AUSTRALIAN Clinicallabs

NSW/ ACT

June 2025 - Issue 30

PATHOLOGY *focus*

Medical Newsletter

RSV UNDER THE MICROSCOPE:

Surveillance trends and vaccine breakthroughs

By Dr Eric Chu

Respiratory Syncytial Virus (RSV) is highly contagious virus responsible for respiratory tract illness. While it causes a mild illness in most people, it is one of the most common causes of hospitalisation and death in newborns and infants. It is also a significant cause of mortality and morbidity among older adults with chronic health conditions. Consequently, it is a significant public health issue, with substantial research into preventing infection among vulnerable populations.

Article continues over page

National surveillance: Identifying needs

While first identified in 1956, RSV has only recently been classified as a notifiable disease and was included in the Australian national surveillance program in July 2021 (Department of Health and Age Care 2025), with all states and territories contributing data since September 2022. Positive RSV cases are collected from all laboratory testing in Australia, including Australian Clinical Labs. In addition, hospitalisation and outcome data are collected from hospitals reporting to FluCAN, a respiratory illness surveillance network. The result has provided us with a clearer picture of the epidemiology and the burden of this disease in Australia, allowing for targeted intervention in those most at risk.

Australian epidemiological trends (2023–2024)

RSV season occurs from April to September in Australia, although variation can occur from year to year. It usually starts 1-2 months before the influenza season (see Figure 1). From 2023 to 2024, there was a 30% increase in notified cases, rising from 128,123 to 175,918 (Department of Health and Aged Care, 2025). Mortality involving RSV also increased from 363 to 462 between 2023 and 2024. 50%, 8.2%, and 12.4% of those cases occurred in the 0-4, 5-9, and over-70 age groups, respectively (see Figure 2).

Number of RSV cases notified by month

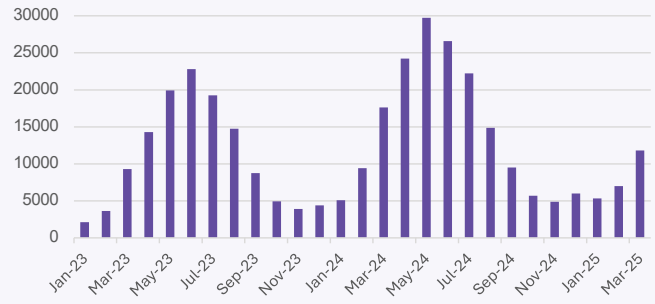


Figure 1. Number of RSV notifications by month. Source: National Notifiable Diseases Surveillance System (NNDSS), extracted 21 April 2025.

Number of notified RSV cases in 2024 by age group

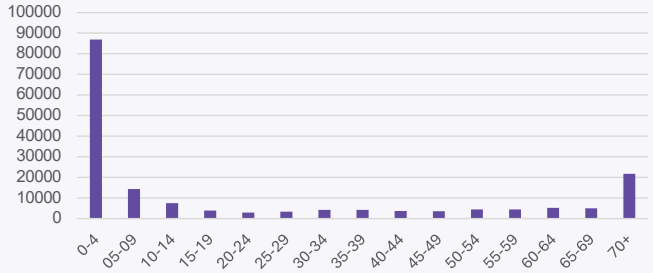


Figure 2. Number of notified RSV cases in Australia in 2024 by age group. Source: National Notifiable Diseases Surveillance System (NNDSS), extracted 20 April 2025.

Infants and children: The youngest at risk

In children, hospitalisation due to RSV is higher than for influenza and COVID (Department of Health and Aged Care 2025). Hospitalisation occurs overwhelmingly in infants and young children under 2. In this age group, 4.4% of hospitalisations require admission to ICU, and a small number of deaths have occurred. The risk factors for severe RSV in infants include any underlying cardiac or respiratory illness, immunocompromised conditions and preterm infants <32 weeks' gestation.

Older adults: A growing concern

RSV is also increasingly recognised as a cause of illness and hospitalisation in older adults, particularly those with risk factors. In Australia, hospitalisation due to RSV in adults is lower than for influenza or COVID, but it has a similar rate of admission to ICU (8.5%) and mortality (4.3%) among those hospitalised. The risk factors predicting more severe diseases include underlying lung or cardiac diseases, including COPD, asthma and congestive heart disease. Other risk factors include diabetes mellitus, chronic kidney disease and immunocompromised adults. Among immunocompromised adults, the risk is highest for lung transplant patients or those who have had a haematopoietic cell transplant. Those undergoing chemotherapy for a haematological malignancy are also considered at higher risk.

Vaccine development

RSV contains eleven proteins (see Figure 3). Among these, two are responsible for viral infectivity, while also eliciting the most antigenic response. The fusion (F) protein is responsible for enabling entry of the virus into the host cell by fusing with the cell membrane, essential for viral function. The G protein is responsible for attachment of the virus to ciliated cells in the respiratory tract. There are two subtypes (A and B) for G proteins, making it a less ideal target for vaccines, as antibodies targeting the G protein may be subtype-specific, while those targeting the F protein should affect both subtypes. As understanding of these proteins and the pathogenesis of RSV has improved, vaccine development has also improved, leading to vaccines targeted to the F protein.

Palivizumab is a monoclonal antibody that was approved by the FDA in 1998, and the TGA in 2015. It targets the F protein; however, it was found to provide only modest effectiveness and would require monthly injections throughout the RSV season. Palivizumab is therefore generally considered an unrealistic option beyond hospital settings in those at the highest risk.

