

Welcome

The WHO Collaborating Centre for Reference and Research on Influenza welcomes you to the **15**th **Australian Influenza Symposium 2023** at the Doherty Institute for Infection and Immunity, Melbourne, Victoria. We would especially like to thank all of the speakers for agreeing to present their work at the Symposium. Finally, we wish to acknowledge the following:

Symposium Organising Committee:

WHO Collaborating Centre for Reference and Research on Influenza:

- Prof. Ian Barr
- Prof.Kanta Subbarao
- Ms Symone Mercuri









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We are especially thankful for the financial support from:





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Acknowledgement of Country:

In the spirit of reconciliation the WHO Collaborating Centre for Reference and Research on Influenza, VIDRL and the Doherty Institute, acknowledges the Traditional Custodians of country throughout Australia and their connections to land, sea and community. We pay our respect to their Elders past and present and extend that respect to all Aboriginal and Torres Strait Islander peoples today.

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Social Media

- Social media is permitted at AIS
- WHO CC Melbourne's Twitter handle is @WHOFluCCMelb
- AIS event hashtag is #AIS2023Melbourne
- Please do not include any talks/slides speakers specifically request NOT be included in social media

Program Day 1

Thurs	sday, 2 November 2023	
9:00	Meeting opening and logistics: Ian Barr, WHO CC, Dohe	erty Institute, Melbourne, VIC
9:10	Opening remarks	•
Plenar	y Session 1: Chair: Kanta Subbarao, WHO CC,	Doherty Institute, Melbourne,
09:15	Cheryl Cohen NICD, Johannesburg, South Africa	Burden and transmission of Influenza & SARS-CoV-2 in South Africa
09:45	Ben Cowling Hong Kong University, Hong Kong	Repeat vaccination effects for influenza.
10:15	Seema Lakdawala Emory University, Atlanta, USA	Every breath you take: Airborne transmission of influenza viruses
10:45	Morning tea	
Plenar	y Session 2: Chair: Siobhan St George, Dep. of	Health and Aged Care, Canberra
11:15	Kristine Macartney NCIRS, Sydney	Understanding respiratory virus epidemiology and impact in Australia to inform public health responses: Influenza, COVID-19 and RSV
11:35	Andrew Lloyd Kirby Institute, Sydney	Long COVID: old wine in new bottles?
11:55	Alicia Arnott VIDRL, Doherty Institute, Melbourne	The role of public health genomics in surveillance and control of respiratory viruses
12:15	Erik Karlsson Pasteur Institute, Phnom Penh, Cambodia	The Confluence of Poultry Practices and Avian Influenza at the Animal-Human Interface: Insights from Cambodia
12:35	Avram Levy Path West, Perth	Waste-water surveillance for respiratory viruses
13:00	Lunch	
Plena	ry Session 3: Virology Chair: Sophie Valkenbu	rg, Uni. Melbourne, Doherty Institute, Melb.
13:45	Patrick Schaeffer James Cook University, Townsville	Rapid comparison of the analytical sensitivity of COVID-19 RATs in Australia and Canada
14:00	Maryam Shojaei Nepean Hospital, Penrith	Blood transcriptome responses in patients correlate with severity of COVID-19 disease
14:15	Wuji Zhang University of Melbourne, Doherty Institute	Robust and prototypical immune responses towards COVID-19 vaccine in First Nations people are impacted by comorbidities
14:30	Alicia Stein CSL Seqirus, Australia	Superior effectiveness of cell-based versus egg-based quadrivalent influenza vaccines against test-confirmed influenza over three consecutive seasons in the United States
14:45	Zubair Akhtar Kirby Institute, Sydney	Optimal timing of influenza vaccination among patients with Acute Myocardial Infarction
15:00	Joanne Grimsey CSIRO, Australian Centre for Disease Preparedness, East Geelong	Optimisation of antiserum production to highly pathogenic avian influenza viruses at ACDP
15:15	Afternoon tea	
Roun	dtable Discussion Chair: Jodie McVernon, Uni.	
15:45	Michelle Wille University of Melbourne, Doherty Institute, Melbourne	Evolutionary ecology of avian influenza viruses in Australia, and how this may inform our preparation for HPAI
16:05	Eddie Holmes University of Sydney, Sydney, NSW.	Metagenomics at the human-animal interface
16:30	For discussion: How can a One Health approach help us to be better prepared for, or ideally prevent the next pandemic?	Panel members: Kanta Subbarao, Eddie Holmes, Michelle Wille, Erik Karlsson
17:15	Day 1 concludes: Drinks and finger food in foyer	

Program Day 2

Frida	Friday, 3 November 2023		
	ry Session 4: Industry –Commercial & product	updates Chair: Ian Barr, WHO CC, Doherty	
Institu	te, Melbourne		
08:30	Darrin Gilchrist; Biocelect, Sydney	Safety & immunogenicity of COVID-Influenza combination vaccine in adults aged 50-80y in Australia	
08:50	Chris Clarke Moderna, Sydney	Targeting Respiratory viruses using mRNA vaccine technology	
09:10	James Baber r Pfizer, Sydney	Safety and Efficacy of a Respiratory Syncytial Virus bivalent stabilized prefusion F subunit vaccine (RSVpreF) in Maternal and Older Adult Populations.	
09:30	Frank DeRosa mRNA Center of Excellence, Sanofi, France	Elderly RSV vaccines	
09:50	Jules Bayliss CSL Seqirus Ltd, Melbourne	Self-amplifying mRNA vaccines: a second-generation approach	
10:15	Morning tea		
Plenar	y Session 5: Chair: Annette Fox, WHO CC for In	fluenza, VIDRL, Doherty Institute, Melbourne.	
10:45	Yoshi Kawaoka, University of Wisconsin, Madison, USA and University of Tokyo, Japan	SARS-CoV-2: What we have learned so far?	
11:35	Seema Lakdawala Emory University, Atlanta, USA	Uncovering influenza viral RNA assembly networks	
12:00	Stephanie Gras Latrobe Uni, Melbourne	How some of us dodge COVID: genetic association and mechanism of asymptomatic profile of COVID-19	
12:30	Lunch		
Plena	ry Session 6: Epidemiology Chair: Sheena Su	llivan, WHO CC for Influenza, VIDRL, Doherty	
Institu	te, Melbourne.		
13:15	Siobhan St George and Anna Rafferty Australian Govt Dept of Health and Aged Care	The Winter Trifecta: Activity, Distribution and Severity of Influenza, RSV, and COVID-19 in Australia in 2023	
13:30	Anne Maree Baldwin Sunshine Coast Hospital and Health Service	COVID-19 epidemiology across four waves in Sunshine Coast-Gympie residential aged care	
13:45	Lauren Bloomfield WA Department of Health, Perth	Population data linkage for rapid seasonal influenza vaccine effectiveness estimates, Western Australia	
14:00	George Milne Marshall Centre for Infectious Disease Research, Perth	Individual-based, age-specific modelling estimates significant indirect protection among the very young and elderly achieved by increasing influenza vaccination rates in children and adolescents	
14:15	Oliver Eales Melbourne School of Population and Global Health, The University of Melbourne	A mathematical modelling framework to simulate the short- and long-term dynamics of influenza A H3N2	
14:30	William W. Davis Influenza Division, U.S. CDC, Atlanta	Determining associations between nonpharmaceutical interventions and influenza circulation: one approach	
14:45	Sandra Carlson Hunter New England Local Health District	FluTracking Australia's contribution to the COVID-19 Pandemic	
15:00	15:00 Afternoon tea		
RSV S	ession Chair: Nigel Crawford, MCRI/-RCH, Pa	rkville	
15:30	Cheryl Cohen NICD, Johannesburg, South Africa	RSV burden in South Africa or Africa in general	
15:50	Jane Tuckerman, MCRI, Melbourne	Clinical characteristics, seasonality and burden of RSV infections at The Royal Children's Hospital, Melbourne	
16:10	Chris Atkinson Royal Hobart Hospital, Hobart	Respiratory Syncytial Virus: Defining the Genomic Landscape in Tasmania	
16:30	Closing comments		
16:35	Australian Influenza Symposium concludes		
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Abstracts

Day 1	Plenary Session 1
9:15	Burden and transmission of Influenza and SARS-CoV-2 in South Africa
Speaker	Cheryl Cohen, NICD, Johannesburg, South Africa

Both in-depth cohort studies and population-level serologic analyses can provide important data to understand the role of immunity in shaping the burden of illness and transmission of respiratory viruses. The PHIRST and PHIRST-C intensive cohort studies demonstrated high attack rates of influenza and SARS-CoV-2 in a rural and an urban community in South Africa. The combination of serologic data with PCR follow-up allowed examination of the effects of pre-existing immunity on the duration and intensity of viral shedding and onward transmission to others. This novel platform could also be used to conduct clinical trials aiming to evaluate the effect of new vaccines on shedding and transmission. Population-level serology data, combined with national burden of disease data, showed a shift in the epidemiology of SARS-CoV-2 over the first five waves in South Africa. Over successive waves, infection fatality ratios reduced and the age distribution of cases shifted to be more similar to a typical respiratory pathogen U-shaped distribution. The role of ongoing sousveillance for respiratory pathogens should be more clearly defined, including consideration of a global serum bank.

