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Evolution of COVID-19 testing criteria and methods in New South Wales

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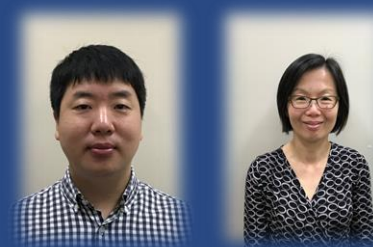
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COVID-19 testing criteria

In January 2020, a novel beta-coronavirus, named Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2), was recognised as the etiologic agent of a cluster of pneumonia cases occurring in Wuhan City, Hubei Province, China since early December 2019. The testing criteria for detecting SARS-CoV-2 (the virus that causes COVID-19) as outlined in the Series of National Guidelines (SoNG) developed by the Communicable Diseases Network Australia (CDNA), has undergone significant changes and modifications since it was first published as the pandemic unfolded [1].

In New South Wales (NSW), recommendations guiding SARS-CoV-2 testing have been widely promoted by NSW Health since 20th January 2020 [2]. During the initial stages, there were approximately 300 confirmed cases (largely confined to Wuhan City), although this most likely under-represented the true number of infections. The criteria for testing persons with suspected COVID-19 were therefore restricted to (i) history of travel from Wuhan City, China in the 14 days before illness onset or close contact with a confirmed case of COVID-19, and (ii) fever or history of fever with symptoms of acute respiratory infection involving at least one of shortness of breath, cough or sore throat.

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With increasing activity of COVID-19 within China, travel restrictions for visitors from China were announced by the Australian Government on the 1st of February. By 4th February, the clinical criteria in the SoNG were broadened to capture either fever or acute respiratory infection symptoms. The geographical area of travel rapidly expanded with the worldwide spread of SARS-CoV-2 – initially Hubei Province was included (rather than Wuhan City alone) followed by the whole of China. By mid-February, testing was recommended for symptomatic people returning from the following Asian countries: Thailand, Hong Kong, Japan, Singapore and Indonesia. This recommendation was based on the growing number of cases outside China (including those linked to the Diamond Princess cruise ship) and the high travel volumes between these countries with Australia and China [3]. By the end of February; Iran, South Korea, Italy, and Cambodia were added to the list due to increased number of cases, and by mid-March, investigation of symptomatic individuals extended to all overseas travellers.

With the onset of locally transmitted cases, the testing criteria expanded further to include those without a travel history. Notably, testing was extended to healthcare workers and hospital in-patients with COVID-19-like presentations from early March. Initially, these presentations were restricted to moderate to severe pneumonia, but later included fever or symptoms consistent with an acute respiratory infection. The testing criteria has now expanded to include symptomatic people in high-risk settings (aged care, boarding schools, correctional/detention facilities as well as Aboriginal rural and remote communities).

In early April, NSW Health broadened the testing criteria again to include symptomatic people in geographical areas with an elevated risk of community transmission, particularly those local government areas (LGAs) with locally acquired cases and clusters. By mid-April, these included LGAs within metropolitan Sydney and regional NSW (Blacktown, Cumberland, Inner West, Liverpool, Penrith, Ryde, Waverley, Woollahra, Randwick, Bryon Shire, Greater Taree and Lake Macquarie).

Laboratory testing for SARS-CoV-2

The ability to accurately identify persons with SARS-CoV-2 infection underpins the national strategy for managing COVID-19. As of 1st April 2020, Australia had the highest rate of diagnostic pathology testing for SARS-CoV-2 in the world (per 100,000 population) [4]. Apart from identification of individual cases, testing plays a critical role in guiding public health responses to prevent ongoing transmission and ultimately, control of the pandemic. Testing provides the evidence base for understanding the characteristics and epidemiology of an emerging infectious disease previously unknown six months ago.

Currently, there are tests that detect (i) viral nucleic acid, (ii) the virus itself and (iii) host antibody responses following SARS-CoV-2 infection. These tests need to be utilised at the appropriate timepoints to optimise yield, for example testing for antibodies during the acute phase of infection prior to development of host immune responses is not recommended [5].