In 2011, a breakthrough occurred in the identification of two major structural conformations of the F protein: the known post-fusion (postF) and a pre-fusion (preF) form. The postF protein is more stable and subsequently identified as the target of palivizumab. The preF protein contains different antigenic sites and is found to be more vulnerable to neutralising antibodies. This led to the development of new vaccines, all targeting the preF protein, three of which have been approved for use in

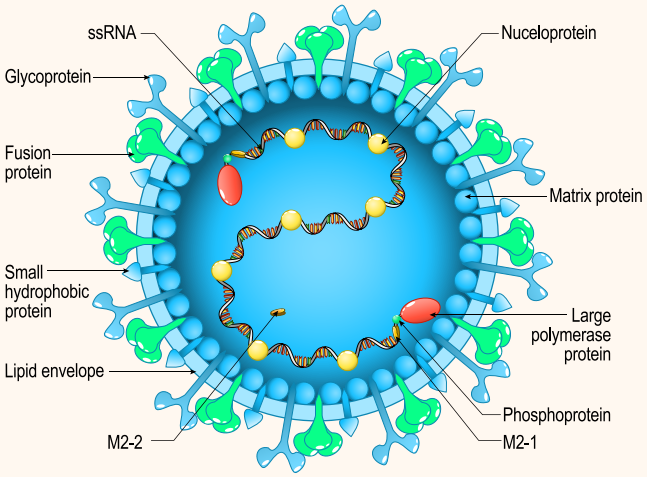


Figure 3. Respiratory syncytial virus structure.

Australia since 2023. These are nirsevimab (Beyfortus), Abrysvo and Arexvy. There is also an mRNA vaccine, but it is not currently approved in Australia.

New vaccines

Nirsevimab (Beyfortus): For infants

Nirsevimab is a human recombinant monoclonal antibody. It has a longer half-life and 50-fold higher neutralising activity compared to palivizumab (Wilkins D 2024). In two phase 3 clinical trials, it demonstrated 83.2% vaccine effectiveness in protecting against infection and hospitalisation, first in at-risk infants (Drysdale S 2023). More importantly, in healthy late pre-term and term infants, the vaccine effectiveness is 74.5% (Hammitt L 2022).

It has replaced palivizumab as the vaccine of choice for infants. In addition to this, it is now recommended for all infants for their first RSV season. It maintains neutralising antibody levels for around 5 months; therefore, only one dose is required at the beginning of the RSV season.

Abrysvo: For pregnant women and older adults

This is a recombinant bivalent vaccine containing RSV preF protein subgroups A and B. This is the only vaccine available for pregnant women. Its efficacy was shown in a phase 3 randomised trial including 7,148 births (Kampmann B 2023). When compared to placebo in infants, it demonstrated a vaccine efficacy of 81.1% and 57.1% at 90 days after birth against severe RSV-associated lower respiratory tract illness (LRTI) and RSV-associated medical presentation respectively, with sustained efficacy of 69.4% and 51.3% at 180 days after birth. Another trial in older adults demonstrated 67% vaccine efficacy in preventing RSV-associated LRTI (Walsh EE 2023).

Arexvy: For older adults

This is monovalent adjuvanted RSV preF protein. Because it is an adjuvanted vaccine, it is potentially more immunogenic than Abrysvo, although no head-to-head studies have been performed. Clinical trials demonstrate vaccine efficacy of 82.6% when compared to placebo for confirmed RSV infection, and 94.1% for severe RSV-related LRTI (Papi A 2023). Despite being a monovalent vaccine, it is similarly effective against both RSV serogroups A and B.

Current immunisation recommendations

Given the number of new vaccines, the recommendations are complex. They are listed in Table 1.

Abrysvo in pregnant women is currently funded through the National Immunisation Program. Other vaccines may be funded through state programs, which vary; for example, nirsevimab is funded in some states.

Regarding vaccination in older adults, while vaccine efficacy decreases in subsequent years, current data suggests efficacy for at least two years. There is insufficient data beyond this, and it is unclear whether boosters will provide any additional benefits.

Table 1. Immunisation recommendations for RSV.

Populations	Criteria	Recommendations
Pregnant women	All women between 28-36 weeks' gestation. Should be given >2 weeks before birth but can be given after 36 weeks' gestation.	Receive 1 dose of Abrysvo
Infants and children	< 8 months old going into first RSV season, and: • Born to a mother who did not receive the RSV vaccine or was born within 2 weeks of receiving the RSV vaccine; or • Mother is immunosuppressed and unlikely to mount immune response to RSV vaccine; or • Infants at risk for severe RSV disease	Receive 1 dose of nirsevimab
	8-24 months going into their second RSV seasons: • Conditions at risk for severe RSV disease	Receive 1 dose of nirsevimab
Adults >60 years old	Conditions that increase risk of severe RSV disease	Arexvy or Abrysvo *Not enough data on booster recommendation currently.*
Adults >75 years old	No exclusion criteria	

Article continues over page

Conclusion: Looking ahead

The recent progress in RSV immunisation represents a pivotal moment in respiratory disease prevention. The integration of these vaccines into routine immunisation schedules promises to significantly reduce the incidence and severity of RSV infections among the most vulnerable members of our population. Ongoing surveillance data, including vaccination data, will help us further assess the real-world efficacy of vaccines and the need for boosters in older adults, as well as identify any current gaps in vaccine coverage. Improving the quality of surveillance and outcomes for RSV requires coordination among primary health care providers, laboratories, hospitals, and public health services to enable recognition and confirmation of cases through testing. It is the responsibility of every health care provider. As we continue to monitor and refine our strategies, the hope is that we can further reduce the impact of RSV on vulnerable members of our society.

How to Order Respiratory Pathogen PCR Testing at Clinical Labs (NSW/ACT)

What to request:	Panels included:		
Respiratory Multiplex PCR	• Influenza A • Influenza B • RSV A/B • Parainfluenza 1 & 3 • Parainfluenza 2	• Human metapneumovirus • Human adenovirus • Human enterovirus • Human rhinovirus • *Bordetella pertussis*	• *Bordetella parapertussis* • *Mycoplasma pneumoniae* • COVID-19 / SARS-CoV-2 (M, N Gene)

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

References

Department of Health and Aged Care. 2025. National notifiable disease surveillance dashboard. Accessed April 14, 2025. https://nindss.health.gov.au/pbi-dashboard/.

