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PATHOLOGY *focus*

Medical Newsletter

TRIPLEDEMIC: ALONG WITH THE COMMON COLD, SHOULD WE BE CONCERNED?

By Dr Kwee Chin Liew

COVID-19

Coronavirus disease (COVID-19) is an infectious disease caused by the novel SARS-CoV-2 virus that has not demonstrated clear seasonality. The World Health Organization (WHO) declared the outbreak a public health emergency of international concern (PHEIC) on 30 January 2020 and assessed that the outbreak had become a pandemic on 11 March 2020.

The head of the WHO declared “with great hope” an end to COVID-19 as a public health emergency on 5 May 2023. However, they emphasised that it does not mean the disease is no longer a global threat – it was here to stay: “It is still killing, and it is still changing. The risk remains of new variants emerging that cause new rises in cases and deaths.”

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For over 12 months, the pandemic “has been on a downward trend”, with immunity increasing due to highly effective vaccines developed in a timely manner to fight the disease. Death rates have decreased, and the pressure on once overwhelmed health systems has subsided. This trend has allowed most countries, including Australia, to return to life as we knew it before COVID-19. More details on Australia’s COVID-19 spread, vaccination, and treatment metrics are available via the Australian Government’s Department of Health and Aged Care COVID-19 reporting, which was last updated on the 10th of May, 2024.

“The risk remains of new variants emerging that cause new rises in cases and deaths.”

SARS-CoV-2 PCR percent positivity was around 8.0% from 69 countries during the week ending on 31 March 2024, as detected in integrated sentinel surveillance as part of the Global Influenza Surveillance and Response System (GISRS) and reported to FluNet. Globally, JN.1 was the most reported variant of interest (VOI), now reported by 121 countries, accounting for 95.1% of sequences in week 13 compared to 93.0% in week 10. Its parent lineage, BA.2.86, has been declining and accounted for 1.6% of sequences in weeks 13 and 10. The last risk evaluation for JN.1 was published on 9 February 2024, with an overall evaluation of low additional public health risk at the global level based on available evidence.

Influenza

It can be difficult to predict the severity of influenza every winter season. So far, this season seems like the typical flu season that was seen prior to the pandemic. However, even a typical flu season can result in many outpatient healthcare visits, hospitalisations, and even deaths in children.

National Influenza Centres (NICs) and other national influenza laboratories from 139 countries, areas, or territories reported data to FluNet for the period from 4 March 2024 to 17 March 2024* (data as of 15/04/2024 07:53:24 AM UTC). The WHO GISRS laboratories tested more than 558,758 specimens during this period.

Influenza A: 57.84% (37,790 flu A/65,337 total flu)

- Influenza A (H1N1)pdm09: 47.16%
- Influenza A (H3N2): 52.84%

“Influenza A (H3N2) can cause more severe epidemics than other Influenza A and Influenza B viruses.”

Influenza B: 42.16% (27,547 flu B/65,337 total flu)

- B-Yamagata lineage: 0%
- B-Victoria lineage: 100%

Source: Laboratory-confirmed data from the Global Influenza Surveillance and Response System (GISRS).

Influenza A (H3N2) can cause more severe epidemics than other Influenza A and Influenza B viruses.

Respiratory Syncytial Virus (RSV)

RSV is a common cause of respiratory infection, mostly affecting young children. Adults can also become ill from RSV. Symptoms are usually mild; however, some children and adults can become severely ill, requiring hospitalisation for treatment. Some babies and older individuals can receive RSV immunisation or vaccines.

Since 2016, the World Health Organization has included RSV in the Global Influenza Surveillance and Response System (GISRS) platform, with the goal of providing epidemiologic and virologic evidence to inform the introduction of RSV vaccines and monoclonal antibodies.

In Australia, RSV was made notifiable in July 2021 and was formally reported in the notification system in 2022. Generally, RSV circulates during autumn and early winter before influenza. The severity of RSV is comparable to influenza in terms of hospitalisation and mortality. Existing monoclonal antibodies such as Palivizumab and new long-acting monoclonal antibodies such as Nirsevimab are recommended options for RSV prevention in newborns.