Currently the mainstay of laboratory diagnosis for acute infection is nucleic acid testing using real time polymerase chain reaction (RT-PCR). Worldwide, there is considerable variation in the gene targets employed for detection of SARS-CoV-2; typically two or more targets from the following: viral envelope (E), RNA dependent RNA polymerase (RdRp), membrane (M), nucleocapsid (N), spike (S), open reading frame (ORF) and non-structural protein helicase (H) (Table 1)[6]. Although SARS-CoV-2 is a RNA virus, phylogenetic analyses of available strains suggest that the mutation rate is lower than human seasonal influenza [7]. The performance of different gene targets may evolve dependent on acquired mutations localised to the target of interest.

The average laboratory turnaround times for RT-PCR is four to six hours following receipt in the testing laboratory. In response to considerable interest and demands for a faster test, the commercial diagnostic sector has developed rapid diagnostic tests (RDT) or point of care tests (POCT). Currently there are two main approaches to RDT/POCT using lateral flow immunoassays for i) the detection of viral antigen in respiratory samples, and ii) detection of human antibodies (IgM and IgG) in blood samples, including finger pricks [8]. Due to the accelerated development of RDT/POCT tests within a few short months, evaluations of these assays for use in Australia remain limited. As of 17th April, 2020, NSW Health Pathology has conducted evaluations of three RDT detecting IgM and IgG antibodies, and have concluded that these tests are not recommended for the diagnosis of acute SARS-CoV-2 infection or for population serosurveys when compared to in-house developed pathogen-specific serology assays [9]. Furthermore, the supply of self-tests for COVID-19 is prohibited under the Therapeutic Goods (Excluded Purposes) Specification 2010 [10].

In conclusion, the testing criteria for COVID-19 in Australia continues to evolve with revisions of case definitions based on updated clinical and epidemiological information. Within NSW, laboratory testing capacity has kept up with increasing demand as the testing criteria has broadened while case numbers continue to grow. There are an increasing number of diagnostic options offered by the commercial sector including RDT/POCT. Prior to adoption, appropriate evaluation of these tests are essential to determine their analytical performance and clinical utility.

Table 1: RT-PCR primer targets

International Reference laboratory	RT-PCR Primer targets
CDC, China	ORF1ab and N
Institut Pasteur, Paris, France	RdRP (IP2 and IP4) Confirmatory assay E gene assay from Charite protocol
CDC, USA	N1 and N2
National Institute of Infectious Diseases, Japan	ORF1a, S
Charité, Germany	RdRP, E, N
Public Health England, UK	RdRP
HKU, Hong Kong SAR	ORF1b-nsp14, N
National Institute of Health, Thailand	N

References

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<https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-novel-coronavirus.htm>
- 2) NSW Health. Novel Coronavirus 2019 (2019-nCoV). Identification and initial management of cases (20th January 2020).
<https://www.health.nsw.gov.au/Infectious/diseases/Documents/novel-coronavirus-interim-clinical-guideline.pdf>
- 3) COVID-19 case definition and testing advice. NSW Health (15th April 2020).
<https://www.health.nsw.gov.au/Infectious/diseases/Pages/2019-ncov-case-definition.aspx>
- 4) RCPA Media release. Australia delivering highest rates of Covid-19 testing in the world (1st April 2020).
<https://www.rcpa.edu.au/getattachment/d2923020-f2b9-41ec-92a0-42957ee715dd/Australia-has-highest-levels-of-testing-in-the-world.aspx>
- 5) RCPA Position Statement. Subject: COVID19 IgG/IgM RAPID POCT TESTS (March 2020).
<https://www.rcpa.edu.au/getattachment/bf9c7996-6467-44e6-81f2-e2e0cd71a4c7/COVID19-IgG-IgM-RAPID-POCT-TESTS.aspx>
- 6) WHO. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. Interim guidance (19th March 2020).
<https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117>
- 7) Wang, C, Liu, Z, Chen, Z, et al. The establishment of reference sequence for SARS-CoV-2 and variation analysis. J Med Virol. 2020; 1–8.
<https://doi.org/10.1002/jmv.25762>
- 8) World Health Organisation (WHO). Advice on the use of point-of-care immunodiagnostic tests for COVID-19 (8th April 2020).
<https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19>
- 9) NSW Health Pathology position statement. Rapid antibody COVID-19 test kits (16th April 2020).
<http://internal.health.nsw.gov.au/communications/covid-19/rapid-antibody-test-kit.html>
- 10) Therapeutic Goods Administration. Legal supply of COVID-19 test kits (30th March 2020).
<https://www.tga.gov.au/legal-supply-covid-19-test-kits>

