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The management of type 2 diabetes (T2D) is rapidly evolving with the introduction of an increasing number of new medicines, updating of guidelines and emerging clinical outcome data. Medicine selection for treatment of T2D has become increasingly complex — especially when considering the Pharmaceutical Benefits Scheme subsidy of certain medicine combinations. On the other hand, some things have not changed; optimising glycaemic control, managing risk of complications and promoting a healthy lifestyle are still the cornerstones of diabetes care. Despite the new medicines available for the treatment of T2D, prescribers should continue to individualise their choice of therapy at each point of escalation based on patient and medicine factors.

Beyond selecting the most appropriate therapy lies the challenge of improving adherence to diabetes medicines. Better adherence to medicines ensures that patients achieve their glycaemic targets and reduce the risk of short and long term diabetes complications. It is important to assess adherence before intensifying diabetes therapy, which may help identify adverse events.

An emerging change, opportunity and challenge for prescribers will be the use of biosimilars in diabetes management, beginning with insulin analogues. Biological agents come with their own set of efficacy and safety considerations, which may influence prescribing in primary care settings. The diabetes environment is soon to be affected by these considerations by way of the new insulin glargine biosimilar.

By being better informed about medicine choices, health professionals can help people with T2D to achieve improved glycaemic control, reduce associated long term complications and minimise medicine-related adverse effects. The new educational program from NPS MedicineWise — “Type 2 diabetes: what’s next after metformin?” — provides general practitioners, pharmacists, practice nurses and diabetes educators with the latest evidence on second and third line medicines for lowering blood glucose levels and with strategies for improving adherence to metformin therapy. To access the educational program, visit www.nps.org.au/diabetes.
Snail venom key to better diabetes treatment

An international team of researchers led by scientists from the Walter and Eliza Hall Institute of Medical Research, Flinders University, the University of Melbourne and Monash University has found that venom from certain fish-hunting cone snails could hold the key to developing “ultra-fast-acting” insulins, leading to more efficient therapies for diabetes management. “One such insulin, Conus geographus G1 (Con-Ins G1), is the smallest known insulin found in nature and lacks the C-terminal segment of the B chain that, in human insulin, mediates engagement of the insulin receptor … We found that Con-Ins G1 … strongly binds the human insulin receptor and activates receptor signaling. Con-Ins G1 thus is a naturally occurring mimetic of insulin, mediates engagement of the insulin receptor … These structural findings provide a platform for the design of a novel class of therapeutic human insulin analogs that are intrinsically monomeric and rapid acting.” The study was published in Nature Structural and Molecular Biology on 13 September.

Sugar industry sponsored anti-fat research

A report published online by JAMA Internal Medicine examined the sugar industry’s role in coronary heart disease research and suggested the industry sponsored research in the 1960s and 1970s designed to influence the scientific debate to cast doubt on the hazards of sugar and to promote dietary fat as the culprit in heart disease. Researchers from the University of California used archival documents from the Sugar Research Foundation (SRF), which later evolved into the Sugar Association, historical reports and other material to create a chronological case study. The SRF initiated coronary heart disease research and examined its conclusions is circumstantial, the authors acknowledged. There also is no direct evidence that the sugar industry wrote or changed the review manuscript and evidence that the industry shaped its conclusions is circumstantial, the authors acknowledged. The review focused on the Sugar Association, historical reports and other material to create a chronological case study. The SRF initiated coronary heart disease research and examined its conclusions is circumstantial, the authors acknowledged. There also is no direct evidence that the sugar industry wrote or changed the review manuscript and evidence that the industry shaped its conclusions is circumstantial, the authors acknowledged. 

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2. Research: Variation in coronary angiography rates in Australia: correlations with socio-demographic, health service and disease burden indices
   Chew et al; doi: 10.5694/mja15.01400

   Chew et al; doi: 10.5694/mja16.00368

4. Research: Contemporary type 1 diabetes pregnancy outcomes: impact of obesity and glycaemic control
   Abell et al; doi: 10.5694/mja16.00443

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The possible risks of proton pump inhibitors

These drugs have revolutionised the management of gastrointestinal diseases, but their long term use may have risks

Proton pump inhibitors (PPIs) suppress gastric acid secretion by selectively inhibiting the enzyme hydrogen–potassium adenosine triphosphatase, located in gastric parietal cells. These drugs superseded H2-receptor antagonists as first-line acid suppressants in the 1980s, and their potent effect has revolutionised the management of common upper gastrointestinal (GI) disorders, including gastro-oesophageal reflux disease, peptic ulcer disease, and functional dyspepsia. These drugs are also widely used as part of regimens designed to eradicate Helicobacter pylori infection, and as prophylaxis against the deleterious effects of non-steroidal anti-inflammatory drugs on the GI tract.

PPIs are among the most commonly administered medications worldwide. In recent years, there has been a marked increase in prescribing PPIs,1 concurrent with an overall reduction in their cost with the advent of inexpensive generic formulations. This reduction in cost is likely to have contributed to injudicious overprescribing of PPIs, with up to 60% of primary care physicians making no attempt to reduce patients’ doses over time, and almost 50% of patients receiving long term PPI therapy having no clear indication for its continuation.2 Despite their well documented benefits, the use of PPIs may be associated with an increased risk of certain GI and non-GI conditions.