“The severity of RSV is comparable to influenza in terms of hospitalisation and mortality.”

The RSV vaccine, Arexvy, is available on the private market in Australia for adults aged ≥60 years to prevent illness and severe complications associated with RSV infection. The Australian Technical Advisory Group on Immunization (ATAGI) have issued a Statement on the clinical use of the Arexvy (RSV PRE-F3) vaccine for respiratory syncytial virus (RSV) in older adults in Australia. The Arexvy RSV vaccine is not currently funded under the National Immunization Program.

Mycoplasma pneumoniae

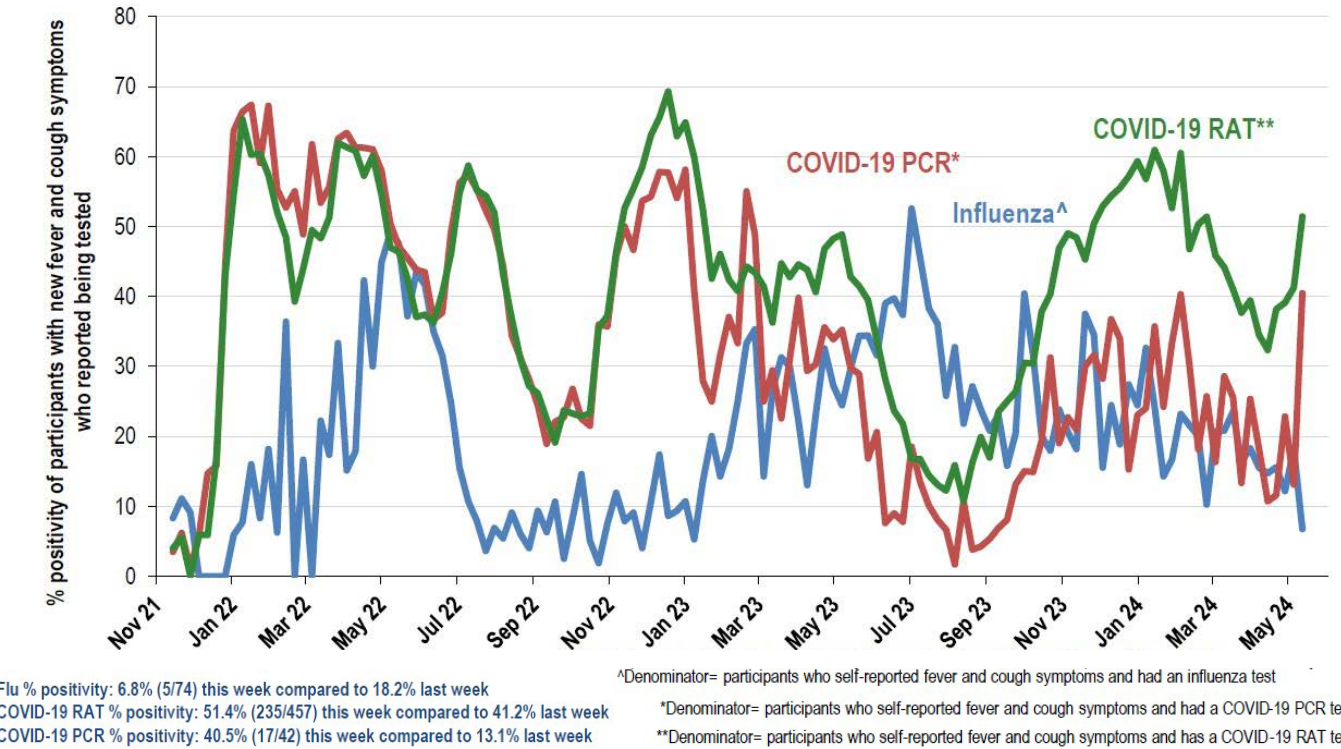
Mycoplasma pneumoniae infection is caused by the bacterium *Mycoplasma pneumoniae*. The number of confirmed cases of *M. pneumoniae* has been increasing, particularly in children and adolescents. An increase in emergency department presentations and hospital admissions has also been reported in Australia and globally. This typically happens every 3-7 years as population immunity wanes.