Department of Health and Aged Care. 2025. 2024 Annual Australian Respiratory Surveillance Report . Commonwealth of Australia (Australian Centre for Disease Control).

Drysdale S, Cathie K, Flamein F, *et al.* 2023. "Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants." *NEJM* 389:2425-2435.

Hammitt L, Dagan R, Yuan Y, *et al.* 2022. "Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants." *NEJM* 386:837-846.

Kampmann B, Madhi SA, Munjal I, *et al.* 2023. "Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants." *NEJM* 388:1451-1464.

Papi A, Ison MG, Langley JM *et al.* 2023. "Respiratory Syncytial Virus Prefusion F Protein Vaccin in Older Adults." *NEJM* 288:595.

Ruckwardt, Tracy J. 2023. "The road to approved vaccines for respiratory syncytial virus." *npj Vaccines* 8:138.

Walsh EE, Pérez Marc G, Zareba AM *et al.* 2023. "Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults." *NEJM* 288:1465-1477.

Wilkins D, Hamren U, Chang Y, *et al.* 2024. "RSV Neutralizing Antibodies Following Nirsevimab and Palivizumab Dosing." *Pediatrics* 154:e2024067174.

About the author:

Dr Eric Chu

MBBS FRCPA FRACP

Lab: Osborne Park (WA)
Speciality: Infectious Diseases, Microbiology
Areas of Interest: General infectious diseases, infection prevention and management, antimicrobial stewardship, as well as the use of molecular methods in diagnostic microbiology
Phone: 1300 134 111
Email: eric.chu@clinicallabs.com.au

Local pathologist:

Dr Stella Pendle

MSc MBBCh DTM&H FRCPA

Lab: Bella Vista (NSW)
Speciality: Microbiology
Areas of Interest: General bacteriology, infectious serology, VRE and hepatitis
Phone: (02) 8887 9999
Email: stella.pendle@clinicallabs.com.au

Managing Vitamin D Deficiency:

A clinical guide to diagnosis and treatment

By Dr Phoebe Stanford

Understanding Vitamin D: Function, sources and metabolism

Vitamin D is a fat-soluble vitamin which plays a key role in calcium and phosphate homeostasis and is important for bone and muscle function.

As there are few vitamin D-rich foods, skin production through the action of UV radiation is generally the main natural source of vitamin D. Vitamin D (calciferol) from the diet or supplements, or produced in the skin, requires conversion in the liver to the main circulating form, 25-hydroxyvitamin D (25OHD), which has a half-life of 2–3 weeks (see Figure 1). This is then converted in the kidneys to the biologically active form, 1,25-dihydroxyvitamin D, which has a half-life of just 4-6 hours.[1]

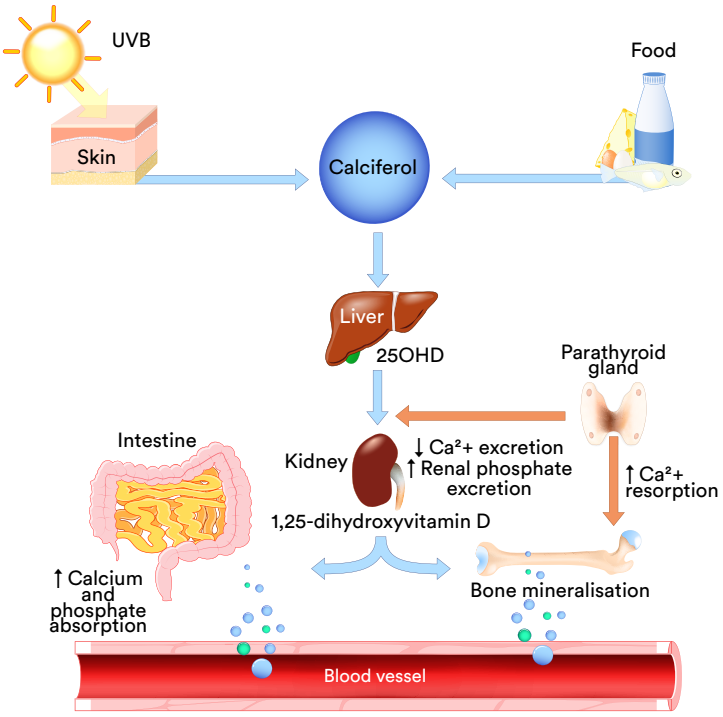


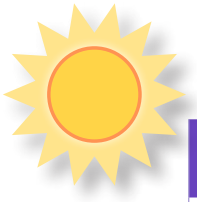
Figure 1. Vitamin D metabolism

Certain medications (including some anticonvulsants) can increase the breakdown of vitamin D. Patients taking these medications are at increased risk for vitamin D deficiency and may require higher doses of vitamin D supplementation.

Vitamin D is taken up and stored in adipose tissue and may not be released unless there is fat breakdown, resulting in reduced circulating levels of 25OHD in obese individuals.

Recommended UV exposure for adequate vitamin D

The amount of sun exposure required for adequate endogenous vitamin D production depends on several factors, including time of the day/year, latitude, skin colour and the area of skin exposed. As a guide, to achieve adequate endogenous production of vitamin D, the following sun exposure times (in minutes per day) are recommended for individuals with moderately fair skin (based on exposure of hands, face and arms).[2] For people with highly pigmented skin, the required exposure time would be 3–6 times longer.



	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

The required UV exposure for vitamin D synthesis needs to be balanced against the risk of skin cancer. For patients at very high risk of skin cancer, vitamin D supplements may be preferable to sun exposure as a source of vitamin D. Infants, the elderly in high care, indoor workers or those who cover their skin for various reasons also may not be able to achieve adequate sun exposure.

Clinical implications of vitamin D deficiency

Vitamin D deficiency results in reduced intestinal absorption of phosphate and calcium, which causes hypophosphataemia, hypocalcaemia and impaired mineralisation of bone. In addition, secondary hyperparathyroidism develops in response to the reduced calcium, promoting mobilisation of calcium from bone and phosphaturia, further exacerbating the bone mineralisation defect. With ongoing severe deficiency, this results in osteomalacia in adults and rickets in children.