Gastrointestinal risks of proton pump inhibitor use

Commensal bacteria are thought to influence and maintain metabolic and immune pathways in the gut. Manipulation of GI microbiota has been identified as a potential target for therapeutic intervention in the management of several GI disorders, including irritable bowel syndrome and inflammatory bowel disease, by means of faecal microbial transplantation or the use of prebiotics, probiotics, symbiotics or antibiotics. Changes in the faecal microbiome have also been identified in PPI users, with a reduction in the diversity of bacterial communities observed in the gut,3 presumably secondary to the alteration in pH of the intestinal luminal contents. This reduction in bacterial diversity may be associated with an increased risk of developing GI infections. A meta-analysis of observational studies reported increased odds of taking PPIs for patients with Clostridium difficile-associated diarrhoea (odds ratio [OR], 1.96; 95% CI, 1.28–3.00) and other enteric infections, including with Salmonella and Campylobacter species (OR, 3.33; 95% CI, 1.84–6.02).4 Aside from any potential association with enteric infection, diarrhoea is a common side effect of PPI use. The cause of this is uncertain, although a case–control study noted increased odds of microscopic colitis (OR, 3.37; 95% CI, 2.77–4.09),5 and, in a meta-analysis, small intestinal bacterial overgrowth (SIBO) was found to be more common in PPI users (OR, 2.28; 95% CI, 1.24–4.21).6 Given that both of these conditions present with diarrhoea, which is a side effect of PPIs, it may be that this association is the result of detection bias, as individuals using PPIs are more likely to be investigated to rule out microscopic colitis or SIBO.

The hypergastrinaemia documented in long term PPI users has led to concerns about the possibility of enterochromaffin-like cell hyperplasia being associated with PPIs, and therefore a theoretical increase in the risk of neuroendocrine tumour development, although this has not been substantiated.7 Observational studies also report an increase in the incidence of gastric fundic gland polyps (FGPs) in patients using PPIs long term. Although these polyps are benign, this has raised the possibility that long term PPI use could lead to an increased risk of gastric cancer. A recent systematic review and meta-analysis investigating the association between PPI use and the incidence of FGPs suggested a statistically significant increase in the odds of developing such polyps (OR, 2.45; 95% CI, 1.24–4.83), with a longer duration of exposure further increasing this risk.8 In the same meta-analysis, the risk of PPI-associated gastric cancer was examined in a small number of studies of heterogeneous design, and a small increase in the risk of gastric cancer was observed (risk ratio [RR], 1.43; 95% CI, 1.23–1.66). However, follow-up in these studies extended to a maximum of 36 months, a timeframe one would consider too short to develop gastric cancer de novo. This suggests that the association may be the result of protopathic bias, or reverse causation, with PPI therapy more likely to be initiated in individuals presenting with dyspepsia, which may herald early gastric cancer.

The anti-secretory properties of PPIs can also lead to the development of vitamin B12 and magnesium deficiencies. Gastric acid is required to facilitate the breakdown of digestible vitamin B12, and the risk of vitamin B12 deficiency may be increased in people with achlorhydria. In a retrospective case–control study investigating risk factors for the development of vitamin B12 deficiency, PPI exposure greater than 2 years was associated with a significant increase in the odds of vitamin B12 deficiency (OR, 1.65; 95% CI, 1.58–1.73), with a dose–response relationship observed.9 Similarly, the intestinal absorption of magnesium is adversely affected by an increase in luminal pH. A meta-analysis of studies examining this question also suggested increased odds of hypomagnesaemia with PPI use (OR, 1.78; 95% CI, 1.08–2.92).10 The United States Food and Drug Administration recommends monitoring of serum magnesium levels before commencing PPI therapy and periodically thereafter if long term use is likely to be required.
Conflicting evidence regarding the association between PPI use and the risk of bone fracture has been reported. Potential pathophysiological mechanisms include impaired intestinal calcium absorption and alterations in bone metabolism, mediated by inhibition of osteoclast proton pumps. A meta-analysis reported increased odds in patients taking PPIs of hip fracture (OR, 1.25; 95% CI, 1.14–1.37) or vertebral fracture (OR, 1.50; 95% CI, 1.32–1.72). However, no dose–response relationship was observed and significant heterogeneity was noted. Given the observational nature of the included studies, it is likely that these findings are secondary to unmeasured confounding, with PPI users being more likely to have a comorbid condition, such as obesity or tobacco smoking, that is associated with both PPI use and an increased risk of fracture.

The association between PPI use and community-acquired pneumonia (CAP) has been investigated, again with conflicting results from the numerous observational studies. A meta-analysis of these studies indicated an increase in the odds of developing CAP with short term PPI use (OR, 1.92; 95% CI, 1.40–2.63), but not with prolonged use (OR, 1.11; 95% CI, 0.90–1.38). This lack of a dose–response relationship, the absence of any plausible pathophysiological mechanism to explain the association, and the significant heterogeneity of the included studies cast doubt on this association, again suggesting prescription channelling may have influenced the study findings.

The most common side effect of antiplatelet medication is GI haemorrhage secondary to peptic ulcer disease, resulting in the prophylactic use of PPIs for gastrointestinal protection in many patients with cardiovascular disease. A reduction in the in vitro antiplatelet effect of clopidogrel, when used in conjunction with omeprazole, led to concerns about a possible increase in cardiac event rates when these drugs were co-prescribed after percutaneous coronary intervention. However, a randomised controlled trial (RCT) investigating the incidence of GI complications and subsequent cardiac events in patients randomly allocated to receive either dual antiplatelet therapy and omeprazole, or dual antiplatelet therapy and placebo found that there was no difference in the cardiac event rate in patients receiving omeprazole or placebo (hazard ratio [HR], 0.99; 95% CI, 0.68–1.44), but a significant reduction in overt upper GI bleeding was noted with omeprazole (HR, 0.13; 95% CI, 0.03–0.56).

The incidence of dementia is increasing. A recent cohort study suggested PPI use may be a risk factor for the onset of dementia in patients aged over 75 years, after adjusting for potential cardiovascular, cerebrovascular, and pharmacological confounders (HR, 1.44; 95% CI, 1.36–1.52). However, morbidity and mortality associated with adverse events, including those associated with GI bleeding, were not assessed, meaning that the effect of unmeasured confounding could not be accounted for, and, in a case–control study, PPIs appeared to protect against dementia (OR, 0.93; 95% CI, 0.90–0.97). Despite this, it is plausible that PPIs may increase the risk of dementia, as there is evidence suggesting that PPIs cross the blood–brain barrier, and may promote the production, or impair the degradation, of amyloid, although another potential mechanism could be through the effects of PPIs on vitamin B₁₂ absorption, as discussed above.