M. pneumoniae infection usually causes mild, self-resolving respiratory illness; however, in some cases, it can lead to severe pneumonia and rarely, other atypical presentations. People may also appear well, as it is sometimes referred to as “walking pneumonia”. Signs of atypical pneumonia on a chest x-ray may include a bilateral lower lobe reticulonodular pattern or patchy infiltrates. Transmission from person-to-person occurs through respiratory droplets.

Figure 1. Notification for COVID-19, Influenza (laboratory confirmed), and Respiratory Syncytial Virus (RSV) from National Communicable Disease Surveillance Dashboard [Last Refreshed on 15/5/2024 6:30:31 AM]

Year						
DISEASE GROUP	DISEASE NAME	2024 (Notified cases as of 15 May 2024)	2023	2022	2021	2020
Respiratory diseases	COVID-19	130,833	864,460	10,318,196	538,954	29,117
	Influenza (laboratory confirmed)	51,884	288,993	233,448	749	21,350
	Respiratory syncytial virus (RSV)	66,260	128,016	95,973	1,553	8
Total		248,977	1,281,469	10,647,617	541,256	50,475

Figure 2. Fever, cough and reported a positive result for COVID-19 or Influenzae through FluTracking Australia Weekly Report (Reporting week Monday 06 May 2024 - Sunday 12 May 2024) [Data used in this report received up to 09:00 AM, Tuesday 14 May] Source: FluTracking Australia Weekly Report.



Co-infections

Respiratory virus infection is an important cause of morbidity and mortality in humans. With advances in molecular diagnostic assays, multiple respiratory viruses are often detected in clinical specimens from patients with respiratory tract infections. The contribution of respiratory virus co-infection to the pathogenesis and clinical outcome of respiratory tract infections remains unclear for many viruses.

Who is at risk for complications?

- Elderly people
- Children under 6 months old
- Pregnant women, including up to 2 weeks postpartum
- People with chronic conditions or immunosuppression (see Table 1 on the following page)

Why should you test for respiratory viruses?

- Clinical, public health, and infection control impact
 - o Diagnose infections that are treatable early
 - o Reduced unnecessary antibiotic use
 - o Better define epidemiology of some infections (clusters)
 - o Enable more rapid public health notifications
 - o Facilitate early implementation of infection control
- Economic impact
 - o Reduce hospital stays

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Table 1: Medical conditions associated with an increased risk of respiratory virus complications.

Category	Example medical conditions
Cardiac disease	Congenital heart disease, congestive heart failure, coronary artery disease
Chronic respiratory condition	Suppurative lung disease, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, chronic emphysema, severe asthma (requiring frequent medical consultations or the use of multiple medicines)
Immunocompromising condition	HIV infection, malignancy, immunocompromise due to disease or treatment, asplenia or splenic dysfunction, solid organ transplant, haematopoietic stem cell transplant, CAR-T cell therapy
Chronic metabolic disorder	Type 1 or 2 diabetes, amino acid disorders, carbohydrate disorders, cholesterol biosynthesis disorders, fatty acid oxidation defects, mitochondrial disorders, organic acid disorders, urea cycle disorders, vitamin/cofactor disorders, porphyria
Chronic kidney disease Stage 4 or 5	
Chronic neurological condition	Hereditary and degenerative central nervous system diseases, seizure disorders, spinal cord injuries, neuromuscular disorders, conditions that increase respiratory infection risk

Note: These examples are not exhaustive, and providers may include individuals with conditions like those listed above based on clinical judgement. Source: Australian Immunisation Handbook