Article continues over page

Pregnancy

In pregnancy, maternal vitamin D deficiency not only places the mother at risk of accelerated bone loss, but also puts the baby at risk of rickets, hypocalcaemia/seizures and myopathy due to neonatal vitamin D deficiency.

Patients treated for osteoporosis

In addition to a negative effect on bone mineralisation, patients taking potent antiresorptive therapy are at risk of severe hypocalcaemia when these are used in the presence of vitamin D deficiency.

Eligibility for vitamin D testing

Vitamin D testing should be performed in those with risk factors for deficiency or in patients being investigated and/or treated for bone or mineral disorders. This is also required for funding by the Medicare Benefits Schedule (MBS).

Indications for vitamin D testing (MBS criteria):[3]

- Signs, symptoms and/or planned treatment of osteoporosis or osteomalacia
- Increased alkaline phosphatase with otherwise normal liver function tests
- Hyperparathyroidism, hypo- or hypercalcaemia, hypophosphataemia
- Malabsorption (e.g. cystic fibrosis, short bowel syndrome, inflammatory bowel disease, untreated coeliac disease, bariatric surgery)
- Deeply pigmented skin, or chronic and severe lack of sun exposure for cultural, medical, occupational or residential reasons
- Medications known to decrease 25OHD levels (e.g. anticonvulsants)
- Chronic renal failure and renal transplant recipients

And in children:

- Signs, symptoms and/or planned treatment of rickets
- Infants of mothers with established vitamin D deficiency
- Exclusively breastfed babies in combination with at least one other risk factor
- Siblings of infants or children with vitamin D deficiency

Measurement of vitamin D is not recommended as a screening test in the general population (including pregnant women and infants or children without risk factors).

Interpreting vitamin D test results

25OHD, the main circulating form of vitamin D, is the analyte routinely measured to assess vitamin D status. While there is no consensus on the optimal concentration of 25OHD, Australian guidelines recommend a target threshold of 50 nmol/L (60-70 nmol/l at the end of summer to allow for seasonal decrease) as adequate for mineral homeostasis, bone health and muscle function.[5]

Most laboratories in Australia, including Australian Clinical Labs, measure vitamin D by automated immunoassay. While there are differences in analytical precision between assays, a difference of ± 20% for repeated tests on the same sample is considered acceptable measurement uncertainty.[4] On this basis, together with the seasonable variability, results between 50–70 nmol/L may be considered borderline for sufficiency.

Excessive vitamin D supplementation may rarely cause toxicity, manifesting as hypercalcaemia and hypercalciuria. The 25OHD level at which hypercalcaemia occurs is not well defined. 25OHD concentrations greater than 250 nmol/l may be considered a risk for toxicity, although hypercalcaemia is not usually reported until concentrations exceed 500 nmol/l.[5]

How to Order Vitamin D Testing at Clinical Labs

What to request

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

Due to the long half-life, repeat testing should not be performed earlier than 3 months after either starting or changing the dose of vitamin D supplements.

Additional tests

Serum calcium, phosphate and parathyroid hormone will assist in placing the vitamin D level within the context of overall calcium homeostasis.

If osteoporosis is present, assessment of bone turnover markers (fasting C-terminal telopeptide of type 1 collagen [CTX] and procollagen type 1 N propeptide [P1NP]) may be considered to provide a way of monitoring bone turnover in response to therapy.

References

1. Pazirandeh S and Burns D. Overview of vitamin D. Uptodate, Updated Sep 08 2023. Accessed April 2025.
2. Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. Vitamin D and adult bone health in Australia and New Zealand: a position statement. *MJA* 2005; 182: 281–28.
3. Australian Government Medicare Benefits Schedule Online. Medicare Benefits Schedule Item 66833 [Accessed 5 April 2025].
4. RCPA Position Statement: Use and Interpretation of Vitamin D testing. The Royal College of Pathologists of Australasia, May 2013.
5. Vitamin D and health in adults in Australia and New Zealand: a position statement. *MJA 196*(11), 18 June 2012.

About the author:

Dr Phoebe Stanford

MBBS FRCPA FRACP

Lab: Bella Vista (NSW)
Speciality: Chemical Pathology
Areas of Interest: Endocrinology
Phone: (02) 8887 9999
Email: phoebe.stanford@clinicallabs.com.au

Dr Stanford graduated from the University of New South Wales in 2005. She completed Basic Physician Training, followed by Advanced Training in Chemical Pathology and Endocrinology. This included undertaking a year with a focus on bone disease at St Vincent's hospital (Sydney), followed by a year of general clinical endocrine training at Prince of Wales Hospital. Dr Stanford then completed her joint training based at the Prince of Wales and Royal North Shore Hospital Laboratories. In 2019, she was awarded fellowship of both the Royal Australasian College of Physicians and The Royal College of Pathologists of Australasia. Dr Stanford then worked at Tan Tock Seng hospital laboratory in Singapore before returning to Australia to take up a Chemical Pathologist position at Australian Clinical Labs.

Placental Growth Factor for Early-Onset Pre-eclampsia Screening

By Associate Professor Mirette Saad

As part of our antenatal screening offering and in alignment with the updated guidelines, Clinical Labs offers Placental Growth Factor (*PlGF 1-2-3™*) for pre-eclampsia (PE) screening using the Fetal Medicine Foundation's (FMF) approved algorithm to estimate the risk of early-onset pre-eclampsia (EO-PE) in pregnancy.