A POWERFUL DUO: REVEALING COVID-19 TRANSMISSION BY SARS-CoV-2 GENOME SEQUENCING AND AGENT BASED MODELLING

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Community transmission of new coronavirus SARS-CoV-2 is a primary public health concern that remains difficult to assess. This collaborative multi-method study presents a genomic survey of SARS-CoV-2 in a subpopulation of infected patients during the first ten weeks of COVID-19 activity in Australia. This survey allowed prospective monitoring of local transmission events in the critical time of implementation of national control measures. Virus genomes were sequenced from 209 patients diagnosed with COVID-19 infection between January and March 2020. Only a quarter of cases appeared to be locally acquired and genomic-based estimates of local transmission rates were concordant with predictions from a computational agent-based model. This convergent assessment indicates that genome sequencing of 13% of cases provides key information to inform public health action and has improved our understanding of the COVID-19 evolution from outbreak to epidemic.

Highlights

- This study applied genomic epidemiological methods to investigate a significant proportion of cases diagnosed in New South Wales, Australia, during the early phase of the epidemic, with SARS-CoV-2 genomes sampled from 209 COVID-19 patients diagnosed from January to March 2020
- Genomic analysis enabled delineation of local community-based transmission events from multiple independent introductions of the virus into Australia from overseas areas of ongoing COVID-19 activity
- Genomic epidemiological analyses and agent-based modelling of the first weeks of COVID-19 activity in Australia provided convergent understanding of the development of locally acquired clusters into an epidemic
- Concordant inferences from genomic epidemiology of laboratory confirmed cases and agent-based modelling suggest that both methods can add value to public health surveillance.

URL: doi: <https://doi.org/10.1101/2020.04.19.048751>

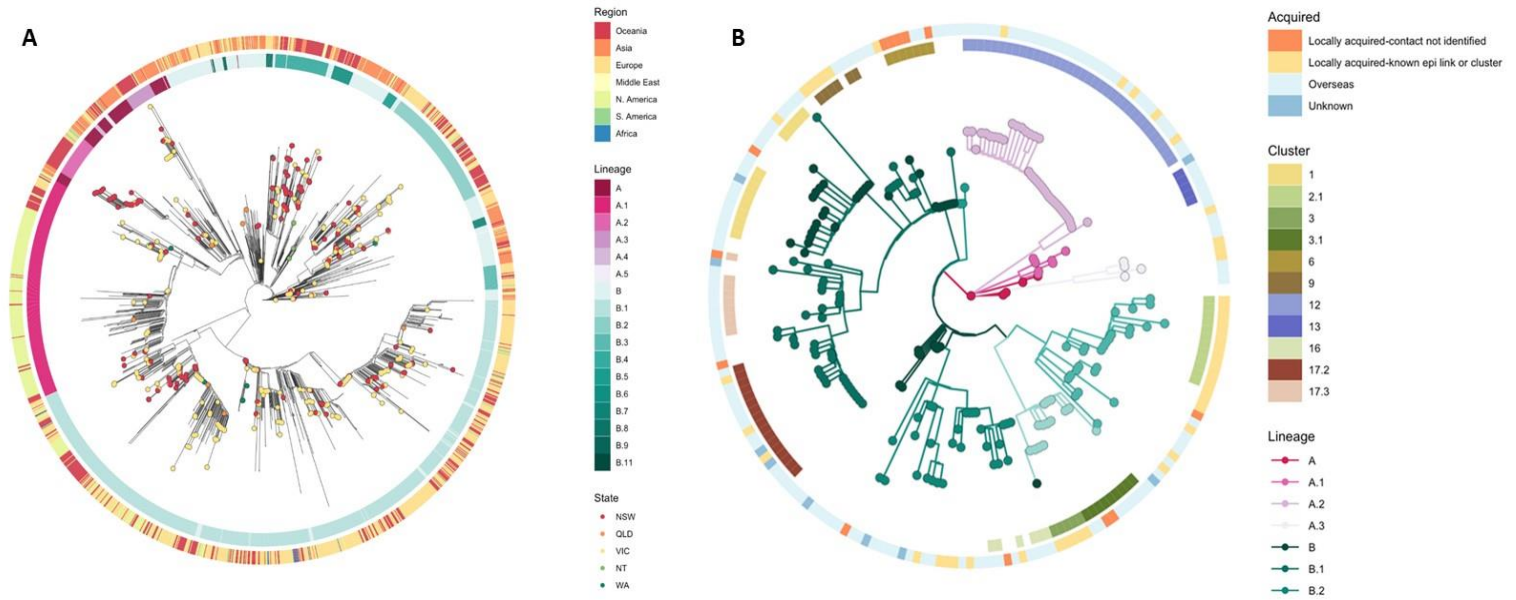
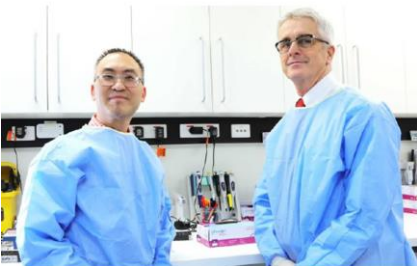