Day 1	Plenary Session 1
9:45	Repeat vaccination effects for influenza
Speaker	Ben Cowling, School of Public Health, Hong Kong University, Hong Kong

A number of studies have reported that repeated annual vaccination may influence the effectiveness of the influenza vaccination in the current season. I will share some data from randomised trials of repeated influenza vaccinations in Hong Kong, investigating some of the issues surrounding repeat vaccination effects. In our "RETAIN" trial, we randomised older adults 70-79 years of age to receive influenza vaccination either once or twice per year and investigated how the potential levels of protection were affected by strain updates as well as by the frequency of vaccinations. In our "DRIVE" trial, we randomised adults 18-45 years of age to receive various sequences of placebo or influenza vaccination across five years, and preliminary data from the first three years will be presented and discussed. In both studies we see clear attenuation of immune responses in repeat vaccinees starting from the second year, with similar degrees of attenuation subsequently rather than further deteriorations. Stored samples provide a platform for additional analyses of immune focusing, ceiling effects, and other hypotheses underlying observations of repeat vaccination effects.

Day 1	Plenary Session 1
10:15	Every breath you take: Airborne transmission of influenza viruses
Speaker	Seema Lakdawala, Emory University, Atlanta, USA

Influenza viruses transmit through multiple modes including contact (either direct or through a contaminated surface) and inhalation of expelled aerosols. Successful human to human transmission requires an infected donor who expels virus into the environment, a susceptible recipient, and persistence of the expelled virus within the environment. The relative efficiency of each mode can be altered by viral features, environmental parameters, donor and recipient hosts characteristics, and viral persistence. We have experimentally evaluated many of these parameters in a multitude of approaches including animal models, humans, and environmental engineering. Our holistic approach provides a unique perspective on transmission of influenza viruses.

Day 1	Plenary Session 2
11:15	Understanding respiratory virus epidemiology and impact in Australia to inform public health responses: Influenza, COVID-19 and RSV
Speaker	Kristine Macartney NCIRS, Sydney

The emergence of SARS-CoV-2 as a pandemic and changes in the epidemiology of other major seasonal respiratory viruses, such as influenza and RSV, has resulted in the need for very dynamic and detailed assessments of disease interactions and impact at a population level. Understanding respiratory virus epidemiology and disease burden is key to inform public health policy, especially vaccine policy and programs, including cost effectiveness. This talk will provide an overview of changes in respiratory virus epidemiology, as well as knowledge and gaps in understanding of disease outcomes that are needed in Australia to inform vaccine policy and more.

Day 1	Plenary Session 2
11:35	Long COVID: old wine in new bottles?
Speaker	Andrew Lloyd, Viral Immunology Systems Program, Kirby Institute, University of New South Wales

Initial estimates have suggested that as many as 400,000 Australians are suffering with protracted and disabling symptoms after SARS CoV-2 infection, often termed 'Long COVID' (or post-COVID condition [PCC] or post-acute sequelae of COVID-19 [PASC]). This condition has attracted widely divergent social commentary, ad hoc approaches to clinical care, substantive research funding commitments, and over 10,000 peer reviewed publications in the last 3 years.

Research into new conditions such as Long COVID requires a case definition with carefully formulated inclusion and exclusion criteria to allow reliable designation of the prevalence and burden of disease, as well as to underpin pathophysiological research and intervention studies. Early in the pandemic numerous studies simply asked subjects to record a checklist of symptoms, many of which are otherwise prevalent in primary care and hence should be regarded as entirely non-specific. This open-ended approach gave rise to 12-month prevalence estimates as high as 81% in a cohort of patients originally hospitalised with acute COVID.

The most widely utilised case definition of Long COVID was formulated by investigators from the World Health Organisation (WHO) using Delphi methodology and identified fatigue, shortness of breath, cognitive dysfunction as the key symptoms. Importantly however, the WHO definition was intended for clinical purposes (rather than research) and contained several areas of ambiguity, such as allowing onset of symptoms following initial recovery (making the link to SARS CoV-2 infection uncertain), including symptoms with no functional impact (making their clinical significance uncertain), and an open-ended approach to seeking out alternative medical and psychiatric conditions which may explain the ongoing symptoms. Nevertheless, with the application of this case definition and inclusion of relevant infective and non-infective control cohorts, the 3-6-month prevalence estimates are now closer to 10% above that in the control cohorts. These cardinal symptoms, and this case rate, are both closely concordant with post-viral fatigue syndromes which occur after many other acute infections such as glandular fever caused by Epstein Barr virus infection.

The pathophysiology of Long COVID remains obscure – at least partly reflecting the ambiguities in the case definition. The obvious candidates have been explored, including persistence of the pathogen and aberrant immunopathology, with the alterations generally dissipating in advance of the clinical illness, and hence inadequately explanatory. In addition, investigations of less intuitive candidates including dysautonomia and gut dysbiosis appear to point to consequences or epiphenomena, rather than causative mechanisms. Recent reports suggest virus-induced neuroinflammation and altered neurotransmitter function may be a plausible mechanism.

In the absence of clear pathophysiology, the only evidence-based interventions for Long COVID are prevention by immunisation and rehabilitative treatments including exercise and cognitive behavioural therapy.

The Commonwealth-funded Australian Partnership for Preparedness Research on Infectious Diseases Emergencies (APPRISE) Long COVID Initiative has resolved a stringent working research case definition and is now undertaking a large prospective cohort study (OUTcomes Post-COVID, OUTPOST) based in primary care. It is hoped that this cohort will inform better understanding of the ongoing burden of disease in Australia and provide a platform for both pathophysiology and treatment studies.

Day 1	Plenary Session 2
11:55	The role of public health genomics in surveillance and control of respiratory viruses
Speaker	Alicia Arnott, Victorian Infectious Diseases Reference Laboratory, Parkville, Victoria, Australia Department of Microbiology and Immunology, Doherty Institute, Melbourne, VIC

Prior to 2020, the field of pathogen genomics was emerging and the capacity to perform high throughput whole genome sequencing (WGS) was limited to a handful of sites worldwide. The subsequent COVID-19 pandemic required WGS to be performed at an unprecedented scale to directly inform public health action, highlighting the clear public health utility of genomic data. As a direct result, the field of pathogen genomics is rapidly expanding, with genomic data fast becoming a key tool in the public health toolkit to combat a range of viral pathogens. This talk will focus on how we can apply translational genomics in a public health context for the identification, containment, and surveillance of viral pathogens.

Day 1	Plenary Session 2
12:15	The Confluence of Poultry Practices and Avian Influenza at the Animal- Human Interface: Insights from Cambodia TBC
Speaker	Erik Karlsson, Pasteur Institute, Phnom Penh, Cambodia

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Cambodia is a hotspot for endemic and emerging diseases, including avian influenza. The country has a high dependence on poultry production coupled with widespread formal and informal live bird markets/slaughterhouses, creating a poultry value chain conducive to areas of high spillover risk. Longitudinal surveillance in Cambodian markets and other interfaces has revealed continued presence of A/H5, A/H7, and A/H9, as well as numerous other subtypes. Longitudinal analysis shows peaks of AIV prevalence align with yearly celebrations; periods marked by heightened poultry demand. This association was further confirmed when COVID-19 closed markets and cancelled festivals, significantly reducing avian influenza prevalence. Recently, Cambodia detected A/H9N2 infections in single cases in 2021 and 2022, both close to the Lunar New Year. In 2023, Cambodia has recently faced two sets of human A/H5N1 cases (2 per incident) coinciding with Lunar New Year and Pchum Ben festivals, respectively. While there are has been no evidence of human-to-human transmission, these recurrent spillover events highlight the persistent risk of avian influenza at the animal-human interface in Cambodia. Enhanced surveillance and targeted intervention measures are critical to reduce zoonotic transmission of endemic and emerging avian influenza viruses that circulate in Cambodian poultry populations and markets, especially around cultural festivals with increased poultry consumption. Improved sampling, detection, and sequencing techniques have been critical to facilitate identification of avian influenza hotspots, identifying subtypes, and performing genomic epidemiology for spillover events.

Day 1	Plenary Session 2
12:35	Wastewater surveillance for respiratory viruses
Speaker	Avram Levy, Path West Laboratory Medicine WA

Authors: Avram Levy1,2, Jake Gazeley1, Terence Lee1, Paul Knight3, Daniel Knight1,2, Sandra Sjollema1, Meredith Hodge1,2, Jelena Maticevic3, David Speers1

Affiliations: 1. Department of Microbiology NWC Division, PathWest Laboratory Medicine WA. 2. University of Western Australia. 3. Communicable Disease Control Directorate, WA Health Department.

Wastewater surveillance programs were rapidly implemented in Australia, Europe and North America early in the COVID-19 pandemic, with most Australian jurisdictions establishing programs to detect SARS-CoV-2 in wastewater. Wastewater surveillance for SARS-CoV-2 was remarkably sensitive, cost effective and provided anonymous community-level information with viral load estimates and genomic data including lineage frequencies subsequently reported. Statistically significant correlation with clinical case data was observed, both for viral load estimates and lineage frequencies in wastewater. Public health units found value in the wastewater surveillance results which were included in prevention and control response plans. The introduction of rapid antigen testing, the decrease in availability of PCR testing and the cessation of mandatory reporting galvanised the relevance of wastewater as a surveillance tool which does not rely on health-seeking behaviour.