Pre-eclampsia (PE)

PE, a multi-system disorder associated with hypertension, can occur in any pregnancy. The incidence is increasing with the global rise in maternal age, obesity, and the use of assisted reproductive techniques, along with all known co-morbidities that predispose sufferers to PE during pregnancy (see Table 1). Thus, preventing PE would bring substantial improvements to maternal and perinatal health.[5-8]

Pre-eclampsia is a spectrum disorder[2,3,4] that can be sub-classified into:

- **Early-Onset PE** (with delivery at <34^{+0} weeks of gestation)
- **Pre-Term PE** (with delivery at <37^{+0} weeks of gestation)
- **Late-Onset PE** (with delivery at ≥34^{+0} weeks of gestation)
- **Term PE** (with delivery at ≥37^{+0} weeks of gestation)

These sub-classifications are not mutually exclusive.

Pre-eclampsia is more common than aneuploidies[5,6,7,8]

PE affects 2-8% of pregnancies globally.[7] The prevalence of PE and related conditions (fetal growth restriction and pre-term birth) is much higher than that of Down syndrome. Unlike Down syndrome, PE (especially EO-PE) is associated with a much higher risk of short- and long-term maternal and perinatal morbidity and mortality.[2,3,4]

PE definition update

In 2021, the International Society for the Study of Hypertension in Pregnancy (ISSHP) broadened the definition of PE to provide further clarity by including additional examples of maternal organ dysfunction[1,27] (see Table 1). This was adopted by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG),[25,28] and international guidelines, NICE and ACOG, as PE is considered a major cause of maternal death and morbidity. In the absence of proteinuria, the finding of maternal organ dysfunction is sufficient to make the diagnosis of PE.[1]

> ***"The prevalence of PE and its role as a major cause of maternal and perinatal morbidity and mortality highlights the importance of prevention."***

Table 1. International Society for the Study of Hypertension in Pregnancy (ISSHP) Revised Definition of PE, 2021

Pre-Eclampsia	ISSHP 2021	PE Predisposing Risks	Laboratory investigations
De novo	Pre-eclampsia (de novo) is gestational hypertension accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation: 1. Proteinuria 2. Other maternal end-organ dysfunction, including: • Neurological complications • Pulmonary oedema • Haematological complications • AKI • Liver involvement 3. Uteroplacental dysfunction	• Nulliparity or multiple gestations • First pregnancy • PE in a previous pregnancy • FHx of pre-eclampsia • Body mass index (BMI) >30kg/m2 • Maternal age >40 years • Sub-fertility • IVF pregnancy • Inter-pregnancy interval ≥ 10 years • Gestational hypertension • Diabetes • Migraine • Polycystic ovary syndrome (PCOS) • Autoimmune disease • Renal disease • Cardiovascular disease • Chronic hypertension	• Urinalysis for quantitative proteinuria • Liver function • Urate & LDH • Kidney function tests • Placental Growth Factor • Coagulation screen • Fetal ultrasound
Superimposed on chronic hypertension	Among women with chronic hypertension, development of new proteinuria, another maternal organ dysfunction(s) or evidence of uteroplacental dysfunction		

Quoted from L.A. Magee et al., 2022.

Article continues over page

Placental growth factor (PlGF)

PlGF, a glycoprotein expressed in the villous syncytiotrophoblast that belongs to the vascular endothelial growth factor (VEGF) subfamily, is a potent angiogenic factor. PlGF, together with VEGF, regulates the development of the placental vasculature.[13,14,15]

Biochemical markers are reduced in pre-eclampsia[9,10]

Biochemical markers that reflect placental function, such as PlGF and pregnancy-associated plasma protein-A (PAPP-A), are significantly reduced in the first trimester and throughout pregnancy in patients who will later present with pre-term PE, with delivery before 37 weeks' gestation, contributing to many adverse obstetric outcomes.[13,14,15] Of these two markers, PlGF is a better PE screening marker (PPV 56%) than PAPP-A (PPV 16%)—i.e. it has higher sensitivity.[9,10]

PlGF 1-2-3™ for early-onset pre-eclampsia (EO-PE) screening[13,14,15,22,23]

A systematic review and meta-analysis demonstrated that PlGF is superior to the other biomarkers for predicting PE.[24] The serum PlGF biomarker can identify up to 75% of women who develop pre-term PE with delivery at <37 weeks' gestation, and 90% of those with early PE at <32 weeks, at a screen-positive rate of 10%. Women with suspected pre-eclampsia who have low circulating maternal PlGF concentrations (<5th centile or ≤ 100 pg/ml) have a high sensitivity (96%) and negative predictive value (98%) in diagnosing pre-eclampsia that requires delivery within 14 days.[13,14,15]

The COMPARE[16] Study

COMPARE states that the high negative predictive values (NPV) support the role of PlGF-based tests as 'rule-out' tests for PE. Among the tests compared, the DELFIA Xpress® PlGF 1-2-3™ assay has the highest NPV.

ASPRE Study[17]

Using the PlGF 1-2-3™ assay (PerkinElmer) in PE screening, ASPRE was the largest prospective, randomised, placebo controlled trial showing that the use of aspirin was associated with a significant 62% reduction in the incidence of pre-term PE (<37 weeks' GA) and an 82% reduction in EO-PE (<34 weeks' GA). Studies[15,18,19,20] have shown that the administration of aspirin in pregnancies at high risk of PE reduces the length of stay in the neonatal intensive care unit (NICU) by about 70%, mainly through the prevention of EO-PE.

Guidelines recommend early screening for pre-eclampsia [9,10,11,12]

The NHMRC recommends an assessment of all women for clinical risk factors for PE early in pregnancy.[26]

In July 2021, the International Federation of Gynecology and Obstetrics (FIGO) updated the 2019 guidelines to raise global public awareness on managing and monitoring PE by adopting and supporting the Fetal Medicine Foundation (FMF) position that all pregnant women should be offered screening for pre-term PE, performed at 11-13^{+6} weeks' gestation. Screening should involve a combination of maternal demographic characteristics and medical history, as well as biophysical markers, including mean arterial blood pressure (MAP), the mean uterine artery pulsatility index (UTPI) and measurements of the PlGF biochemical marker as a one-step procedure.[4,9,10,11,12,29]

How to Order Placental Growth Factor (PlGF) Testing at Clinical Labs

When to offer the test

The optimal time for screening is between 11 and 13^{+6} weeks of gestation.