Conclusion

Although PPIs have revolutionised the management of several upper GI disorders, their use may be associated with intestinal and extra-intestinal complications. Most studies that have exposed these risks are observational and retrospective in nature. In the only RCT that has examined the impact of one of these associations on patients, no increase in the risk of cardiac events was observed with PPIs. Unlike RCTs, the inherent flaws of observational studies do not account for unmeasured bias and confounding, and only provide evidence for the presence or absence of an association, rather than a causal link between PPI use and the risk of such complications. Moreover, the magnitude of the increased associations observed in many of these studies, although statistically significant, is unlikely to be large enough to be clinically relevant, and is probably explained by a combination of residual confounding, prescription channelling, and protopathic bias. Patients should therefore be informed that the benefits of PPIs outweigh any potential deleterious effects.

Nevertheless, just like any other drug, PPIs should be prescribed judiciously, with a clear indication and a long term use to minimise these theoretical risks. Currently, no routine monitoring of PPIs is recommended other than periodic measurement of serum magnesium levels if long term use is required.

Competing Interests: No relevant disclosures.

Provenance: Commissioned; externally peer reviewed.
Biosimilars in inflammatory bowel disease

Cost savings are welcome but evidence supporting equivalence of biosimilar and originator drugs is currently limited

The management of inflammatory bowel disease has undergone major changes in the last decade with the availability on the Pharmaceutical Benefits Scheme (PBS) of targeted biological therapies. The first of these was the anti-tumour necrosis factor α (anti-TNF-α) monoclonal antibody infliximab, followed by another anti-TNF-α antibody adalimumab, and, more recently, the first gut-specific T-cell trafficking inhibitor vedolizumab, an anti-α-4 β-7 integrin monoclonal antibody. These drugs have resulted in a shift in the management paradigm from symptom control and the minimisation of exposure to corticosteroids to now aiming for healing of the intestinal mucosa, prevention of damage and subsequent disability.

The development of biologic medication is comparatively long and the manufacturing process very expensive, resulting in a high cost for these agents. In Australia, the most expensive single drug in absolute dollar value for the 2015 financial year was adalimumab, with biologic agents making up five of the top eight most costly drugs and accounting for over 12% of the total PBS spend. Given the increasing incidence of diseases that may be best managed by biologic agents, and the prolonged duration of therapy involved, the costs of these drugs are rising annually. These cost increases could pose a significant risk to the sustainability of the PBS system.

The patents for the initial biologic agents are starting to expire, which has led to the development of what are known as biosimilar versions of the originator product. These competitor drugs have created pressure to reduce the cost for the health system. The first biosimilar to infliximab was listed on the PBS in December 2015.

Biologic therapies are very different from chemically synthesised drugs, typically being large protein-containing agents produced from recombinant DNA and cell culture techniques, with complex post-translational modification and glycosylation. The technique of production can result in significant variability even between batches of production and requires strict quality assurance and in vitro assessments. The Therapeutic Goods Administration (TGA) has harmonised with and adopted a number of the guidelines of the European Medicines Agency regarding the assessment and approval of biosimilar medicines. To be considered a biosimilar medicine in Australia, the new product must have “demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety”. Despite this, these drugs are not considered to be identical or to have demonstrated bioequivalence with the originator biological medicine.

The major difference in the approval process between an originator drug and a biosimilar is that if the originator drug has more than one indication, the efficacy and safety of the biosimilar may only need to be demonstrated in one indication and this will be extrapolated to the other disease indications in which the originator drug is approved. The randomised controlled trials for the biosimilar infliximab CT-P13 (now commercially available in Australia) were only required in ankylosing spondylitis and rheumatoid arthritis and not Crohn disease or ulcerative colitis. The listing for the biosimilar infliximab on the PBS covers all the indications of the originator infliximab.

Cost savings accompany the listing of biosimilar agents on the PBS, with a mandated 16% drop in the PBS rebate and a move from the F1 to F2 formulary, where the drugs are then subject to application of the PBS price disclosure policy. This assesses the actual cost of supplying the drug to retail pharmacies and results in further adjustment and reduction of the PBS rebate over time to more accurately reflect the cost price.

Despite the welcome cost reductions that have accompanied the arrival of the first biosimilars, unanswered questions remain about their long term interchangeability with the originator product. All biologics are immunogenic and can result in antibody formation, reactions, and loss of efficacy with time. Up to 20% of patients on maintenance therapy may develop antibodies to anti-TNF-α monoclonal antibodies. Given
that biosimilar drugs are not identical, there is a theoretical risk that switching between agents may result in the development of neutralising anti-drug antibodies (ADAs) and subsequent loss of response. At present, there are some reassuring data from the open label extension studies of the PLANETAS and PLANETRA studies, where there were no significant differences in the rate of ADA formation between patients who continued on the biosimilar product and those who had a single switch from originator infliximab to the biosimilar infliximab at 1 year; however, trough drug levels were not reported.\(^9\)\(^10\) ADAs in the presence of low or absent drug levels are strongly associated with clinical loss of efficacy.\(^11\) Since the introduction of the biosimilar infliximab in Europe, several countries have mandated a single switch. The early data are reassuring but, as yet, only reported in small numbers and in abstract form, and a large Norwegian randomised controlled trial has recently been completed (https://clinicaltrials.gov/ct2/show/NCT02148640).

