

CI = Confidence interval (Clopper-Pearson)

**Table 7: RT-PCR positive serum dilution series for lot to lot comparison, highest dilution recording a positive test result**

| Assay, Sponsor and lot number | Test Sample 1 [MN titre 1016 at 1:1] | | Test Sample 2 [MN titre 905 at 1:1] | | Test Sample 3 [MN titre 1280 at 1:1] | |
|---|---|---|---|---|---|---|
| | IgM | IgG | IgM | IgG | IgM | IgG |
| Innovita, AM Diagnostics 20200404 | 1:64 | 1:64 | 1:4 | 1:16 | 1:16 | 1:128 |
| Innovita, AM Diagnostics, 20200405 | 1:64 | 1:16 | 1:4 | 1:8 | 1:32 | 1:128 |

MN = Microneutralisation

When only samples collected more than 14 days following symptom onset were considered, the sensitivity of the Genbody COVID-19 IgM/IgG was 58.% (95% CI: 45.6-70.6%), the Innovita 2019-nCoV Ab Test was 56.9% (95% CI 44.0-69.2%), and the Wantai SARS-CoV-2 Ab Rapid Test was 84.2% (95% CI: 68.6-91.4%), (Table 9).

The specificity of the respective assays was as follows: Genbody COVID-19 IgM/IgG was 100% (95% CI: 96.0-100%), the Innovita 2019-nCoV Ab Test was 100% (95% CI: 96.0-100%), and the Wantai SARS-CoV-2 Ab Rapid Test was 98.0% (95% CI: 93.0-99.8%), (Tables 8, 9).

Summary tables of overall performances characteristics (Table 8), and performance characteristics for samples collect more than 14 days post symptoms onset (Table 9) are presented. Although the Wantai SARS-CoV-2 Ab Rapid Test is included for comparison, note that testing with a different serum panel will influence findings.

**Table 8: Comparative performance of serological assays with RT-PCR, regardless of day of serum collection post-symptom onset.**

| Performance Characteristic / Test Assay | Sensitivity (%) [95% CI] | Specificity (%) [95% CI] | Positive Predictive Value (%) [95% CI] | Negative Predictive Value (%) [95% CI] | Total (samples/ patients) |
|---|---|---|---|---|---|
| **Genbody IgM***  | 18.5 [12.4, 26.1] | 100 [96.0, 100] | 100 [86.3, 100] | 45.3 [38.3, 52.4] | 226/182 |
| **Genbody IgG***  | 38.5 [30.3, 47.3] | 100 [96.0, 100] | 100 [93.2, 100] | 52.3 [44.6, 59.9] | 226/182 |
| **Genbody IgM or IgG***  | **38.5 [30.3, 47.3]** | **100 [96.0, 100]** | **100 [93.2, 100]** | **52.3 [44.6, 59.9]** | 226/182 |
| **Innovita IgM***  | 31.4 [23.7, 39.9] | 100 [96.1, 100] | 100 [91.8, 100] | 49.5 [42.1, 56.9] | 229/183 |
| **Innovita IgG***  | 33.6 [25.7, 42.1] | 100 [96.1, 100] | 100 [92.3, 100] | 50.3 [42.8, 57.7] | 229/183 |
| **Innovita IgM or IgG***  | **39.4 [31.2, 48.1]** | **100 [96.1, 100]** | **100 [93.4, 100]** | **52.6 [44.9, 60.2]** | 229/183 |
| **Wantai Test Results** | **82.0 [68.6, 91.4]** | **98.0 [93.0, 99.8]** | **95.3 [84.2, 99.4]** | **91.6 [84.6, 96.1]** | 150/149 |