Once capacity was developed and methods refined for SARS-CoV-2, expansion to other respiratory viruses shed at lower levels became feasible. In Western Australia, the wastewater surveillance program was expanded from June 2023 to incorporate a pilot program for influenza A, influenza B and RSV for the duration of the 2023 season. Good concordance with notification data was observed, with the rise in cases for clinical and wastewater concentrations occurring during the same week or prior to clinical cases. However, the wastewater baselines may be more stable, allowing early identification of the season's commencement.

Wastewater surveillance is increasingly recognised as a powerful tool that complements clinical testing data, together providing a more complete picture whilst remaining cost-effective.

Day 1	Plenary Session 3
13:45	Rapid comparison of the analytical sensitivity of COVID-19 RATs in Australia and Canada
Speaker	Patrick Schaeffer, College of Public Health, Medical and Veterinary Sciences, James Cook University, Douglas, Queensland, Australia

Authors: Patrick Schaeffer1, Casey Toft1, Brad Stocks2

Affiliations: College of Public Health, Medical and Veterinary Sciences, James Cook University, Douglas, Queensland, Australia2.Metrology, National Research Council Canada, Ottawa, Ontario, Canada

Aggressive diagnostic testing remains an indispensable strategy for health and aged care facilities to prevent the transmission of SARS-CoV-2 in vulnerable populations. The preferred diagnostic platform has shifted towards COVID-19 rapid antigen tests (RATs) to identify the most infectious individuals. As such, RATs are being manufactured faster than ever yet lack relevant quantitative analytics required to inform on absolute analytical sensitivity, limiting end-users to accurately compare brands for decision making. To date, more than 1000 different COVID-19 RATs are commercially available in the world, most of which detect the viral nucleocapsid protein (NP).

We have recently developed a fluorescent NP to facilitate analytics and quality control measures for production of SARS-CoV-2 NP reference material and evaluated its practicality with commercially available RATs. Ten commercial COVID-19 RATs readily available in Australia were initially tested and ranked using fluorescent NP as a reference standard (Toft et al. 2023). We found that the analytical sensitivity data of the selected devices did not correlate with the median tissue culture infectious dose (TCID50) assay values reported by manufacturers as recommended by the WHO. Our findings highlighted an urgent need for a reliable and practical reference standard for independent rapid evaluation and benchmarking of the analytical sensitivity of RAT devices.

In 2022, the NRC Canada had developed a SARS-CoV-2 NP reference material (NCAP-1) (Stocks et al. 2022) but had yet to evaluate RATs with it. We decided to join efforts to examine and compare our respective reference materials extending our previous study (Toft et al. 2023) to evaluate and rank all RATs that are readily available in Canada and Australia.

Here, I will present: (1) a comparative evaluation of the analytical sensitivity of 26 RATs with our fluorescent NP produced in a bacterial expression system and NCAP-1 produced in a mammalian expression system; (2) the applicability of an influenza NP reference protein with COVID-19/Influenza A&B combination RATs and highlight differences in their relative sensitivities in terms of absolute concentrations of proteins that are detected; and (3) important logistics and analytics considerations, and highlight the robustness and ease of international shipping of these reference proteins.

Our data highlight the need for and practicality of readily available, reliable analytics that will ensure that manufacturers maintain batch-to-batch quality and accuracy of RATs. They will aid public health and government agencies, as well as health/aged care facilities to reliably benchmark RAT brands now and in the future to select the best device to curb transmission of future SARS-CoV-2 and influenza outbreaks. International public health and government agencies should encourage adoption of these reference proteins to facilitate brand comparison, decision making and approval processes, ultimately ensuring that RAT performance is accurately communicated to healthcare providers and the public.

Day 1	Plenary Session 3
14:00	Blood transcriptome responses in patients correlate with severity of COVID-19 disease
Speaker	Maryam Shojaei; Department of Intensive Care Medicine, Nepean Hospital, Penrith, NSW, Australia, Centre for Immunology and Allergy Research, The Westmead Institute for Medical Research, Westmead, NSW, Australia, Faculty of Medicine and Health, Sydney Medical School Nepean, Nepean Hospital, University of Sydney, Penrith, NSW, Australia

Authors: Maryam Shojaei1,2,3, Ya Wang1,2,3, Klaus Schughart4,5, Ben Tang2 and Anthony McLean1,2

Affiliations: 1Department of Intensive Care Medicine, Nepean Hospital, Penrith, NSW, Australia2Centre for Immunology and Allergy Research, The Westmead Institute for Medical Research, Westmead, NSW, Australia 3Faculty of Medicine and Health, Sydney Medical School Nepean, Nepean Hospital, University of Sydney, Penrith, NSW, Australia 4Department of Microbiology, Immunology and Biochemistry, University of Tennessee Health Science Centre, Memphis, TN, United States 5Institute of Molecular Virology, University of Münster, Münster, Germany

Background Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Infected individuals display a wide spectrum of disease severity, as defined by the World Health Organization (WHO). One of the main factors underlying this heterogeneity is the host immune response, with severe COVID-19 often associated with a hyperinflammatory state.

Aim Our current study aimed to pinpoint the specific genes and pathways underlying differences in the disease spectrum and outcomes observed, through in-depth analyses of whole blood transcriptomics in a large cohort of COVID-19 participants.

Results All WHO severity levels were well represented and mild and severe disease displaying distinct gene expression profiles. WHO severity levels 1-4 were grouped as mild disease, and signatures from these participants were different from those with WHO severity levels 6-9 classified as severe disease. Severity level 5 (moderate cases) presented a unique transitional gene signature between severity levels 2-4 (mild/moderate) and 6-9 (severe) and hence might represent the turning point for better or worse disease outcome. Gene expression changes are very distinct when comparing mild/moderate or severe cases to healthy controls. In particular, we demonstrated the hallmark down-regulation of adaptive immune response pathways and activation of neutrophil pathways in severe compared to mild/moderate cases, as well as activation of blood coagulation pathways.

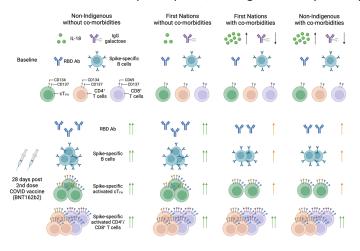
Conclusions Our data revealed discrete gene signatures associated with mild, moderate, and severe biomarker discovery.

Day 1	Plenary Session 3
14:15	Robust and prototypical immune responses towards COVID-19 vaccine in First Nations peoples are impacted by comorbidities
Speaker	Wuji Zhang, University of Melbourne, Doherty Institute

Zhang W1, Kedzierski L1,2, Chua BY1, Mayo M3, Lonzi C3, Rigas V3, Middleton BF3, McQuilten HA1, Rowntree LC1, Allen LF1, Purcell RA1, Tan H-X1, Petersen J4, Chaurasia P4, Mordant F1, Pogorelyy MV5, Minervina AA5, Crawford JC5, Perkins GB6,7, Zhang E8,9, Gras S4,10, Clemens EB1, Juno JA1, Audsley J11, Khoury DS12, Holmes NE13, Thevarajan I11,14, Subbarao K1,15, Krammer F16, Cheng AC17,18, Davenport MP12, Grubor-Bauk B7, Coates PT6,7, Christensen B7,19, Thomas PG5, Wheatley AK1, Kent SJ1,20,21, Rossjohn J4,22, Chung AW1, Boffa J23, Miller A24, Lynar S3,25, Nelson J3, Nguyen THO1*, Davies J3* and Kedzierska K1,26*

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High-risk groups, including Indigenous peoples, are at risk of severe COVID-19. Here we found that Australian First Nations peoples elicit effective immune responses to COVID-19 BNT162b2 vaccination, including neutralizing antibodies, anti-RBD-antibodies, SARS-CoV-2 Spike-specific B cells, CD4⁺ and CD8⁺ T cells measured by activation-induced marker assay, IFN-γ/TNF production and peptide-HLA tetramer staining *ex vivo*. In First Nations participants, RBD IgG antibody titres positively correlated with body mass index, while



negatively correlated with age. Importantly, however, reduced SARS-CoV-2 antibody axis (anti-RBD-antibodies, Spike-specific B cells, T follicular helper cells) was found in vaccinated **Nations** participants with conditions (diabetes, renal disease). This was strongly associated with altered glycosylation and increased IL-18 levels. These immune perturbations were also found in nonpeople with comorbidities, indicating they were related to comorbidities rather than ethnicity. Our findings, however, are highly relevant to First Nations peoples who have disproportionate rates of comorbidities.

Our study provides key insights into immune responses following COVID-19 vaccination in Indigenous peoples and emphasizes the importance of vaccine-induced T cells in individuals with co-morbidities.

Day 1	Plenary Session 3
14:30	Superior effectiveness of cell-based versus egg-based quadrivalent influenza vaccines against test-confirmed influenza over three consecutive seasons in the United States
Speaker	Alicia Stein, CSL Seqirus, Australia

Alicia N. Stein1, Caroline Mills2, Ian McGovern3, Kimberly W. McDermott2, Alex Dean2, Alina Bogdanov2, Sheena G. Sullivan4, Mendel D. M. Haag⁵

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Background: During influenza vaccine production in fertilized hen's eggs, influenza vaccine viruses sometimes acquire egg-adaptive mutations in key viral sites that can result in antigenic mismatch to circulating viruses and may contribute to reduced vaccine effectiveness. Several recently published studies have demonstrated improved effectiveness of cell-based quadrivalent influenza vaccines (QIVc) compared with egg-based quadrivalent influenza vaccines (QIVe) in preventing influenza-related medical encounters in primary care and hospital settings. However, there are limited data using test-confirmed influenza outcomes. The objective of this study was to estimate the relative vaccine effectiveness (rVE) of QIVc versus QIVe in preventing test-confirmed influenza among individuals aged 4-64 years in the outpatient care setting, during the 2017-18, 2018-19, and 2019-20 influenza seasons in the United States.