Who to offer it to

Patients with high blood pressure, advanced age pregnancy, high BMI, a history of pre-eclampsia or eclampsia, diabetes or kidney disease, multiple pregnancies or IVF-assisted pregnancies.

The PlGF test can be offered to pregnant women of any age or risk category. It is available for all naturally conceived or in vitro fertilisation (IVF) singleton or twin pregnancies, including those with egg donors.

The PlGF test is viewed as a screening test and clinical interpretation is always recommended.[13,14]

Can it be offered with cFTS?

Yes, the same blood sample is used for the measurement of biochemical markers for both pre-eclampsia screening and aneuploidy (Down syndrome) screening, using the same instrument at Clinical Labs.[21]

Specimen Requirements

Plain tube or serum gel, 7 ml.

Blood samples can be collected at any of our 1,300+ Clinical Labs collection centres. For locations, visit clinicallabs.com.au/location

Test cost

Medicare does not cover the cost of the Placental Growth Factor (PlGF) blood test. An out-of-pocket fee applies.

For assistance, please call the Biochemistry Department on (03) 9538 6790 or FTS (MSS) service on 0429 116 049.

References

1. Tranquilli, A. L., *et al. Pregnancy Hypertens* 2014; 4:97 - 104.
2. Wright, D., *et al. Fetal Diagn Ther* 2012; *32*(3):171 - 178.
3. Wright, D., *et al. Am J Obstet Gynecol* 2015; 213:62.e1-10.
4. Poon, L. C., *et al. Int J Gynecol Obstet* 2019; 145 (Suppl. 1): 1–33.
5. Parker, S., *et al. Birth Defects Res A Clin Mol Teratol* 2010.
6. WHO Media Centre, Fact Sheet, 2016. Available at: http://www.who.int/mediacentre/factsheets/ fs363/en/
7. Duley, L. *Semin Perinatol* 2009.
8. Romo, A., *et al. Pediatr Endocrinol* Rev 2009.
9. Tsiakkas, A., *et al. Ultrasound Obstet Gynecol* 2015; 45:591-598.
10. Wright, A., *et al. Ultrasound Obstet Gynecol* 2016; 47:762-767.
11. Poon, L. C., *et al. Fetal Diagn Ther* 2012; 31:42-48.
12. O'Gorman, N., *et al. Ultrasound Obstet Gynecol* 2016; 47:565-567.
13. Royal College of Obstetricians and Gynaecologists, Patient Information Leaflet: Information for you: Pre-eclampsia. RCOG Patient Information Committee, London, UK, Aug 2012.
14. Rolnik, D. L., Nicolaides, K. H. *Ultrasound Obstet Gynecol* Jul 25, 2017.
15. Bujold, E., *et al. Obstet Gynecol 2010;* 116:402-414.
16. McCarthy, F. P., *et al. Ultrasound Obstet Gynecol* 2019; 53:62-67.
17. Rolnik, D. L., *et al. N Engl J Med* 2017 Aug 17; *377*(7):613-622.
18. Roberge, S., *et al. Fetal Diagn Ther* 2012; *31*(3):141-146. doi: 10.1159/000336662. Epub 2012 Mar21.
19. Roberge, S., *et al. Am J Obstet Gynecol* 2017 Feb; *216*(2):110-120.e6.
20. Wright, D., *et al. Am J Obstet Gynecol* 2018; 612.e6.
21. PerkinElmer PlGF Assay Product Inserts 13908271, 13907817.
22. Chau, K., *et al. J Hum Hypertens* 2017; 31:782–786.
23. Wortelboer, E.J., *et al. Ultrasound Obstet Gynecol* 2011; 38:383–388.
24. Zhong, Y., *et al. BMC Pregnancy Childbirth* 2015; 15:191.
25. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Pre-eclampsia and High Blood Pressure During Pregnancy. Available at: https://www.ranzcog.edu.au/Womens-Health/Patient-Information-Resources/Pre-eclampsia-and-High-Blood-Pressure-DuringPregn
26. National Health and Medical Research Council (NHMRC), October 2017. Evidence Based Recommendations.
27. Magee, L. A. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 2022;27:148–169.
28. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. https://ranzcog.edu.au/wp-content/uploads/Screening-Prevention-Preterm-PET.pdf
29. MelaMed *et al. Int J Gynecol Obstet*. 2021;152

About the author:

Assoc. Prof. Mirette Saad

MBBS (HONS) MD (HONS)
MAACB FRCPA PHD

National Director of Molecular Genetics

Lab: Clayton (Vic)
Speciality: Chemical Pathology
Areas of Interest: Molecular genetics, precision medicine, cancer genetics, antenatal screening, NIPT, endocrine, fertility testing and research, medical teaching
Phone: (03) 9538 6777
Email: mirette.saad@clinicallabs.com.au

Associate Professor Mirette Saad is an RCPA Consultant Chemical Pathologist and the National Director of Molecular Genetics at Australian Clinical Labs. She has a Fellowship with Honours in Chemical and Molecular Pathology, with a Microbiology sub-speciality, from Suez Canal University, Egypt. A/P Saad received her NHMRC-sponsored PhD degree in Cancer Genetics from Melbourne University and Peter MacCallum Cancer Institute. Along with her teaching and research roles, A/P Saad is a registered medical practitioner with AHPRA, a Chemical Pathology Fellow (FRCPA) at the Royal College of Pathologists of Australasia and a Member of the Australasian Association of Clinical Biochemists (MAACB). She is a Chair of the RCPA Chemical Pathology Advisory Committee, a Member of the RCPA Genetic Advisory Committee and AACB and Chair of the Precision Medicine Services at Australian Clinical Labs. At Clinical Labs, A/Prof Mirette Saad leads the Molecular Genetic testing for non-invasive prenatal testing (NIPT), antenatal screening, personalised drug therapy and cancer.