* Not all serum able to be tested in duplicate

**Table 9: Comparative performance of serological assays with RT-PCR for samples collected >14 days post symptom onset.**

| Performance Characteristic / Test Assay | Sensitivity (%) [95% CI] | Specificity (%) [95% CI] | Positive Predictive Value (%) [95% CI] | Negative Predictive Value (%) [95% CI] | Total (samples/ patients) |
|---|---|---|---|---|---|
| **Genbody IgM***  | 24.6 [14.8, 36.9] | 100 [96.0, 100] | 100 [79.4, 100] | 65.0 [56.5, 72.9] | 156/154 |
| **Genbody IgG***  | 58.5 [45.6, 70.6] | 100 [96.0, 100] | 100 [90.8, 100] | 77.1 [68.5, 84.4] | 156/154 |
| **Genbody IgM or IgG***  | **58.5 [45.6, 70.6]** | **100 [96.0, 100]** | **100 [90.8, 100]** | **77.1 [68.5, 84.4]** | 156/154 |
| **Innovita IgM***  | 43.1 [30.9, 56.0] | 100 [96.1, 100] | 100 [87.7, 100] | 71.3 [62.7, 78.9] | 157/155 |

| | | | | | |
|---|---|---|---|---|---|
| **Innovita IgG*** | 52.3 [39.5, 64.9] | 100 [96.1, 100] | 100 [89.7, 100] | 74.8 [66.2, 82.2] | 157/155 |
| **Innovita IgM or IgG*** | **56.9 [44.0, 69.2]** | **100 [96.1, 100]** | **100 [90.5, 100]** | **76.7 [6801, 83.9]** | 157/155 |
| **Wantai Test Result** | **84.2 [68.8, 94.0]** | **98.0 [93.0, 99.8]** | **94.1 [80.3, 99.3]** | **94.2 [87.9, 97.9]** | 138/138 |

\* Not all serum able to be tested in duplicate

## 3.2   Comparison of Specimen Type for PoCT

A subset of 20 serum and plasma samples, collected simultaneously from participants, were tested in the Genbody COVID-19 IgM/IgG, the Innovita 2019-nCoV Ab Test, and the Wantai SARS-CoV-2 Ab Rapid Test. Concordance between serum and plasma samples ranged from 80 - 100% (95% CI: 56.1-100%), (Table 10).

**Table 10: Comparison of positive results for 20 patients with RT-PCR confirmed COVID-19 infection for serum and plasma sample types**

| Sample Type<br>**Test Assay** | Positive Serum Samples (%) [95% CI] | Positive Plasma Samples (%) [95% CI] | Concordance (%) [95% CI] |
|---|---|---|---|
| **Genbody IgM** | 6 (30.0) [11.9, 54.3] | 6 (30.0) [11.9, 54.3] | 100% [83.2, 100] |
| **Genbody IgG** | 13 (65.0) [40.8, 84.6] | 10 (50.0) [27.2, 72.8] | 85% [62.1, 96.8] |
| **Innovita IgM*** | 11 (55.0) [31.5, 76.9] | 10 (50.0) [27.2, 72.8] | 95% [75.1, 99.9] |
| **Innovita IgG*** | 11 (55.0) [31.5, 76.9] | 11 (55.0) [31.5, 76.9] | 90% [68.3, 98.8] |
| **Wantai#** | 13 (65.0) [40.8, 84.6] | 15 (75.0) [50.9, 91.3] | 80% [56.3, 94.3] |

\* Assessed for lot 20200402; # Assessed for lot JNB20200301

## 4. Discussion

Here, we present results of our post-market validation of the Genbody COVID-19 IgM/IgG, Innovita 2019-nCoV Ab Test, and the Wantai SARS-CoV-2 Ab Rapid Test. Our findings were

that all tests did not meet their stated performance characteristics with respect to sensitivity, but were within the stated IFU range for specificity.

The sensitivity for the Genbody COVID-19 IgM/IgG and the Innovita 2019-nCoV Ab Test in particular were found to be low, even for specimens collected more than 14 days following symptom onset. Direct comparison with the manufacturers IFU is limited as information regarding the patient / sample cohort used for validation is not provided in the IFUs. Although a standardised testing method and testing panel were used for this validation, the relatively poor performance compared to previously evaluated kits is of note and should be monitored in ongoing post-market surveillance.  Importantly, the sensitivity and specificity of serological assays may differ across studies due to differences in the sample cohorts; it is likely that the amount and timing of the antibody response may differ according to factors such as patient age, time-course of disease and clinical severity of illness.

In summary, our data describe the performance characteristics of three further PoCT devices. Despite consistency in the serum panel and testing protocol, we believe the lower sensitivity of the Genbody COVID-19 IgM/IgG and the Innovita 2019-nCoV Ab Test in particular, which are out of keeping with previous evaluations, warrant further investigation.

## 5.  Acknowledgements

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