Respiratory Multiplex PCR testing at Clinical Labs

What to request:	Panels included:
Respiratory Multiplex PCR	<div><div><ul style="list-style-type: none">Influenza AInfluenza BRSV ARSV BParainfluenza 1 & 3</div><div><ul style="list-style-type: none">Parainfluenza 2Human MetapneumovirusHuman AdenovirusHuman EnterovirusHuman Rhinovirus</div><div><ul style="list-style-type: none">Bordetella PertussisBordetella ParapertussisMycoplasma PneumoniaeCOVID-19 / SARS-CoV-2 (M, N Gene)</div></div>

Test ordering:

When ordering the Respiratory Multiplex PCR, you will still receive a COVID test. If you do not want a COVID test included, please specify “No COVID test”. If you only request a COVID-19 PCR, you will only receive a result for COVID-19. Example of options:

- Respiratory Multiplex PCR
- COVID-19 PCR
- Respiratory Multiplex PCR [No COVID test]

Specimens required

- [Preferred] Nose/throat or nasopharyngeal swab(s) in Viral Transport Medium (VTM) collection device (After collection, break off swab tip into the vial of VTM using the molded break point.) or
- Nasopharyngeal/tracheal aspirates or
- Nose/throat/nasopharyngeal dry swabs or
- Sputum

NSW is currently experiencing a high number of infections due to *Mycoplasma pneumoniae*. For patients presenting with clinical symptoms suggestive of *Mycoplasma*, it is recommended to order both the Respiratory Multiplex PCR and *Mycoplasma pneumoniae* serology (acute and convalescent paired sera).

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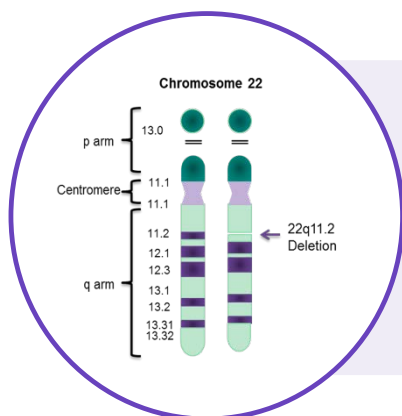


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Non-Invasive Prenatal Screening: The quality choice for detecting 22q11.2 deletion

By Associate Professor Mirette Saad



As part of the Harmony non-invasive prenatal screening (NIPT) test menu, Clinical Labs is offering 22q11.2 deletion or DiGeorge Syndrome testing in pregnancy using circulating cell-free fetal DNA (cffDNA) microarray technology.

What is 22q11.2 deletion syndrome?

Also known as DiGeorge syndrome, 22q11.2 deletion syndrome is caused by a submicroscopic deletion (microdeletion) on the long arm of chromosome 22. Most cases are de novo (new mutations), and approximately 10% are inherited. Inherited cases follow an autosomal dominant pattern, with a 50% chance of having an affected child.

How do we test for 22q11.2 deletion syndrome?

22q11.2 deletions are usually too small to be identified with standard cytogenetic studies (karyotype). Typically, it can be diagnosed by FISH or microarray.

Why is it important to screen for 22q11.2 deletion?

22q11.2 deletion is the most common microdeletion syndrome, occurring in as many as 1 in 1,000 pregnancies¹, and is the second most common cause of developmental delay after Down syndrome².

“22q11.2 deletion occurs in as many as 1 in 1,000 pregnancies¹ and is the second most common cause of developmental delay after Down syndrome².”

Conventional screening methods, such as first-trimester screening, do not reliably detect 22q11.2 deletion in the prenatal period². Additionally, maternal age is not a risk factor for microdeletions, meaning that 22q11.2 deletion syndrome can occur in any pregnancy¹. Studies have shown that early prenatal screening for 22q11.2 deletion, combined with diagnosis, allows for appropriate medical management of the pregnancy, as well as for the child in the neonatal period and into childhood³.

What are the clinical implications of 22q11.2 deletion screening?

The features of this syndrome vary widely. Common signs and symptoms include heart abnormalities, immune deficiency, characteristic facial features, developmental delays, along with some laboratory biochemical abnormalities.

Are all pregnancies eligible for 22q11.2 deletion screening?