Further reassuring data were seen in the cross-reactivity of ADA from patients with the originator infliximab having near identical binding to the biosimilar infliximab CT-P13; however, this has not been demonstrated in reverse.\(^12\) The vast majority of ADAs to anti-TNF-\(\alpha\) monoclonal antibodies appear to be against the fragment antigen-binding region and may be neutralised by the addition of TNF-\(\alpha\). This reaction to TNF-\(\alpha\) would be expected to be identical for originator and biosimilar agents and less prone to interference due to glycosylation and conformational changes.\(^13\)

At present, studies have investigated a single switch between the originator and the biosimilar anti-TNF-\(\alpha\) agent, whereas multiple switch and switch-back strategies have not been assessed. The Australian government has stated that biosimilar and originator anti-TNF-\(\alpha\) agents can be considered interchangeable at the point of dispensing from the pharmacy, as is the case with small-molecule generic medicines. This practice known as “a-flagging” and requires patient consent.\(^4\) This may result in patients electing to receive a different anti-TNF-\(\alpha\) agent at each time point of dispensing. Under the legislation, the only way a prescriber can ensure that a patient is continued on the initially prescribed biologic agent, be that either a biosimilar or an originator biologic, is to tick the “brand substitution not permitted” box on the prescription.

This decision has caused the greatest concern for prescribing clinicians and representative bodies. The absence of data to suggest adverse reactions or the development of ADA from multiple switching does not imply safety.

At the point of registration, biosimilars are required to satisfy the criteria of similarity to the originator, but the TGA has stated that it is “inevitable that reference and biosimilar medicines will diverge to some degree after comparability has been established”.\(^14\) In theory, this increases the chance of antigenic changes developing, and no clinical studies have assessed this to date. There has been no additional pharmacovigilance program instituted to monitor the outcomes of a-flagging, with only the drug sponsor required to develop a risk management plan and a reliance on voluntary reporting by prescribers of adverse outcomes to the TGA. This could be considered equivalent to conducting a clinical trial on the Australian public without the means to accurately capture data such as loss of response, requirement for corticosteroid therapy, or milder adverse reactions that may not result in reporting. However, a consultation process by the government on this with relevant stakeholders is ongoing.

Infliximab is only given intravenously, but the next biologic agents to come off patent that will result in biosimilars entering the market will be self-injectable (for example, etanercept and adalimumab for rheumatoid arthritis). The parenteral administration of these agents is far more complex than the taking of an oral agent and requires familiarity and ability to use the delivery devices. Further, many patients utilise and are dependent on patient support programs that are supplied by third party providers while being funded by the pharmaceutical companies. The viability of these important programs for patients who are potentially undergoing switches between biologic products is unknown.

A significant number of inflammatory bowel disease patients also require dose escalation to maintain clinical response, beyond the fixed dosing regimens funded by the PBS. At present, the compassionate access programs of the pharmaceutical companies provide these additional doses, with the PBS recently rejecting a submission to provide dose tailoring. With the potential for a patient to receive multiple versions of the same biologic, where there are no safety data supporting this practice, the provision of compassionate doses is also under threat.

The arrival of biosimilars is welcomed by clinicians for the cost savings they bring to our health system, but ongoing studies and pharmacovigilance are required in a framework that captures clinical response data. The decision to allow a-flagging in this area of limited evidence has caused concerns for clinicians and patients alike. Ongoing education of prescribers, pharmacists and patients is required, and the minimisation of unnecessary switches until more safety data are available is recommended.

Competing interests: I am the current chair of the Australian Inflammatory Bowel Disease Association of the Gastroenterological Society of Australia, a board member of Crohn’s & Colitis Australia, and have been on advisory boards and/or received speaker fees from the following manufacturers of biological medicines: AbbVie, Janssen, Hospira and Takeda.

Provenance: Commissioned; externally peer reviewed.

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References are available online at www.mja.com.au.
No Jab, No Pay — no planning for migrant children

Migration should be considered by immunisation policy

The Social Services Legislation Amendment (No Jab, No Pay) Act 2015 (Cwlth) was passed in November 2015, closing the conscientious objection exemption to immunisation requirements for family assistance payments. The intention was to reinforce the importance of immunisation and protect public health, especially for children. While these aims are sound, there are far-reaching, presumably unintended, consequences for migrant and refugee children.

The legislative changes (which took effect in January 2016) require children and young people under 20 years of age to be up to date for their early childhood immunisations in order to qualify for the Child Care Benefit, Child Care Rebate and Family Tax Benefit Part A supplement (Box). These Centrelink payments are available for Australian citizens and people holding a permanent visa (including offshore humanitarian entrants), special category visa or certain temporary visas (including temporary protection visas). Immunisation status is assessed through the Australian Childhood Immunisation Register (ACIR), which is linked to Medicare.

Medical contraindications (including immunosuppression and anaphylaxis) and natural immunity are still grounds for vaccination exemption. However, the legislation now specifies that only general practitioners can certify exemptions, with the expectation that specialists will refer back to GPs. The legislation is paired with a number of supporting measures, including funded catch-up immunisations (time-limited for people aged 10–19 years), expansion of the ACIR to include all people under 20 years of age, and provider incentive payments for catch-up vaccination in children aged less than 7 years.

There are multiple issues arising for refugee and migrant children. First, any child arriving and receiving catch-up vaccination in Australia after the age of 7 years who is eligible for these Centrelink payments will lose them until their ACIR record is updated, even if he or she is fully immunised. Before 1 January 2016, the upper age limit for data entry into the ACIR was 7 years — overseas and catch-up vaccinations could not be recorded on the register for older children. Australia’s Humanitarian Programme intake has been 13750 people annually, with around 50% aged less than 18 years on arrival. Therefore, up to 35 000 refugee children and young people (those who have arrived at the age of 7 years or older and are currently under 20 years of age) will need their vaccination status assessed and ACIR records entered. This number will increase when other migrant children meeting the residency requirements for Centrelink payments are included.

The workforce challenges regarding the No Jab, No Pay measures are substantial. Immunisation providers across Victoria report that refugee families have received (multiple) letters from Centrelink. This has resulted in large numbers of people presenting to services, and an increased demand for providers to clarify previous vaccination history, notify the ACIR of these details, and provide catch-up vaccines where needed. Providers report being inundated, under-prepared and inadequately resourced to meet demand.

Family assistance payments affected by the No Jab, No Pay measures

- Family Tax Benefit Part A (FTB-A) is a two-part payment supporting disadvantaged families with dependent children or secondary students younger than 20 years of age, consisting of an adjusted base rate and a supplement of up to $726.35 per child at the end of the financial year. The maximum adjusted taxable income limits for FTB-A are over $100 000, and it is likely most refugee background families will be eligible for this payment.