Figure. Phylogenetic analysis of SARS-CoV-2 genomes. (A) SARS-CoV-2 genomes from Australia in the global context provided by GISAID. Australian SARS-CoV-2 genomes are colour coded by the state of the initial diagnosis. The inner ring represents global phylogenetic lineages inferred from the final alignment using pangolin (<https://github.com/hCoV-2019/lineages/>). Outer ring demonstrates the country of origin of GISAID genomes. (B) Phylogenetic relationships between SARS-CoV-2 genomes recovered from patients in NSW. The inner ring represents the allocation of clusters in NSW (only clusters equal or larger than 5 genomes are presented). Outer ring demonstrates the classification of cases as locally or overseas acquired based on genomic and epidemiological data. Bootstrap data for phylogenetic trees is presented in Table S3

CIDM-PH in the spotlight

CIDM-PH senior investigators and researchers are part of the hard working team at Westmead, in the fight against COVID-19.

Professor Dominic Dwyer & Dr Jen Kok



Professor Dominic Dwyer, Director of Public Health NSW Health Pathology, and Dr Jen Kok, Medical Virologist within the Centre for Infectious Diseases and Microbiology, are part of the team of scientists, researchers and pathologists at Westmead who delivered a coronavirus breakthrough by successfully growing the live virus from NSW patients, in hope to better understand the virus, and support the race to develop an effective treatment and vaccine.

Dr Matthew O'Sullivan

Dr Matthew O Sullivan, Senior Staff Specialist within the Centre for Infectious Diseases and Microbiology was part of the Australian Medical Assistance Teams (AUSMAT), responding to the relatively unknown coronavirus threat in January. Dr O'Sullivan was treating four patients with COVID-19 at Westmead Hospital, before he was called upon to manage 278 Australians in quarantine on Christmas Island. Dr O'Sullivan continues to treat COVID-19 patients at Westmead.



Dr Rebecca Rockett



Dr Rebecca Rockett, Postdoctoral Fellow of the Centre for Infectious Diseases – Public Health, explains to reporter Liz Hayes from 60 Minutes how the team at Westmead are working in parallel to the contact tracers at the Ministry of Health, and are using the coronavirus genome to look at how coronavirus is spreading in the population.

Watch the interview:

<https://www.youtube.com/watch?v=mQufJqfbpYI>

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Useful COVID-19 Quick Links....

New South Wales Health:

<https://www.health.nsw.gov.au/Infectious/covid-19/Pages/default.aspx>

Australian Government:

<https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-current-situation-and-case-numbers#in-australia>

World Health Organization (WHO):

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>