Navigating the Revised Medicare Items for Vitamin B12 Investigations

MBS UPDATES as of 1 July 2025

By Dr David Deam

Vitamin B12 deficiency represents a significant clinical concern, particularly within at-risk populations. These include the elderly, vegetarians and vegans, individuals with malabsorptive disorders (such as Crohn's disease, coeliac disease and post-bariatric surgery patients), those with pernicious anaemia, and individuals taking certain medications like metformin and proton pump inhibitors. The insidious onset and potentially severe, irreversible neurological sequelae underscore the critical importance of timely and accurate diagnosis. Prompt identification and management are essential to prevent complications such as megaloblastic anaemia, peripheral neuropathies, cognitive impairment and other neuropsychiatric manifestations.

Challenges in diagnosis

The diagnostic landscape for B12 deficiency is complex, notably due to the absence of a single, definitive diagnostic gold standard. This requires the careful integration of the patient's clinical presentation with the interpretation of various biochemical markers. The primary biomarkers traditionally employed are total serum vitamin B12 and holotranscobalamin (also known as Active B12), which represents the metabolically active fraction of B12 bound to its transport protein. Although Active B12 often offers better sensitivity and earlier detection of deficiency compared to total B12, it is a much more expensive test.

MBS revisions and implications

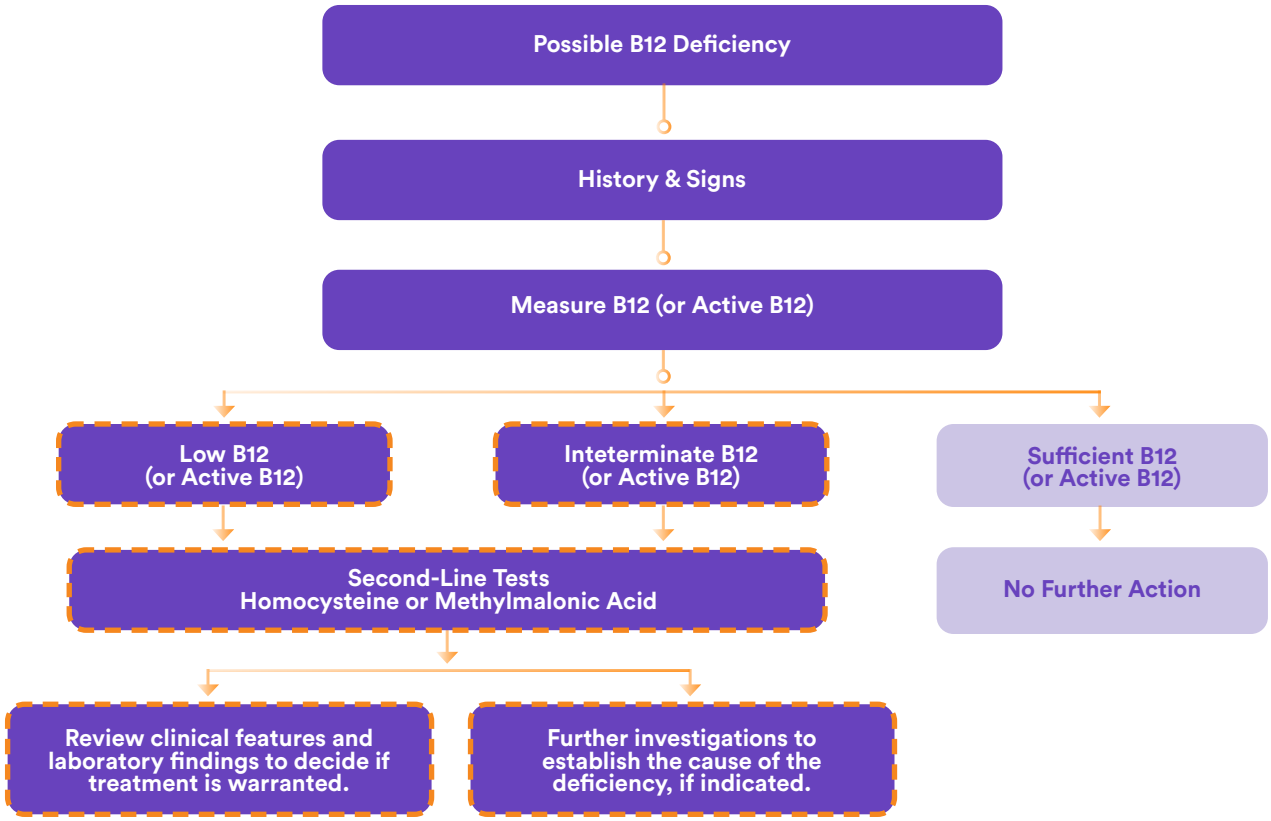
The recent revision to the Medicare Benefits Schedule (MBS) has introduced changes to the reimbursement structure for investigations related to vitamin B12 metabolism. Previously, the schedule promoted Active B12 levels for confirming low or borderline results. Under the revised schedule, while the option to test either total B12 or holotranscobalamin exists, the reimbursement provided by Medicare is now aligned with the lower cost of a total B12 assay. This adjustment presents a significant challenge for laboratories' ability to offer Active B12 testing.

Ongoing availability of Active B12 testing

Australian Clinical Labs will continue to perform Active B12 tests but patients may have an out-of-pocket cost if they do not meet the criteria for a rebate.

An outline of the new diagnostic pathway is shown below.

New diagnostic pathway for B12 testing



Inclusion of second-line biomarkers

The updated MBS acknowledges the multi-faceted nature of B12 deficiency diagnosis by including reimbursement for alternative, albeit indirect, biomarkers. Specifically, the schedule now provides for the testing of homocysteine (HCY) and methylmalonic acid (MMA) levels in the context of B12 deficiency investigation. Elevations in these metabolites can provide supplementary evidence supporting a diagnosis of B12 deficiency, particularly in cases where total B12 levels are equivocal or discordant with the clinical picture.