- The Child Care Benefit supports costs of registered/approved childcare and outside-school-hour care, with current rates of $4.17 per hour or $208.50 per week (85% for school-aged children), which is income-tested and adjusted for family size, service type and hours attended.

- The Child Care Rebate (non-income-tested) covers 50% of out-of-pocket expenses for childcare to an annual limit for each child, in addition to other childcare assistance.

- Together, these benefits are a substantial support for families with children. For further information, go to https://www.humanservices.gov.au/customer/subjects/payments-families.
Establishing prior vaccination is difficult, time consuming, and may not be possible. Refugee-background families tend to be mobile in the early years of settlement, and often see multiple providers for health care, which may (or may not) include immunisation. Children may receive vaccinations in different parts of the health system — from GPs, from specialists, at school, and, particularly in Victoria, through local government areas (LGAs). However, comprehensive records are rare, and information about past vaccinations is often unavailable.

Reporting to the ACIR is time consuming, and there is variation in how information is handled. Providers estimate it takes 20 minutes to enter a full vaccine history into the ACIR online, and longer if overseas vaccinations are recorded. They report delays between submission and registration of data on the ACIR. While on-site vaccines are usually registered within 24 hours, prior vaccines (administered in Australia or overseas) take 1–3 weeks, and individual errors can result in batches of ACIR entries being rejected, affecting ACIR registration for multiple individuals. Many services are now faxing records to the ACIR due to inadequate capacity to enter information directly; these are taking up to 8 weeks to register and delays appear to be increasing. Providers report discrepancies between Centrelink and the ACIR, and cases where families have been sent Centrelink letters, despite children being registered as fully immunised on the ACIR. Paediatricians are the key workforce in childhood immunisation; however, unlike GPs, they are not automatically registered with the ACIR and the process to obtain or activate specialist ACIR registration is complicated. While specialists may have prescribed catch-up vaccines, they are usually not able to enter this information onto the ACIR, which reduces the opportunity to disseminate the workload and enhance ACIR recording.

Catch-up immunisation generally requires three visits over at least 4 months (four visits over 10 months for children aged 4–9 years), with several vaccines on each visit. Calculating catch-up schedules for migrant children is complex and far more difficult than providing a missed dose schedule point for an Australian-born child. Primary Health Networks and LGAs report that many GPs feel poorly equipped to deal with this complexity and the time requirements and, in Victoria, are deferring this work to LGAs.

The increase in workload is not reflected in funding arrangements, and the new provider catch-up incentive payments are not structured to support best practice immunisation. Catch-up incentive payments ($6 additional to ACIR notification payments) are only available for children aged less than 7 years, and for vaccines given after 1 January 2016 that are more than 2 months overdue. Thus, if an immunisation provider gives the first doses of a catch-up schedule and recalls the child 1 month later (the minimum interval and best practice), the second vaccinations will not trigger a catch-up incentive payment, as they are not considered to be overdue in relation to the first. Further, the national due and overdue rules in relation to hepatitis B are not consistent with the minimum catch-up dosing intervals recommended by the Australian immunisation handbook.9 Hepatitis B vaccination at 0, 1 and 4 months (minimum intervals) will register the child as overdue at the time of the final dose (3 months from previous dose), risking loss of Centrelink payments.

Finally, there is complexity concerning medical contraindications and natural immunity, in that the new legislation specifies that only GPs can provide this information. Many refugee children do not require hepatitis B (or other) immunisations, on the basis of natural immunity from infection or immunity from (undocumented) overseas vaccination. Hepatitis B serology is part of the routine post-arrival refugee health assessment, detecting both infection and immunity. Available Australian data suggest that around 30% of East African and 50% of Karen refugee children have immunity to hepatitis B,10,11 and 2–5% of African children are infected with hepatitis B.12 Many children have thus completed catch-up vaccination without needing hepatitis B (or other) vaccines, but will not be regarded as up to date on the ACIR. They will need a medical exemption form completed by a GP; however, many families have changed GPs in the years after settlement and/or were initially managed and immunised at specialist or nurse-led clinics. GPs will likely be asked to enter historical information on behalf of other providers (which will be almost impossible to verify) and there may be considerable reluctance to do so.

These issues are likely to create duplications within the health system in:

- appointments — where children had specialist refugee health screening, it is feasible that an LGA may refer children to GPs who may refer them to specialists to clarify immunisation history and serology, who will then refer children back to the GPs for the medical exemption form, who in turn refer them back to the LGA for vaccine delivery;
- serology — where there is no documentation, GPs and specialists (and families) may choose repeat hepatitis B serology instead of undertaking three immunisation visits; or
- vaccines — where vaccination history or natural immunity cannot be established.

All these options incur additional costs and represent inefficiencies in the health system.

While the No Jab, No Pay policy offers an opportunity to improve immunisation coverage rates, the legislation will exclude thousands of Australia’s most disadvantaged families from Centrelink payments as a result of system issues rather than any form of conscientious objection. Clinical experience suggests that refugee background families are extremely pro-immunisation, which is consistent with the large numbers presenting to clarify their children’s immunisation status and access catch-up vaccinations. Unfortunately, the legislative and policy changes presume continuity of care, administration of early childhood vaccines during early childhood, prior use of the ACIR, and centralised immunisation delivery, which is not the reality for migrant families.
There are several strategies that could reduce the impact of the No Jab, No Pay measures on migrant children. There is a strong argument to apply the legislation prospectively (to children born 2009 onwards) or to extend the period before Centrelink payments are affected, allowing adequate lead time for entering data into the ACIR and obtain catch-up vaccination if needed. Due and overdue rules and catch-up incentive payments should be structured to support best practice, including removal of the payment age limit. Funding for catch-up vaccinations in those aged 10 years and older should be ongoing, and better resources to support providers, including a whole-of-life calculator and information on refugee immunisation, would increase efficiency and remove barriers to service delivery. Extending the ACIR across the lifespan offers an opportunity to address usability issues and capture relevant demography to monitor immunisation in this group. Finally, authority to document medical exemptions, specialist ACIR registration and workforce pressures require urgent attention. Fundamentally, good policy development should recognise that migration is part of the fabric of Australia, and it is not clear this has been adequately considered in the implementation of No Jab, No Pay.