Methods: The study applied a retrospective test-negative design among individuals aged 4-64 years who were vaccinated against influenza with either QIVc or QIVe and who had an influenza test obtained in routine outpatient care within +/- 7 days of a documented acute respiratory or febrile illness. Exposure, outcome, and covariate data were obtained from patient-level outpatient electronic health records linked to pharmacy and medical claims. Season-specific rVE was estimated by comparing the odds of vaccination with QIVc versus QIVe among influenza test-positive (cases) and influenza test-negative (control) patients. A doubly robust analysis combined inverse probability of treatment weighting (IPTW) with multivariate adjustment by age, sex, geographic region, calendar time and other covariates, including influenza risk factors, that remained unbalanced after IPTW (standardized mean difference > 0.1). Pre-specified sensitivity analyses included additional adjustment for the propensity to be tested, limiting to the peak influenza epidemic period, and matching on the test-week.

Results: The study included 31,824, 33,388 and 34,398 tested patients in the 2017-18, 2018-19 and 2019-20 influenza seasons, respectively, of whom approximately 10% received QIVc and 90% received QIVe. QIVc demonstrated superior effectiveness compared to QIVe in prevention of test-confirmed influenza in the outpatient care setting, with estimated rVEs (95% CI) of 14.8% (7.0 – 22.0) in 2017-18, 12.5% (4.7 – 19.6) in 2018-19 and 10.0% (2.7 – 16.7) in 2019-20. Results of sensitivity analyses were generally consistent with the main analyses.

Conclusions: This study demonstrates consistently superior effectiveness of QIVc compared with QIVe in preventing outpatient test-confirmed influenza over three seasons characterized by different circulating viruses and degrees of egg adaptation. The findings are aligned with previously published QIVc versus QIVe relative effectiveness studies for the same seasons.

Day 1	Plenary Session 3
14:45	Optimal timing of influenza vaccination among patients with Acute Myocardial Infarction
Speaker	Zubair Akhtar, Kirby Institute, Sydney

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Influenza vaccination reduces the risk of adverse cardiovascular events. The IAMI trial randomly assigned 2571 patients with acute myocardial infarction (AMI) to receive influenza vaccine or saline placebo during their index hospital admission. It was conducted at 30 centers in 8 countries from October 1, 2016 to March 1, 2020. In this sub-study, we compare the trial outcomes in patients receiving early season vaccination (n=1188) and late season vaccination (n=1344). The primary endpoint was the composite of all-cause death, myocardial infarction (MI), or stent thrombosis at 12 months. The cumulative incidence of the primary and key secondary endpoints by randomized treatment and early or late vaccination was estimated using the Kaplan-Meier method. In the early vaccinated group, the primary composite endpoint occurred in 36 participants (6.0%) assigned to influenza vaccine and 49 (8.4%) assigned to placebo (HR 0.69; 95% CI 0.45 to 1.07), compared to 31 participants (4.7%) assigned to influenza vaccine and 42 (6.2%) assigned to placebo (HR 0.74; 95% CI 0.47 to 1.18) in the late vaccinated group (P=0.848 for interaction on HR scale at 1 year). We observed similar estimates for the key secondary endpoints of all-cause death and CV death. There was no statistically significant difference in vaccine effectiveness against adverse cardiovascular events by timing of vaccination. The effect of vaccination on all-cause death at one year was more pronounced

in the group receiving early vaccination (HR 0.50; 95% CI, 0.29 to 0.86) compared late vaccination group (HR 0.75; 35% CI, 0.40 to 1.40) but there was no statistically significant difference between these groups (Interaction P=0.335). In conclusion, there is insufficient evidence from the trial to establish whether there is a difference in efficacy between early and late vaccination but regardless of vaccination timing we strongly recommended influenza vaccination in all patients with cardiovascular diseases.

Day 1	Plenary Session 3
15:00	Optimisation of antiserum production to highly pathogenic avian influenza viruses at ACDP
Speaker	Joanne Grimsey, CSIRO, Australian Centre for Disease Preparedness, East Geelong

Joanne Grimsey, Julie Cooke, Michelle Gagliardi, Ebony Grech, Frank Wong, Jeff Butler

CSIRO, Australian Centre for Disease Preparedness (ACDP), East Geelong, Australia

Highly pathogenic avian influenza (HPAI) viruses continue to cause outbreaks across the globe and pose a pandemic threat to animal and human health. Regular domestic and international surveillance of circulating avian influenza (AI) viruses is pivotal for disease preparedness and vaccine selection. ACDP is a World Organisation for Animal Health reference laboratory for Al. In this role, ACDP regularly generates antiserum in both chickens and ferrets against AI viruses (including HPAI strains) so that we have a panel of up-to-date antiserum reagents capable of subtyping and evaluating antigenic drift in emerging and circulating AI strains. For decades ACDP has employed a prime-boost antiserum production method. This involves a prime inoculation with either live virus (ferrets) or inactivated virus (chickens) followed by an antibody titre check around 3 weeks post inoculation. If sufficient antibody titres are reached, a terminal bleed is conducted (to obtain prime antisera). If antibody titres are lower than desired, a 2nd live/inactivated virus inoculation is administered (boost) to increase antibody levels (and hyperimmune antisera is obtained approximately 3 weeks later). For H5 HPAI viruses specifically, we seek to produce maximum volumes of prime antiserum with high virus titres, but this had been difficult to achieve particularly for H5 strains. In a quest to optimise our antiserum production, in particular prime antiserum against H5 HPAI strains we reviewed our antiserum production methods for both ferrets and chickens and made changes to the virus antigen inactivation method, the concentration of antigen inoculated and assessed different adjuvants. We found by administering concentrated virus antigens inactivated by binary ethylenimine (BEI) inactivated antigen, coupled with the most appropriate adjuvant (TiterMax Gold® for ferrets, Montanide ISA VG70, 71 or 78 for chickens) we are now able to consistently produce high titred prime antiserum in both chickens and ferrets, against viruses of multiple subtypes including H5 HPAI. The Montanide adjuvants which we have selected for use in chickens form an oil-in-water emulsion between the adjuvant and the viral inoculum that is purported to induce a strong short-term protective immune response by stimulating both humoral and cell mediated immune systems. These adjuvants trap the antigen in the oil emulsion leading to sustained release of the antigen at the injection site (depot effect). Our early results show that using the mineral oil based Montanide™ ISA range produced higher prime antibody titres (average=489.60) in chickens than the non-mineral adjuvants (average=98.4).

Day 1	Roundtable Discussion
15:45	Evolutionary ecology of avian influenza viruses in Australia, and how this may inform our preparation for HPAI
Speaker	Michelle Wille, University of Melbourne, Doherty Institute, Melbourne

Low pathogenicity avian influenza viruses have co-evolved with wild waterbirds, which include the order Anseriformes (ducks, geese, swans) and Charadriiformes (shorebirds, gulls, terns). These viruses are found in birds globally, including Australia, and cause no clinical disease signs. This is in contrast to high pathogenicity avian influenza, which in the last 2 years has caused >10,000 outbreaks and resulted in the death or destruction of hundreds of millions in poultry, wild birds and mammals. Herein I will discuss the evolutionary ecology of low pathogenicity avian influenza in Australia, and how this may inform our preparation and surveillance approaches for high pathogenicity avian influenza when it should arrive. Furthermore, I will outline the results of ongoing surveillance of arriving migratory birds and results of recent viral incursions into Australia. We are currently in the highest risk period for an incursion of high pathogenicity avian influenza, coinciding with the arrival of millions of migratory birds from Asia, and continued improvements to biosecurity, enhanced surveillance, and other preparation activities should continue to be of high priority.

Day 1	Roundtable Discussion
16:05	Metagenomics at the human-animal interface
Speaker	Eddie Holmes, University of Sydney, Sydney, NSW.

RNA viruses are major components of global ecosystems. Bulk RNA shotgun sequencing — metatranscriptomics — has transformed our understanding of the virosphere, providing a uniquely powerful means to describe the viral composition of any sample, and helping to reveal how viruses move across the human-animal interface and eventually emerge as new infectious diseases. However, the metagenomic identification of RNA viruses has traditionally been limited to those with sequence similarity to known viruses, such that highly divergent viruses that comprise the "dark matter" of the virosphere remain challenging to detect. Herein, I will show how metatranscriptomics, combined with advances in artificial intelligence (AI) technology that can integrate primary sequence and structural information to accurately and efficiently detect viral sequences, is providing new insights into fundamental aspects of virus evolution and emergence. I will also provide a brief update on the latest data on the origins and emergence of SARS-CoV-2.