The 22q11.2 deletion screening option has been validated in singleton pregnancies, including IVF self and non-self-egg donor pregnancies. This test has not been validated in pregnancies with more than one fetus. Women with a known 22q11.2 deletion are not eligible for this test.

When is 22q microdeletion screening available?

Like Harmony NIPT screening, 22q11.2 deletion can be ordered anytime from 10 weeks gestation until delivery. 22q11.2 microdeletion screening can only be ordered with Harmony NIPT screening and cannot be ordered on its own.

Is Harmony a quality choice for detecting 22q11.2 deletion?

Clinical validation studies for the Harmony Prenatal Test with 22q11.2 show a sensitivity of 75% and a specificity of 99.5%⁴. This corresponds to a “false positive rate” of 0.5%. Therefore, the combined false positive rate for Harmony trisomies 21, 18, 13 with 22q11.2 still remains exceptionally low, at less than 0.6%^{4,5}.



How should the test results be interpreted?

A 22q11.2 deletion may not be detected in all fetuses. Due to the limitations of the test, a “No Evidence of a Deletion” result does not guarantee that a fetus is unaffected by a chromosomal or genetic condition. For “High Probability” results, similar to all positive NIPT chromosomal conditions, confirmatory testing is necessary for diagnosis. It is appropriate to offer genetic counselling, including a discussion of potential risks to offspring and reproductive options, to patients who are affected or at risk.

Non-invasive prenatal testing (NIPT) based on cell-free analysis is not diagnostic; results should be confirmed by diagnostic testing. Before making any treatment decisions, all women should discuss their results with their healthcare provider, who can recommend confirmatory, diagnostic testing where appropriate. The Harmony Prenatal Test is developed by Ariosa Diagnostics and is performed in Australian Clinical Labs in Australia.

How to order Harmony 22q11.2 deletion screening

1. If your patient is at least 10 weeks pregnant, please complete the Harmony Request Form. To download the digital version or for instructions on how to access the request form through Genie, MedicalDirector, and Best Practice, please visit antenatal.clinicallabs.com.au/doctor/harmony/order. Select the ‘**Harmony Prenatal Test (T21, T18, T13) + 22q11.2**’ test option. Please ensure that referring clinician’s details are accurate when completing the form.
2. Please ensure that both you and the patient have signed the request form and read the detailed information on both sides of the form, and that the patient is aware of the additional cost for 22q11.2.
3. Payment is required before collection. Please advise your patient to scan the QR code on their request form or visit pay.clinicallabs.com.au/harmony to pay for their test online. They will need to select and pay for the ‘**Harmony Prenatal Test & 22q11.2**’ test option.
4. Direct your patient to take their signed Harmony request form and payment receipt to their nearest Clinical Labs collection centre (clinicallabs.com.au/location).
5. You will receive your patient’s test results within 5-10 business days of sample receipt at our lab.
6. For high probability cases, an initial telephone consultation with a certified genetic counsellor is available at no additional cost. Follow-up consultations, if required, will incur an out-of-pocket fee.

For more information about Harmony NIPT, please visit antenatal.clinicallabs.com.au/doctor/harmony.

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To watch Associate Professor Mirette Saad’s educational video module ‘Prenatal Screening for 22q11.2 Microdeletion’, scan the QR code. The video is approximately 17 minutes long.

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One-third of Australians are vitamin D deficient