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References are available online at www.mja.com.au.
Central retinal venous pulsations

Diagnosing raised intracranial pressure through ophthalmoscopic examination

The ophthalmoscope is one of the most useful and underutilised tools and it rewards the practitioner with a wealth of clinical information. Through illumination and a number of lenses for magnification, the direct ophthalmoscope allows the physician to visualise the interior of the eye. Ophthalmoscopic examination is an essential component of the evaluation of patients with a range of medical conditions, including diabetes mellitus, systemic hypertension and conditions associated with raised intracranial pressure (ICP). The fundus has exceptional clinical significance because it is the only location where blood vessels can be directly observed as part of a physical examination.

Optic disc swelling and central retinal venous pulsations are useful signs in cases where raised ICP is suspected. Both signs can be obtained rapidly by clinicians who know how to recognise them. Although optic disc swelling supports the diagnosis of raised ICP, the presence of central retinal venous pulsations may indicate the contrary.

In the standard technique for direct ophthalmoscopy, the patient is positioned in a seated posture and asked to fix their gaze on a stationary point directly ahead. Pupillary dilation, removal of the patient’s spectacles and dim room illumination usually aid the examination. To start examining the patient, set the ophthalmoscope dioptres to zero — alternatively, a suitable setting would be the sum of the refractive errors of the patient and the examiner. Use the right eye to examine the patient’s right eye and vice versa. Using a slight temporal approach facilitates the identification of the optic disc, which also minimises awkward direct facial contact with the patient. Examine the red reflex at just under arm’s length. A pale or absent red reflex may suggest media opacity, such as a cataract.

Next, on approaching the patient and obtaining a clear view of a retinal vessel, follow its course toward the optic disc. The presence or absence of venous pulsations should be appreciable (see the video at www.mja.com.au; pulsations of the central vein are clearly visible at the inferior margin of the optic disc). These pulsations, usually of the proximal portion of the central retinal vein, are most readily identified at the optic disc. The examination of the fundus should be concluded by visualisation of the four quadrants of the retina and examination of the macula.

Central retinal venous pulsations are traditionally attributed to fluctuations in intraocular pressure with systole, although this may be an incomplete explanation. Patients with central retinal venous pulsations generally have cerebrospinal fluid pressures below 190 mmHg. Based on the results of Wong and White, the positive predictive value for retinal venous pulsations predicting normal ICP was 0.88 (0.87–0.9) and the negative predictive value was 0.17 (0.05–0.4).

This is important when considering lumbar puncture and when neuroimaging is not available. A limitation of this sign is that about 10% of the normal population do not have central retinal venous pulsations visible on direct ophthalmoscopy. The absence of central retinal venous pulsations does not, by itself, represent evidence of raised ICP; some patients with elevated ICP may still have visible retinal venous pulsations.

Papilloedema (optic disc swelling caused by increased ICP) may develop after the loss of retinal venous pulsations. This change in the appearance of the optic disc and its surrounding structures may be due to the transfer of elevated intracranial pressure to the optic nerve sheath. This interferes with normal axonal function causing oedema and leakage of fluid into the surrounding tissues. Progressive changes include the presence of splinter haemorrhages at the optic disc, elevation of the disc with loss of cupping, blurring of the disc margins, and haemorrhage. In later stages, there is progressive pallor of the disc due to axonal loss. A staging scale, such as that of Frisén, can be used to reliably identify the extent of papilloedema (Box).

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References are available online at www.mja.com.au.
Neurofibromatosis of the tongue

A 45-year-old woman presented with a painless mass in the tongue that had grown gradually over the past 20 years (Figure, arrowheads). She had café-au-lait spots and previous neurofibroma resections. Neurofibromatosis type 1 was also found in her father and two children. Recent speech problems made a resection necessary. Partial removal of the mass immediately improved communication. Pathological analysis showed plexiform neurofibroma without malignant transformation. Neurofibromatosis type 1 is an autosomal dominant disorder characterised by neurofibromas that can potentially affect every site of the body. Malignant transformation is rare and resection is indicated when functional or aesthetic impairment is associated.1

References are available online at www.mja.com.au.

Oral health: an important consideration in patient care

Severe radiation caries, which caused major psychological distress to the patient, occurred in a 57-year-old man after treatment for recurrent squamous cell carcinoma in the base of the tongue. Despite a post-radiation caries prevention program, surgical and radiation complications caused an inability to maintain effective oral hygiene, resulting in the progression of radiation caries (Figure). One month after the photograph in the Figure was taken, the patient underwent total hip replacement surgery. During subsequent post-operative appointments, the patient received antibiotic prophylaxis but dental rehabilitation was delayed by 3 months to avoid potential early infection of the implant. This serves as a reminder to medical practitioners to encourage patients to seek regular dental care and consider a dental assessment before major surgery.
A medical student’s first experience of theatre

Disrupting the neat choreography and finding my part in it

After weeks of trawling through abstracts and entering data into Excel spreadsheets for a summer research project, my supervisor asked whether I would like to go into theatre to watch a thyroidectomy. Of course, my heart leapt at the thought. As a first year student, I had never been into theatre so I had no idea of what to expect. I wondered whether watching all of *Gray’s anatomy* would help and whether my anatomy knowledge would be up to scratch.

I was told to arrive at 6 am outside the change rooms, much too early for me to fit in breakfast. The consultant told me to meet him on the other side and, in my hurry to not hold him up, I put my scrubs on backwards and left my name tag in my bag. At last, I came out the other side feeling confident and ready for action. The start of the surgery was like a ballet, from the elegant pirouette of the surgeon as he spun around to put on his gown to the blinding theatre lights and the exact positioning of everyone in the room — not a centimetre out of place.