Day 1	Roundtable discussion
16:30	How can a One Health approach help us to be better prepared for, or ideally prevent the next pandemic?
Panel	Kanta Subbarao
	Eddie Holmes
	Michelle Wille
	Frank Wong
	Erik Karlsson

Day 2	Plenary Session 4
8:30	Safety and immunogenicity of COVID-Influenza Combination (CIC) Vaccine in adults aged 50-80 years in Australia
Speaker	Darrin Gilchrist; Biocelect, Sydney

Authors: Vivek Shinde, Sharon Liu, Susan Neal, Joyce S. Plested, Tim Vincent, Mingzhu Zhu, Shane Cloney-Clark, Bridget Riviers, Farnaz Mahkhou, Darrin Gilchrist, Iksung Cho, Lou Fries, Wayne Woo Affiliation: Novavax, Gaithersburg, Maryland, USA

Background: To anticipate the future need for annual seasonal immunizations against both SARS-CoV-2 and influenza viruses, we developed a COVID-Influenza Combination (CIC) vaccine, comprised of recombinant SARS-CoV-2 Spike(rS), quadrivalent influenza hemagglutinin (HA) protein nanoparticles (qNIV), and Matrix-MTM adjuvant. rS/Matrix-M (NVX-CoV2373) previously demonstrated efficacy against COVID-19, while qNIV/Matrix-M previously demonstrated induction of broadly cross-reactive hemagglutination-inhibiting (HAI) antibodies. In a previous Phase 1/2 trial, CIC formulations were well tolerated and immunogenic, with various dose combinations achieving responses comparable to standalone qNIV and rS vaccines. We report preliminary results of a Phase 2 CIC dose-confirmation trial.

Methods: 1,579 participants (Australia and New Zealand) aged 50-80 years were randomized equally to receive one intramuscular dose of vaccine in 1 of 20 groups: either 1 of 11 different dose/formulations of CIC vaccine (rS doses: 15, 25, or 35ug; HA doses: 30, 45, or 60ug /strain; Matrix-M doses: 50 or 75ug); or 1 of 3 formulations of standalone qNIV with Matrix-M (HA doses: 30ug, 45ug, or 60ug /strain), or 1 of 4 formulations of standalone recombinant spike (rS) with Matrix-M (rS doses: 5 [reference NVX-CoV2373 dose], 15, 25, or 35ug; Matrix-M dose: 50ug), or one of either influenza vaccine comparators Fluzone-HD® of Fluad®. Pre- and post-vaccination immunogenicity assessments (Day 0 and 21) comprised of anti-spike IgG and SARS-CoV-2 neutralizing antibody (vaccine-homologous and heterologous strains) and wild-type influenza HAI antibody responses (vaccine-homologous strains). Reactogenicity was assessed for 7 days following vaccination, and key safety outcomes assessed through Day 21.

Results: All CIC formulations were well tolerated with local and systemic solicited adverse events being mostly mild and moderate and occurring at rates comparable to Fluad and Fluzone HD. SAEs were infrequent in all groups and none were assessed as vaccine-related. Although some interference was evident between rS and HA antigens, several CIC formulations (eg, HA-30ug/rS-25ug/Matrix-75ug; and HA-60ug/rS-35ug/Matrix-75ug) achieved anti-spike IgG and influenza HAI antibody responses which were simultaneously comparable, as determined by the lower limits of the 95% confidence interval above 0.67, to both the reference standalone rS vaccine (NVX-CoV2373) and Fluad/Fluzone-HD, respectively. Table 1 shows Day 21 pairwise baseline-adjusted GM ratios of the best performing CIC formulation (HA-60ug/rS-35ug/Matrix-75ug) versus Fluzone-HD or Fluad for HAI responses; and versus the reference standalone rS5ug (NVX-2373) for anti-spike IgG responses.

Conclusions: CIC formulations had a reactogenicity/safety profile comparable to Fluzone-HD and Fluad, and were immunogenic, with several CIC dose formulations achieving both anti-spike IgG responses comparable to the prototype NVX-CoV2373 authorized rS vaccine, and HAI responses comparable to Fluad and Fluzone-HD.

Table 1. Day 21 GM ratios (95% CI) of CIC [HA-60ug/rS-35ug/Matrix-75ug] versus comparator	A/Wisconsi n (H1N1)	A/Darwin (H3N2)	B/Austria (B-Vic)	B/Phuket (B-Yam)	Wuhan And BA5
GMT (HAI) ratio of CIC versus Fluzone-HD	1.06 (0.85, 1.32)	1.43 (1.07, 1.9)	0.93 (0.76, 1.13)	0.82 (0.69, 0.97)	N/A
GMT (HAI) ratio of CIC versus Fluad	1.08 (0.87, 1.34)	1.18 (0.89, 1.56)	1.09 (0.9, 1.32)	1.11 (0.94, 1.3)	N/A

GMEUR (anti-spike IgG) of CIC versus standalone rS-5ug (reference NVX-2373)	N/A	N/A	N/A	N/A	1.02 (0.86, 1.22) And 1.11 (0.9, 1.36)
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Day 2	Plenary Session 4
8:50	Targeting Respiratory viruses using mRNA vaccine technology
Speaker	Chris Clarke, Moderna, Sydney

The successful development of Moderna's SARS-CoV-2 vaccine, mRNA-1273, validated the tools that have been developed for mRNA vaccine design and the lipid nanoparticle formulation that was selected for delivery of the mRNA to antigen presenting cells. This established mRNA platform technology has not only been used to develop updated SARS-CoV-2 vaccine formulations, but has also been applied to development of vaccines to help prevent disease due to other respiratory viruses e.g. Respiratory Syncytial Virus (mRNA-1345) and Influenza (mRNA-1010). These vaccine candidates have advanced from Phase I through Phase III in less than 4 years. In looking forwards, the flexibility of the mRNA platform is now enabling the clinical evaluation of combination vaccines targeting up to 3 viruses at once. Although some challenges remain, mRNA technology continues to show promise for reducing the burden of respiratory pathogens.

Day 2	Plenary Session 4
9:10	Safety and Efficacy of a Respiratory Syncytial Virus bivalent stabilized prefusion F subunit vaccine (RSVpreF) in Maternal and Older Adult Populations
Speaker	James Baber, Pfizer, Sydney

Authors: James A. Baber, MBChB, MPH¹, Peter Richmond MBBS², Edward E Walsh MD³, David Radley⁴, Qin Jiang⁵, Kena Swanson PhD⁴, Beate Schmoele-Thoma MD⁶, Iona Munjal MD⁴.

Affiliations:Pfizer Australia Pty Ltd, Sydney, NSW, Australia Vaccine Trials Group, Telethon Kids Institute, Nedlands, WA, Australia University of Rochester Medical Center, Rochester, USA Pfizer Inc, Pearl River, NY, USAPfizer Inc, Collegeville, PA, USA Pfizer Pharma GmbH, Berlin, Germany

Background Respiratory syncytial virus (RSV) is associated with significant morbidity and mortality in infants and older adults, especially in those with high-risk conditions. A bivalent (RSV A and B), stabilised RSV prefusion F subunit vaccine (RSVpreF) has been evaluated in two Phase 3 studies in pregnant persons (MATISSE study) and older adults (RENOIR study). In the MATISSE study 7392 maternal participants ≤49 years of age were randomized 1:1 to receive RSVpreF or placebo and assessed for safety, along with safety and efficacy assessments in their infants through up to 24 months after birth. In the RENOIR study 34284 adults 60 years of age and older were randomized 1:1 to receive RSVpreF or placebo and assessed for safety and efficacy through two RSV seasons.

Results In the MATISSE study the primary efficacy objective was met with a Vaccine Efficacy (VE) of 81.8% (99.5% CI: 40.6%, 96.3%) against severe RSV positive lower respiratory tract illness (RSV-sLRTI) in infants within 90 days after birth and was sustained through 180 days with a VE of 69.4% (97.58% CI: 44.3%, 84.1%). Clinically meaningful efficacy against RSV-LRTI was also observed through 180 days. RSVpreF was safe and well tolerated by maternal participants and their infants. In the RENOIR study, VE against RSV-associated LRTI with \geq 2 symptoms at the end of season 1 was 65.1% (95% CI: 35.9%, 82.0%). VE against LRTI-RSV with \geq 3 symptoms was 88.9% (95% CI: 53.6%, 98.7%). Overall, RSVpreF was well-tolerated with no safety concerns in older adults.

Conclusion The MATISSE and RENOIR studies demonstrated that RSVpreF is efficacious in preventing clinically important RSV disease in infants and older adults, with a favourable benefit/risk profile when administered in maternal and older adult populations.

Day 2	Plenary Session 4
9:30	mRNA in Medicine – The development of a next-generation mRNA vaccine platform for respiratory disease
Speaker	Frank DeRosa, mRNA Center of Excellence, Sanofi France

The successful demonstration of mRNA as a modality for vaccines on a global scale for COVID-19 has unlocked the potential of this technology for effective treatments across multiple fronts. The development of new mRNA vaccines for respiratory disease is a key area of focus for Sanofi. We are rapidly developing a next generation mRNA platform to address current hurdles associated with broad implementation of this technology for vaccine applications and beyond.".