By Dr Tony Mak and Dr David Deam



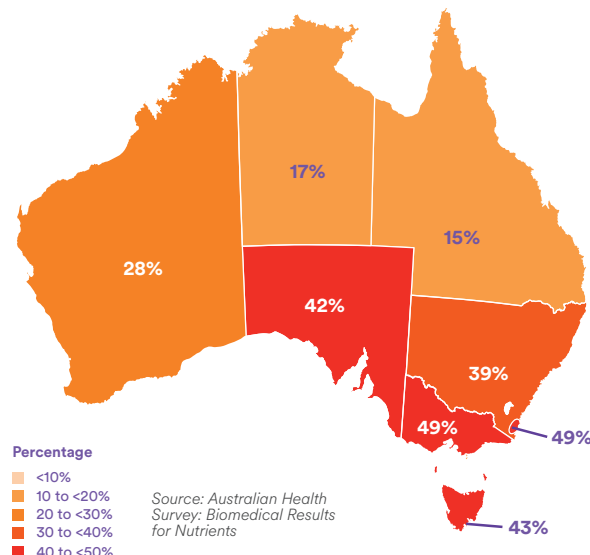
Epidemiology

Due to reduced sunlight exposure, at the end of winter, approximately 36 percent of Australians are vitamin D deficient. This issue is more pronounced in the southern parts of the country, where nearly half the population is insufficient (see Figure 1). Therefore, testing for serum vitamin D levels during winter has the highest yield for identifying such individuals.

Risk of vitamin D deficiency

Vitamin D deficiency, defined as a serum level below 50 nmol/L^{1,2}, is associated with elevated parathyroid hormone (PTH) levels and predisposes patients to a number of adverse effects. These include loss of bone density, osteoporosis, and fractures. Additionally, vitamin D deficiency is associated with cardiovascular disease, diabetes, immune system diseases, microbial and respiratory diseases, cognitive impairment, mental health disorders, and cancer.

Figure 1 - Vitamin D deficiency in winter by state (2011-2012)



Target vitamin D levels

Patients with marginally adequate vitamin D levels ($\geq 50 + 10-20$) during summer are also at risk. These individuals should be reviewed during winter, as decreased sunlight exposure could lead to deficiency in these patients.



Adequate vitamin D levels in nmol/L at the end of winter



Marginally adequate vitamin D levels during summer may become deficient during winter

Who to test

Vitamin D testing should be requested for patients at risk of vitamin D deficiency, including:

- Housebound individuals: such as the sick, disabled, elderly in high care, and indoor workers
- Those with less effective sunlight exposure: including people with darker skin tones, individuals who avoid sunlight, or those who cover their skin for various reasons

Additionally, testing should be considered for patients with:

- Osteoporosis or osteomalacia
- Elevated ALP levels with otherwise normal liver functions tests (LFTs)
- Hyperparathyroidism, calcium abnormalities, or hypophosphataemia

- Malabsorption syndromes
- Medications that may interfere with vitamin D levels (e.g., anticonvulsants)
- Chronic renal failure (CRF) and transplant recipients

Treatment

Sun exposure

Achieving adequate sunlight exposure to generate sufficient endogenous vitamin D production without exposing an individual to excessive risk of skin cancer is a delicate balance. This balance is complicated by a number of variables, notably the season of the year, latitude, and skin colour.³

As a guideline, the following sun exposure times (in minutes per day) are recommended for individuals with moderately fair skin.⁴

	December-January	July-August
PERTH	5-6 mins	20-28 mins
ADELAIDE	5-7 mins	25-38 mins
MELBOURNE	6-8 mins	32-52 mins
HOBART	7-9 mins	40-47 mins
SYDNEY	6-8 mins	26-28 mins
BRISBANE	6-7 mins	5-19 mins
CAIRNS	6-7 mins	9-12 mins

Vitamin D supplement

If adequate sun exposure cannot be achieved, vitamin D supplementation may be required.

A maintenance dose of up to 1000 IU/day is a general guide. Higher dosage may be required for individual cases. Adequate calcium intake of 1 – 1.3g/day through dietary intake or supplementation is advisable.

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Requesting Vitamin D Testing with Clinical Labs

How to order: Note the reason for testing to meet Medicare eligibility criteria for bulk-billing in the 'Clinical Notes' section on a Clinical Labs General Pathology Request Form.

Repeat testing: Vitamin D levels should not be retested within 3 months of initiating vitamin D supplements or altering dosing.

Annual testing: For older individuals or when risk factors for vitamin D deficiency have changed since initial testing, annual assessment should be considered.

Additional tests to consider: When requesting a vitamin D test, concurrent serum calcium and parathyroid hormone assessments will provide an overall calcium homeostasis status. If osteoporosis is present, fasting blood crosslaps (CTX) can monitor bone turnover in response to therapy.

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