I had an awful sense that I was disrupting this neat choreography.

The consultant ushered me closer and told me to place my hands on the patient. Next, he told me to switch positions with the registrar so that I could hold a retractor. I stood like a statue, petrified that I might do something wrong or get in the way. I became fixated on the carotid artery, red and pulsating. I felt terrible. I had never fainted before but I felt as though I was going to. I became acutely aware of the beeping of the monitors and the smell of burning flesh. I looked at the scrub nurse but could not articulate what was going on. She seemed to know and calmly grabbed the instrument off me, while I inched slowly backwards towards the wall. I did not actually lose consciousness but the anaesthetist told me to go and have something to eat. Why did I not have breakfast?

The anaesthetist found me in the kitchen. I was so embarrassed about what had happened. He reassured me that at least once a month a new student faints and that, in fact, I had done an excellent job of recognising the signs and walking away from the table so as not to cause any distraction. He told me I had a decision to make. I could go home or I could come back for the next operation. I decided I should do just that and followed him back inside. I successfully watched three more thyroidectomies without any problem. I was also pleased to learn that the surgeon did not even know that I had left the room.

Early emotional experiences in the theatre can have a detrimental impact on students’ learning and future career choices. Interviews of medical students carried out by Bowrey and Kidd1 suggested that negative feelings surrounding the theatre were common and included concerns about violating theatre protocol as well as a fear of syncope. Jamjoon and colleagues2 reported that 12% of penultimate and final year students experienced near or actual syncope in the theatre and 9% reported being discouraged from pursuing a surgical career by a syncopal episode. The study found that the most useful measures that students could employ to avoid syncope were eating before the surgery and leg movements when standing for prolonged periods.

It is common for medical students to feel anxious about new clinical experiences and their first time in theatre is no exception. In an attempt to foster a positive learning experience, some Australian universities have introduced “surgical skills” as part of their first or second year programs. In these sessions, students learn to scrub in an environment where they feel comfortable and supported. They may also participate in mock theatre demonstrations and explore the role of each member of the surgical team. Students who feel knowledgeable about sterility, surgical attire and the surgical environment before they enter theatre will be more confident and able to focus on their learning. Before the surgery, students can prepare by revising the patient’s condition as well as the planned surgical procedure.3

Orientation days at teaching hospitals could provide students with the chance to familiarise themselves with the operating theatre environment before they attend a surgery. Staff can help remove the stigma around syncope by directly raising the issue and suggesting preventive measures. It helps if they are approachable and encouraging and make students feel socially included within the theatre team.4 These strategies may ensure that students are well prepared and have a positive learning experience.

In theatre, students will learn more about anatomy than they ever could from a cadaver or a textbook. They are able to put their theoretical knowledge into practice and observe the treatment of a condition from start to finish. They begin to appreciate the unique relationship of trust

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between the patient and doctor and the importance of working well within a team. In teaching students, supervisors should reflect on their own early clinical years and be mindful of their ability to inspire a love of surgery in the next generation of doctors.

On a personal note, I have realised that there is no need to be embarrassed about what happened during my first experience of theatre and that I can learn much from it to inform my clinical years. However, it was certainly an experience that I will not forget.

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References are available online at www.mja.com.au.

Poem

Being good

People said: “But you’re so beautiful just as you are”. Eyes fell upon you in the thousands. Colonised.

Your skin would not become translucent. Your flesh kept pushing into the air.

Inside you learned to carve out spaces. Potter’s hand shapes the clay. You feel the hollows between your bones.

Lightness. A relief after all those eyes, all those words about your body. You were good at so many things. Dolls. Reading. Monkey bars. Cupcakes.

You remember the smell of your skin but not when it started to make you feel sick.

They ask: “Why are you doing this?”

It used to make them happy when you were good.

Now they look scared. But you know what a feat it is, this control. The host, starving its unwanted parasites.

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Irritable bowel syndrome, dyspepsia and other chronic disorders of gastrointestinal function

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New diagnostic criteria and knowledge are changing how patients are treated

In this issue of the MJA, we highlight a number of topics of major interest in gastroenterology, including Barrett’s oesophagus,1 the risks of proton pump inhibitors,2 biosimilars for inflammatory bowel disease,3 and gluten intolerance.4 Chronic or recurrent gastrointestinal symptoms are frequently encountered in primary care.5 Most patients who present with gastrointestinal symptoms do not, however, have inflammatory bowel disease, cancer or another sinister pathology, but rather an unexplained or functional gastrointestinal disorder (FGID).6 The best known FGID is the irritable bowel syndrome (IBS), but there are other FGIDs that need to be recognised, as there is effective management that can improve people’s lives.6-9 The expert consensus is that clinicians should strive to make a positive clinical diagnosis of an FGID on the basis of the patient’s history, and not simply wait for negative test results.6 In 2016, new international guidelines on diagnosis were published, the updated Rome (IV) Criteria (www.theromefoundation.org),6,8 and all clinicians who see patients with chronic gastrointestinal symptoms should be familiar with them.