Clinical Labs' testing strategy

Our laboratory is equipped to measure homocysteine levels and will proactively offer this analysis when the initial total B12 result falls within the deficient or potentially deficient range. This sequential testing strategy aims to provide clinicians with additional diagnostic information to guide their management decisions effectively and efficiently within the revised reimbursement structure.

Clinical vigilance remains key

We encourage clinicians to remain vigilant in their clinical assessment of patients at risk for B12 deficiency. Integrating the clinical context with the results of total B12, and where indicated, considering second-line tests such as HCY and potentially MMA, will be crucial in navigating the updated Medicare landscape while ensuring optimal patient care.

The major risk factors and clinical features of B12 deficiency are listed below.

Risk factors for B12 deficiency

- Restricted diet (veganism, vegetarianism)
- Autoimmune gastritis
- Family history of B12 deficiency
- Intestinal diseases (e.g. coeliac)
- Infections & surgical interventions
- Pregnancy & neonates
- Pharmaceutical interactions
- Nitrous oxide abuse
- Age greater than 65 years

Signs and symptoms of B12 deficiency

- Anaemia (weakness, tiredness, dyspnoea on exertion)
- Gastrointestinal (loss of appetite, sore tongue and mouth, epigastric discomfort, nausea, vomiting, heartburn)
- Neurological (numbness, pins and needles, impaired fine finger movements)
- Developmental delay in infants
- Positive Romberg's sign
- Impaired vibration or position sense, impaired vision
- Orthostatic dizziness
- Loss of taste or smell
- Psychological & psychiatric disturbance

When to test for B12 deficiency

If a patient has at least 1 risk factor and 1 or more signs, then B12 assessment is warranted.

It is also warranted if there are 1 or more signs or symptoms even with no risk factors if the clinician is concerned.

Interpretation of B12 results

Total B12	
< 180 ng/L	Consistent with B12 deficiency
180–350 ng/L	Indeterminate results. Second-line testing indicated
> 350 ng/L	Vit B12 replete

OR

Active B12	
< 25 pmol/L	Consistent with B12 deficiency
25–70 pmol/L	Indeterminate results. Second-line testing indicated
> 70 pmol/L	Vit B12 replete

Next steps after diagnosis

If B12 deficiency is diagnosed, then the cause should be established.

If the total B12 or Active B12 is abnormal or inconclusive, then the doctor should review the results alongside the clinical picture to determine if treatment is warranted. B12 deficiency is commonly corrected with oral or intramuscular doses of the vitamin, depending on the extent of symptoms, signs and levels of B12.

Considerations in pregnancy

During pregnancy, there are changes in the level of binding proteins which can cause a low total B12 level. In this situation, the Active B12 test is a more useful first line-test.

Article continues over page

Proposed Updated MBS Items for B12 Testing from 1 July 2025

Amended Items

66838: Quantification of either or both of total vitamin B12 and holotranscobalamin.
Applicable not more than once in 11 months.

66839: Quantification of methylmalonic acid or homocysteine, rendered in the same patient episode as a service to which item 66838 applies, if the result of that service is inconclusive or abnormal.
Applicable not more than once in 11 months.

New Items

66842: Quantification of one or more of total vitamin B12, holotranscobalamin, methylmalonic acid or homocysteine for a patient:
(a) who:
(i) is still experiencing symptoms of vitamin B12 deficiency 3 to 6 months after a service described in item 66838 or 66839 was rendered for the patient; or
(ii) obtained inconclusive results from a service described in item 66839; or
(b) to whom one or more of the following applies:
(i) the patient has a diet low in vitamin B12;
(ii) the patient has a family history of vitamin B12 deficiency or an autoimmune condition;
(iii) the patient has previously had abdominal or pelvic radiotherapy;
(iv) the patient has previously had surgery involving the gastrointestinal tract;
(v) the patient uses, or has a recent history of using, recreational nitrous oxide;
(vi) the patient requires monitoring of vitamin B12 treatment;
(vii) the patient uses vitamin B12-antagonistic medicines;
(viii) the patient has one or more clinical conditions with a recognised risk of vitamin B12 deficiency

References

Vitamin B12 deficiency in over 16s: diagnosis and management. NICE guideline. 6 March 2024. Available from: nice.org.uk/guidance/ng239

About the author:

Dr David Deam

MBBS MAACB FRCPA

Lab: Clayton (Vic)
Speciality: Chemical Pathology
Areas of Interest: Endocrine function testing, protein abnormalities, laboratory automation
Phone: (03) 9538 6777
Email: david.deam@clinicallabs.com.au

Local pathologist:

Dr Eric Law

MBChB BMedSc (1st Hon) PhD FHKAM (Pathology) FHKCPath FRCPA FRCPath FAACB IFCAP

Lab: Bella Vista (NSW)
Speciality: Chemical Pathology
Areas of Interest: Chemical Pathology, Biochemical Genetics, Inherited Metabolic Disorders
Phone: 1300 134 111
Email: eric.law@clinicallabs.com.au

UPDATE: Amendments to MBS for Urine Testing in Asymptomatic Patients

From 1 July 2025, the Medicare Benefits Schedule (MBS) item for urine testing (69333) will be amended. This amendment stipulates that urine testing and examination (including serial examinations) are only required when symptoms of a urinary tract infection or kidney disease are present.

Practitioners are encouraged to consult the most up-to-date guidelines on the indications of urinary tract infection or kidney disease. At the time of publishing, this may include not only pain with urination and frequency of urination, but also systemic presentations such as suspected sepsis, delirium or fever of unknown origin.

Exception to this amendment is made for specified patient groups who may be asymptomatic, including those who are:

- Pregnant
- Less than 16 years of age
- Recipients of renal transplants
- Suffering from recurrent urinary tract infections
- Being investigated or monitored for kidney disease
- Undergoing urinary tract instrumentation, urological procedures or transurethral resection of the prostate

ACLMAR-NEWS-NAT-0798.9 (VIC/QLD) 06/25