Day 2	Plenary Session 4
9:50	Self-amplifying mRNA vaccines: a second-generation approach
Speaker	Jules Bayliss , Steve Rockman , CSL Seqirus Ltd, Melbourne, Australia

In response to the COVID-19 pandemic the world has seen the unprecedented development of mRNA vaccines. While these vaccines were instrumental in reducing the severity of infection and mortality, it was apparent that current mRNA vaccine strategies had several disadvantages. This presentation outlines the development of self-amplifying mRNA (sa-mRNA), a second-generation approach. Utilising a sa-mRNA strategy reduces the initial dose of mRNA, whilst increasing the amount and persistence of expression. Clinical studies of a sa-mRNA expressing SARS-CoV-2 spike protein illustrate the safety, efficacy, breadth and duration of protection. Seasonal and pre-pandemic influenza sa-mRNA strategies are under development and preliminary results will be presented. Next generation sa-mRNA vaccines offer an opportunity to generate broad immunity to multiple viral targets whilst also delivering a safe efficacious vaccine.

Day 2	Plenary Session 5
10:45	SARS-CoV-2: What we have learned so far
Speaker	Yoshi Kawaoka, University of Wisconsin, Madison, USA and University of Tokyo, Japan

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for COVID-19, continues to spread around the world and has caused millions of deaths to date. In an effort to develop therapeutics and preventive measures, we are performing numerous research projects with this virus and its variants. In this presentation, I will discuss our findings regarding animal models and their value as tools for evaluating countermeasures against SARS-CoV-2.

Day 2	Plenary Session 5
11:30	Uncovering influenza viral RNA assembly networks
Speaker	Seema Lakdawala, Emory University, Atlanta, USA

High population vaccine coverage to protect against influenza and SARS-CoV-2 are key to ensuring disease control. While it is known that coverage varies by individual characteristics and in different sub-populations, there is limited information on uptake, particularly in migrants and culturally and linguistically diverse adult groups.

Internationally, Australia has a high proportion of migrants from diverse cultural backgrounds with census data showing that close to a third of the population are migrants. Therefore, understanding and addressing disparities in vaccine uptake in culturally and linguistically diverse groups is important for the success of our vaccine programs.

This presentation will outline research related to influenza vaccine uptake in migrant and culturally and linguistically diverse adults in Australia and suggest some areas for future research and action.

Day 2	Plenary Session 5
11:50	How some of us dodge COVID: genetic association and mechanism of asymptomatic profile of COVID-19
Speaker	Stephanie Gras – Department of Biochemistry and Chemistry, La Trobe Institute for Molecular Science, La Trobe University, Bundoora, Victoria 3086, Australia.

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Although COVID-19 poses a significant threat to human health, around 20% of individuals infected with SARS-CoV-2 remain asymptomatic. While much attention has been given to identifying factors that contribute to severe COVID-19, studying asymptomatic cases offers a valuable opportunity to explore early disease and immunological features that facilitate rapid viral clearance. Human Leukocyte Antigens (HLA) play a crucial role in the immune response and are associated with disease progression or protection. It has been suggested that certain HLA molecules may lead to a more favorable outcome in viral infections. However, to date, no HLA molecule has been definitively linked to a positive outcome in SARS-CoV-2 infection. Therefore, we sought to explore this question. We conducted a study on 29,947 individuals registered in the National Marrow Donor Program who had high-resolution HLA genotyping data available, as part of the UCSF Citizen Science smartphone-based study aimed at tracking COVID-19 symptoms. Our discovery cohort comprised 1,428 unvaccinated, self-identified subjects who had tested positive for SARS-CoV-2 infection. We tested five

HLA loci (HLA-A, -B, -C, -DRB1, -DQB1) and found a strong association between HLA-B*15:01 and asymptomatic infection. This suggests the potential presence of a pre-existing immune response that would protect HLA-B15+ individuals, given the role of HLA in presenting viral peptides to T cells. We found that a SARS-CoV-2 spike-derived T cell epitope (NQK-Q8) shared high sequence identity with a seasonal coronavirus peptide (NQK-A8). We further demonstrated that the reactive T cells displayed a memory phenotype and were highly polyfunctional, showing cross-reactivity towards both NQK-Q8 and NQK-A8. Our crystal structure analysis of HLA-B15:01-peptide complexes revealed that both peptides could be stabilized and presented by HLA-B15:01. Finally, we showed that the structural similarity of the peptides underpins the T cell cross-reactivity of high-affinity public TCRs, providing the molecular basis for HLA-B*15:01-mediated pre-existing immunity.

Day 2	Plenary Session 6
13:15	The Winter Trifecta: Activity, Distribution and Severity of Influenza, RSV, and COVID-19 in Australia in 2023
Speaker	Siobhan St George and Anna Rafferty, Australian Govt Dept of Health and Aged Care

Siobhan St George1, Anna Rafferty1, Aaliya Ibrahim2, Yasmin Lisson2, Tracy Tsang2

- 1. Communicable Disease Epidemiology and Surveillance Section, Australian Government Department of Health and Aged Care
- 2. COVID-19 Epidemiology and Surveillance Section, Australian Government Department of Health and Aged Care

We present an epidemiological summary of the three nationally notifiable viral respiratory infections (influenza, RSV, and COVID-19) in Australia over the 2023 winter season.

The 2023 influenza season commenced in early May, similar to the 2022 and 2019 seasons, but earlier than previous pre-COVID-19 seasons. Notifications peaked in late June, with 18,160 notifications in epi week 26. Excepting the Northern Territory, the majority of cases at the beginning of the season were influenza A (77% influenza A in April), with a shift to a higher proportion of influenza B cases (especially in children and younger adults) throughout the season (57% influenza B in August). Notification rates were highest in children under 14 years, and particularly in those aged 5-9 years. There was an unusually low notification rate in those aged 65 years and over, likely associated with the ongoing COVID-19 mitigation measures in place to protect this at-risk population group. While there were reports of severe disease, especially in children presenting to hospital with influenza B infections, overall, the case fatality rate in 2023 was notably lower than the 5-year average. Influenza-associated deaths reported to the NNDSS were predominantly in the 65 years and over age group. The vast majority of isolates tested were antigenically similar to the corresponding vaccine components.

RSV notifications have only been reported to the NNDSS by all Australian states and territories since September 2022, so 2023 will be the first complete year of nationally collected data. Notifications of laboratory-confirmed RSV rose steadily from late February, peaking in mid-June with 5,391 notifications in epi week 23, and decreasing steadily since. Notification rates were highest in those aged 0-4 years, followed by those aged 85 years and over. Notification trends in 2023 were notably different between jurisdictions. For example, notifications rose early and remained steady over many months in NSW and QLD, while WA and SA observed a later rise and peak in notifications.

In 2023, the national fifth Omicron wave occurred between March and August. COVID-19 case notifications gradually increased from March and peaked in late May 2023 with approximately 41,000 notifications in epi week 20, followed by a steady decline until mid-July 2023. Since then, notifications have remained relatively stable. There has been an overall decreasing trend in the notification of cases with severe illness (defined as admitted to an intensive care unit or died) since late May 2023, with severe case rates remaining highest in those aged 60 years or older.

Overall, it is estimated the 2023 Winter Season has had a moderate impact on society and health services, with relatively high case numbers but comparatively low severity..

Day 2	Plenary Session6
13:30	COVID-19 epidemiology across four waves in Sunshine Coast-Gympie residential aged care
Speaker	Anne Maree Baldwin, Sunshine Coast Hospital and Health Service

Anne Maree Baldwin^{1,2}, Debbie Neucom¹

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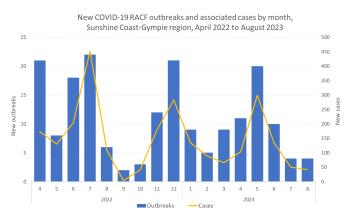
Background: Older people remain at increased risk of severe outcomes from COVID-19 if infected, with residential aged care facility (RACF) environments at increased risk of transmission. With an ageing population and 23% aged 65 years or older, the Sunshine Coast Hospital and Health Service prioritises acute respiratory infection (ARI) primary prevention and appropriate hospital avoidance. While Queensland's *Public Health Act 2005* does not require RACFs to notify ARIs including COVID-19, Sunshine Coast Public Health Unit (PHU) has historically facilitated reporting to enhance opportunities for surveillance and infection control education. During the COVID-19 response, rapid antigen test (RAT) availability and RAT-based national case definitions further facilitated surveillance. This analysis describes the epidemiology of COVID-19 in Sunshine Coast-Gympie region RACF residents since April 2022 including risk factors for hospitalisation and death once diagnosed.

Methods: The PHU supported RACF COVID-19 reporting with data collection processes, Town Halls, and individualised support. Case data was captured in Queensland's notifiable conditions register, via pathology electronic transmission, the state's public RAT-reporting site, and PHU data entry which was complete since April 2022 and included antiviral use, vaccination, hospitalisation and death. Unreported outbreaks were identified via notifications review and published reports. Centralised processes linked notifications with Australian Immunisation Register vaccinations, public hospital admissions and deaths data. Cases were classified in waves as per national reporting. Univariable and multivariable logistic regression for outcomes of hospitalisation and death occurred.

Results: The 52 RACFs had 185 outbreaks with 2,496 case notifications (61% female; median age: 86 years) representing one in two residential places and 153 reinfections. Each wave had 17% (Wave 3) to 28% (Wave 4) of cases. New outbreaks peaked in April, July and December 2022, and May 2023 (20-22 / month) (Figure). Median vaccinations at notification was 3 doses. Antiviral use was reported for 32% of cases, and 47% in Wave 5. Hospitalisation occurred for 6% of cases (from 4% in Wave 2 to 9% in Wave 5). Death was identified for 4% of cases. Once diagnosed, male sex and Wave 5 (c.f. Wave 2) were independently associated with hospitalisation, and male sex and age with death.

Conclusions: This analysis may be unique given the likely highly complete case ascertainment with vaccination, antiviral, and outcomes across four COVID-19 waves in a sizeable RACF population of Australia. The increased risk of severe outcomes with male sex and increasing age corroborates previous findings. The apparent association between increased hospitalisation and Wave 5 may reflect changes in data linkage approach over time and warrants further investigation, given recent variants are not linked to increased severity. The absence of association between antiviral use or vaccine doses and severe outcomes also

warrants further investigation.



Day 2	Plenary Session 6
13:45	Population Data Linkage for rapid seasonal influenza vaccine effectiveness estimates, Western Australia
Speaker	Lauren Bloomfield, WA Department of Health, Perth

Lauren Bloomfield1,2, Sera Ngeh1, Paul Effler1

Communicable Disease Control Directorate, WA Department of Health, Perth, Western AustraliaSchool of Medicine, The University of Notre Dame Australia, Fremantle, Western Australia

In 2021, WA Health developed a comprehensive vaccine data linkage system, which routinely links the Australian Immunisation Register (AIR) to a number of other data collections, including pathology and hospitalisation.1 In 2022, WA Health used this system for the assessment of COVID vaccine effectiveness (VE).2

In 2023, an application has been made to expand this system to include other vaccine preventable diseases. Positive and negative influenza pathology results are now sent weekly from the state pathology laboratory (PathWest), to facilitate mid-season and end-of-season influenza VE estimates using a matched, test-negative design. Briefly, cases and non-cases were linked to the AIR to ascertain vaccination status, and subsequently matched 1:1 on age group, sex, week of test, Aboriginal status and COVID vaccination in the last 6 months. Conditional logistic regression was used to calculate odds ratios (OR), with VE calculated as 1-OR.

There are limitations with using secondary data collected from a single laboratory which will be explored in this presentation, as controlling for potential biases are critical when using population data for VE estimates. This system did, however, allow mid-season estimates to be produced by June 2023. At the end of season, 7,908 positive and negative tests have been included in the matched analysis. End of season results will be presented.

In summary, the linking of immunisation and pathology data has allowed WA Health to produce rapid midseason and end-of-season influenza VE estimates; the former can potentially be used to inform the public about the effectiveness of vaccines during the season, encouraging uptake in groups for whom the vaccine is demonstrating high effectiveness.

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Day 2	Plenary Session 6
14:00	Individual-based, age-specific modelling estimates significant indirect protection among the very young and elderly achieved by increasing influenza vaccination rates in children and adolescents
Speaker	George Milne, Marshall Centre for Infectious Disease Research, Perth

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Influenza causes an ongoing worldwide health burden, with the elderly and other at-risk cohorts prioritised for vaccination. Middle/high-income countries have historically low influenza vaccination rates in schoolage children, an age-group implicated in virus transmission. This study, conducted for the Australian Government, evaluated increasing vaccination rates among a range of target groups to determine those most effective in reducing infections, hospitalisations and deaths.

Methods: Age-specific, individual-based models (c.f. agent-based) for representative Australian population centres were developed using census, workplace and education data sources, capturing household, school and workplace structure, and daily contact and mobility patterns between these contact locales. The models were applied to quantify reduction in infections resulting from increasing vaccination rates to specific cohorts. An associated study collected Australian influenza vaccination and health burden data, providing the relationship between influenza infections and resulting hospitalisations and deaths, giving a baseline from which to compare and quantify age-specific reductions in the health burden resulting from increased vaccination strategies.

Results: Of over 60 increased vaccination strategies considered, the most effective in reducing the health burden per 100,000 additional vaccinations was targeting increases in vaccination to the 5-17-year cohort, Figure 1. Increasing coverage from 7.8% to 20% is estimated to reduce hospitalisations and deaths by 34.2% and 33.7% respectively, prevent 298 hospitalisations in infants (0-4 years) and 1,967 in elderly for Australian population of 24.7 million. Figure 1 illustrates the significant pro-rata reduction in hospitalisations among the very young and substantial indirect protection from hospitalisations and deaths among the elderly which may be achieved. 40% coverage provides further increases in indirect protection, reducing elderly deaths by ~60%. By contrast, the study found that increasing vaccination rates uniformly across all age groups from current age-specific rates was much less effective, requiring significantly more vaccine doses to achieve similar health burden reductions\

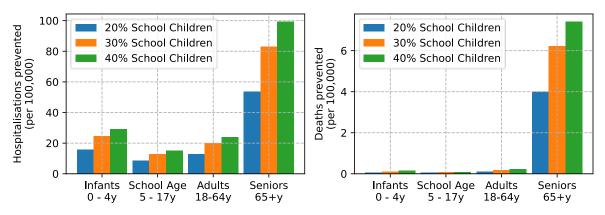


Figure 1: Estimated hospitalisations (left side) and deaths (right side) prevented per 100,000 individuals in each age group resulting from increased influenza vaccinations in school-age children and adolescents.

Conclusions: Application of detailed age-specific simulation models allowed estimates of the benefit achieved by encouraging parents of school age children and adolescents to have their children vaccinated to be made,

resulting in reduction in the influenza health burden among other age groups, particularly the very young and elderly. These results have informed changes to Western Australia's children/adolescent influenza vaccination policy, yet vaccination in this age cohort remains stubbornly low. The indirect protection afforded by this school-age targeted vaccination strategy suggests its cost-effectiveness, particularly if vaccinations were conducted within school settings.

Day 2	Plenary Session 6
14:15	A mathematical modelling framework to simulate the short- and long- term dynamics of influenza A H3N2
Speaker	Oliver Eales Melbourne School of Population and Global Health, The University of Melbourne

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Since its emergence in 1968, influenza A H3N2 has caused yearly epidemics in temperate regions. While infection with a strain of influenza confers immunity against antigenically similar strains, new antigenically distinct strains regularly emerge that are able to evade existing immunity ('antigenic drift'). Immunity at the individual level is complex, depending on both an individual's entire infection history and the time since last exposure. Furthermore, it includes short- and long-term components. An individual's first infection with influenza typically elicits the greatest response with subsequent infections eliciting progressively reduced responses ('antigenic seniority').

We developed an integrated modelling framework by drawing on previous studies of individual-level immune dynamics and global patterns of antigenic drift. A multi-strain agent-based model simulated yearly epidemic dynamics, while a statistical model simulated the antigenic drift between epidemic years. Individual infection and vaccination histories were tracked and used to calculate the probability of infection given contact with an infectious individual. We simulated 160 years of influenza transmission following introduction into an immunologically naive population and investigated the individual-level effects of vaccination.

The attack rate was highest in the pandemic year, followed by an initial decline. In the following 80 years the average annual attack rate increased by almost 20%, before reaching an equilibrium, with greater increases in older age-groups. This increase was due to antigenic seniority, which reduced population-level immunity due to repeated individual-level exposures. Vaccination reduced the expected number of infections an individual would experience in the same flu season, with vaccination effectiveness varying based on age, exposure history, and antigenic mismatch of the vaccine strain. In the following flu seasons, previously vaccinated individuals continued to have a lower expected number of infections than those not vaccinated. However, due to the short-term reduction in infections, strains emerging approximately 10 years after infection were expected to cause a relatively greater number of infections in those previously vaccinated. The timing and magnitude of these effects were sensitive to the parameters describing the immune response due to vaccination relative to the immune response due to infection.

Our analyses suggest that the average attack rate of H3N2 is still in a growth phase. Further increases, particularly in the elderly, may be expected in coming decades, driving an increase in healthcare demand due to H3N2 infections. Vaccination remains paramount in reducing the healthcare burden of influenza, but our analysis suggests there may be nuances to optimising individual- and population-level benefits, which we will seek to explore in further work. Further studies exploring how vaccination and infection histories impact individual-level susceptibility can help us refine our model.

Day 2	Plenary Session 6
14:30	Determining associations between nonpharmaceutical interventions and influenza circulation: one approach
Speaker	William W. Davis, Influenza Division, U.S. CDC, Atlanta

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Circulation of influenza decreased dramatically during the SARS CoV-2 pandemic. Multiple studies documented associations between implementation of nonpharmaceutical interventions (NPIs) for SARS CoV-2 and reduction of influenza circulation, although few identified associations with individual NPIs. We explored associations between individual NPIs and influenza circulation in two studies, one with data from 9 Asian countries and one with data from 13 African countries. Using World Health Organization (WHO) surveillance data from 2015 to 2019 and the WHO shiny app, we constructed expected seasonal influenza epidemic curves from March 2020 to June 2021 and compared the timing, and average percent positivity with observed data. We used data form the Oxford University COVID-19 Response tracker, which measured levels of implementation of these NPIs: school closures, workplace closures, canceling public events, restrictions on gatherings, closing public transportation, stay-at-home requirements, restrictions on internal movement, international travel controls, public information campaigns, and mask mandates. We used multivariate regression to test associations between ordinal NPI data from 4 weeks before the expected 2020/21 epidemics and present adjusted incidence rate ratio (IRR) or relative proportion ratio (RPR) and 95% confidence intervals (CI).

In both studies fewer seasonal epidemic curves were observed than predicted; in the Asia dataset, data from nine countries predicted 18 seasonal epidemics; seven were observed. Five started 6–24 weeks later, and all were 4–21 weeks shorter than expected. Five epidemics had lower maximum peak values (percent positivity), and all but one had lower average percent positivity than expected. All countries implemented NPIs. Each increased level of school closure reduced risk of an epidemic by 43% (IRR = 0.57, CI: 0.34, 0.95). Each increased level of canceling public events reduced the average percent positivity across the season by 44% (RPR = 0.56, CI: 0.39, 0.82) and each increased level in restricting internal movements reduced it by 41% (RPR = 0.59, CI: 0.36, 0.96). Other NPIs were not associated with changes. In African countries, of 48 expected seasonal influenza epidemics, only 26 occurred in 12 countries. Season length was on average x weeks shorter for 17/26 (65%) epidemics. We found that for each step increase in school closings, the average percentage of respiratory specimens testing positive for influenza across the influenza season dropped by 20% (RPR= 0.80; 95% CI: 0.64%-0.99%); no other NPI was significant. In both studies correlation matrices indicated that no two NPI variables were highly correlated (correlation $\geq \pm 0.8$).

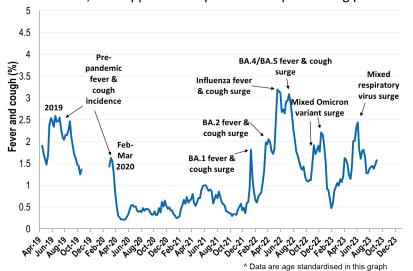
This was an early effort to identify associations between individual NPIs and influenza circulation, and there are many limitations to the approach. This talk focuses on the approach, limitations, and interpretation of the results

Day 2	Plenary Session 6		
14:45	FluTracking Australia's contribution to the COVID-19 Pandemic		
Speaker	Sandra Carlson, Hunter New England Local Health District		

Sandra Carlson1, Alexandra Kerr1, Tom McKenzie1, Craig Dalton1,2,3

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Background: FluTracking, an online respiratory surveillance system, tracks over 100,000 participants across Australia, New Zealand, Hong Kong, and Argentina. It includes a weekly 30-second survey on respiratory symptoms, illness severity, healthcare-seeking behaviour, and COVID-19 and influenza vaccination status. We outline FluTracking's contribution to the COVID-19 pandemic in Australia. Community attack rates: After recording historically low fever and cough activity in 2020-2021 due to stringent COVID-19 public health measures, FluTracking later identified peaks in fever and cough activity coinciding with the timing of each Omicron wave and influenza surges from 2021 to 2023. Notably, FluTracking detected a larger peak during the BA.2 wave compared to BA.1. This highlighted that reduced RAT reporting during BA.2 may have led to a lower peak in case counts compared to BA.1. Community fever and cough rates trends were unaffected by these changes. Severity of illness indicators: Severity of illness is based on time off from work or normal duties due to illness and those seeking medical advice for their symptoms on a weekly basis. Weekly illness severity indicators from 2020 to 2022 correlated with Australian Bureau of Statistics mortality rates for influenza and pneumonia with a three week time lead, offering an early warning for potential increases in related deaths when mortality data is delayed. Test-seeking behaviour and percent positivity: The introduction of rapid antigen tests (RATs) in November 2021 and the emergence of the Omicron variant considerably changed testing behaviour. FluTracking captures both weekly self-reported positive and negative SARS-CoV-2 polymerase chain reaction (PCR) and RATs. For fever and cough symptoms the mean weekly self-reported testing rate increased from 53.2% during May 2020 - November 2021 to 86.8% during November 2021 -January 2023, and from 29.0% to 69.9% for sore throat and runny nose (mild symptoms). This highlights that even during the period when Australia estimated case ascertainment was high (2020 to 2021), a considerable portion of the community went untested for symptoms, likely leading to underestimations of COVID-19 cases. Additionally, FluTracking weekly percent positivity calculations emphasised potential underreporting of COVID-19 cases from November 2022 onwards during the Omicron variant wave due to declining testing. FluTracking SARS-CoV-2 percent positivity offered valuable trend insights where laboratory based percent positivity data was limited.Respiratory Virus Swabbing Cohort: Currently, the FluTracking platform and its community cohort are actively engaged in the 'Pandemic Respiratory Virus Surveillance Trial' (PREVENT). In this ongoing trial since 5 June, 2023, 51 participants from Newcastle/Lake Macquarie NSW conduct weekly self-swabs for 16 respiratory viruses for 12 months. The mean swabbing response rate exceeded 90% for the first 14 weeks, with approximately 15% of samples testing positive for respiratory viruses each week, mainly



rhinovirus. The success of this pilot so far is evidence for FluTracking's utility engaging the system and cohort for future community-based studies.

Conclusion: As other enhanced COVID-19 surveillance methods scale back, FluTracking has consistently maintained data collection across various surveillance domains. Its utility is evident in engaging the system and cohort for future community-based studies.

Day 2	RSV Session		
15:30	RSV burden in South Africa or Africa in general		
Speaker	eaker Cheryl Cohen		

There is a high burden of RSV associated hospitalisation in South Africa (hospitalisation rates >400/100,000 population in the first 6 months of life. Importantly, 45% of severe illness is in the first 3 months of life and 65% in the first 6 months. RSV is estimated to cause approximately 592 (412-777) deaths each year among infants aged <1 year in South Africa with 45% of these in the first 3 months of life. Approximately one third of RSV-associated deaths occur out of hospital. This proportion is estimated to be as high as 66% in some African countries. At a price of 3 US dollars per dose, RSV maternal vaccines would be cost-saving for South Africa. The DALY burden is dominated (95%-97%) by RSV-associated deaths. Long acting monoclonal antibodies could also be cost saving at a price of 6 US dollars per dose. The Pfizer bivalent pre-fusion F maternal RSV vaccine has been demonstrated efficacious against severe RSV-associated lower respiratory tract infection in the first 180 days after birth. The product has been approved for use in the US and Europe. While not statistically significant, there was an increase in preterm birth rate in vaccinated women observed in the phase 3 clinical trial. This signal was strongest in upper middle income countries including South Africa. South Africa is currently considering whether to include this vaccine in the routine immunization programme.

Day 2	RSV Session
15:50 Clinical characteristics, seasonality and burden of RSV infection Royal Children's Hospital, Melbourne	
Speaker	Jane Tuckerman, MCRI

Background: Respiratory syncytial virus (RSV) infections are a leading cause of hospitalisation in infants, with substantial health system costs and clinical burden.

Method: Two studies will be presented. A surveillance study of children <2 years of age hospitalised with RSV infection includes data from 6 RSV seasons (2017-2022) at the Royal Children's Hospital, Melbourne and will describe the seasonality of RSV infections and clinical characteristics amongst infants hospitalised with RSV infection. The seasonality of RSV-related hospitalization's were compared, and characteristics associated with 'severe' disease, prolonged (>75th percentile) length of hospital stay (LOS) and RSV infection in the pre and pandemic era were explored using univariable and multivariable regression. The second study explores the indirect costs to families from RSV infection, using three parental surveys. Survey items included Quality of Life (QoL) items (EQ-5D and DASS-21), employment and lost days of work, child's health status, household illness and health service use.

Results: The surveillance study included 1,748 children, median (IQR) age 4 (1.5 to 12) months. There was dramatic disruption in the usual seasonality of RSV hospitalisations in the pandemic compared the pre-pandemic period. Across the entire cohort, 28% of children had predisposing RSV risk factors (e.g., prematurity, comorbidities) and 33% were classified as having severe RSV. Children with severe RSV were more likely to be younger, premature (<33 weeks) and have a cardiac condition or infection during the peak months. Preliminary data from the cross-sectional study exploring the indirect costs to families from RSV will be presented.

Conclusions and Relevance: Following a shift in RSV seasonality early in the pandemic, RSV has returned to its usual seasonal mid-winter peak. Characteristics of severe infections, e.g., age, prematurity, comorbidities and viral-viral coinfection, remain similar to pre-pandemic studies.

Day 2	RSV Session			
16:10	Respiratory Syncytial Virus: Defining the Genomic Landscape in Tasmania			
Speaker	Chris Atkinson, Royal Hobart Hospital, Hobart			

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Respiratory syncytial virus (RSV) is among the most important causes of acute respiratory morbidity and hospitalisation, with young infants experiencing the greatest share of the burden. In light of globally observed unusual RSV outbreak activity during the COVID-19 pandemic and the imminent availability of RSV vaccines and new antivirals in Australia, it remains important to monitor and sequence RSV. Recent sequencing efforts have led to the increased publication of Australian RSV sequence data, but there remains a relative lack of data available on Tasmanian RSV strains and it is unclear how Tasmanian strains are phylogenetically related to other Australian strains. In this work, 318 RSV extracts collected through routine testing at the Royal Hobart Hospital covering the period of January 2021 – August 2023 underwent whole genome sequencing and phylogenetic analysis. Metadata of extracted specimens were collected, including patient postcode, date of collection and age. Through the construction of time-scaled phylogenetic trees, we describe the diversity of lineages and transmission dynamics of RSV in Tasmania. Evidence for geographic and epidemiological clustering will be presented, and lineages reported in Tasmania will be compared to national sequences, with a focus on evidence of RSV clade introductions into Tasmania.

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