IBS is not a diagnosis of exclusion, but a characteristic symptom complex that can usually be identified by asking a few simple questions. Patients with IBS present with long standing abdominal pain, directly linked to a disturbed bowel habit (diarrhoea, constipation, or both); they often also have bloating (sometimes with visible distention). The pain is often relieved (but is sometimes aggravated) by defaecation, and at the onset of or during pain the stool is often altered in frequency or form (ranging from liquid to separate nut-like lumps).6 IBS does not cause vomiting, dysphagia, weight loss, nocturnal diarrhoea, bleeding, or anaemia; if these features are present, another diagnosis should be considered and the patient referred for further investigation. Psychological distress (anxiety or depression) commonly accompanies IBS, and there is increasing evidence that in some cases these symptoms begin after and are secondary to the gut disturbances, including dysbiosis and moderate inflammation, which can induce a circulating low grade cytokine storm.5,10

Unless there are specific red flags or severe symptoms, testing of people with clear-cut IBS should be limited; a full blood count (detecting anaemia, for example) and elevated levels of plasma C-reactive protein (or of stool calprotectin) might suggest inflammatory bowel disease.6 If diarrhoea fails to respond to simple interventions, coeliac disease, which can mimic IBS symptoms, should be ruled out by assessing tissue transglutaminase levels; total IgA levels should also be measured, as an IgA deficiency will cause false negative test results.6 In older patients (particularly women) with diarrhoea unresponsive to therapy, microscopic colitis, which can be confused with IBS, should be considered; the diagnosis requires colonoscopy and biopsy (but the yield is low).6 New onset IBS symptoms, including constipation, bloating, lower abdominal pain and early satiety, in a post-menopausal woman should raise suspicion of ovarian cancer (although it is rare).

Another cause of constipation that can be confused with IBS is dyssynergic defaecation, which can be a learned behaviour: some patients strain to defaecate, but at the same time involuntarily contract the external anal sphincter, which should be relaxed. A rectal examination can screen for this problem, and biofeedback training can provide long term relief in about 70% of patients.8 A further frequently unrecognised possibility in patients taking narcotics (for any reason) is narcotic bowel syndrome. Paradoxically, opiates often aggravate chronic pain, leading the patient to take increasing doses that aggravate rather than relieve abdominal pain, resulting in constipation; opiate withdrawal may be beneficial.7

There are further FGIDs that should not be overlooked. A patient who presents with “vomiting” may actually be experiencing effortless regurgitation. The patient’s history will be the best guide; the vomiting reflex makes it impossible to keep vomitus in the mouth and to then spit it out. Effortless regurgitation of food after meals is usually related to rumination syndrome, a learned behavioural response now recognised in otherwise healthy adults and children;9 diaphragmatic re-breathing training applied during and after meals can reduce and even eliminate the problem.11 Patients presenting with genuine vomiting may report that the attacks occur as clear episodes lasting a few days, and that they are reasonably well between attacks; cyclic vomiting syndrome should be considered in these cases, also recognised as occurring in adults and children.9 If the patient indicates that their vomiting is improved by a hot shower or bath (which they will do compulsively), it is highly suggestive of cannabinoid hyperemesis syndrome, and eliminating cannabis use (which many are reluctant to do) usually provides relief.9
Dyspepsia is a common presenting complaint. Early satiety (inability to finish a normal meal) and postprandial fullness are more prevalent than epigastric pain, but all can occur together; most of these patients have functional (non-ulcer) dyspepsia (FD).\textsuperscript{9,12} Helicobacter pylori is recognised not only as a cause of peptic ulcer, but also of FD, and treatment can provide long term relief, albeit only in a minority of cases.\textsuperscript{13} A newly recognised but common syndrome is duodenal eosinophilia in FD; a pathologist needs to count eosinophils in duodenal biopsy will indicate low grade inflammation, but the pathologist needs to count eosinophils in five high power magnification fields to avoid overlooking the abnormality.\textsuperscript{14} This key finding has opened up new treatment opportunities, and even hopes for a cure.\textsuperscript{12}

FGIDs are important and costly conditions.\textsuperscript{6-9} Diagnosis depends in many cases on taking a good history; pathology tests supplement clinical judgement, but should not dominate deliberation by the clinician. There is no evidence that a negative endoscopy reassures an FGID patient;\textsuperscript{15} a positive diagnosis should be based, when possible, on a suggestive history. New insights into the pathogenesis of FGIDs, including the observation of subtle structural changes, suggest that many of these disorders are organic in nature, and cures for some may be available in the near future.\textsuperscript{12}

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The prevalence and clinical associations of HTLV-1 infection in a remote Indigenous community

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The known: The human T-lymphotropic virus type 1 (HTLV-1) is endemic to central Australia according to hospital and laboratory data for Indigenous adults admitted to Alice Springs Hospital. However, the data may underestimate the overall community prevalence of HTLV-1 infection in remote communities.

The new: The prevalence of HTLV-1 infection in a remote Northern Territory community was high: 30 of 74 adults tested were HTLV-1-positive, and nine had clinical syndromes potentially attributable to HTLV-1 infection.

The implications: HTLV-1 infection may be more prevalent among Indigenous Australians and be associated with a greater burden of clinical disease than is currently appreciated.

The human T-lymphotropic virus type 1 (HTLV-1) is an oncogenic retrovirus that preferentially infects CD4⁺ T-cells.¹ Worldwide, at least 5–10 million people are infected with HTLV-1, most dwelling in areas of high endemicity in southern Japan, the Caribbean basin, South America or intertropical Africa.² Transmission typically follows exposure to infected lymphocytes in blood, or through breastfeeding or sexual intercourse. A minority of people infected with HTLV-1 experience a rapidly progressive haematological malignancy (adult T-cell leukaemia/lymphoma [ATLL]) or inflammatory disorders³ such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and HTLV-1-associated pulmonary disease.⁴,⁵ Although the lifetime disease-specific risks for HAM/TSP and ATLL in Japan and the Caribbean are low (0.3–1.9%,⁶,⁷ and 1–5%,¹ respectively), the true burden of HTLV-1-associated diseases has not been determined in a community setting.

HTLV-1 was first identified in central Australia in 1988⁸ and each of the major recognised complications of HTLV-1 have since been described in Indigenous residents of this region.⁹,¹⁰,¹¹ HTLV-1-associated pulmonary disease is particularly common⁶,¹² and contributes to the highest reported adult prevalence of bronchiectasis worldwide.⁹ An impaired immune response also contributes to HTLV-1-associated morbidity by increasing the larval burden of Strongyloides stercoralis in people infected with HTLV-1 living in resource-poor areas.¹³ Notwithstanding seropositivity rates that exceed 30% for Indigenous adults admitted to Alice Springs Hospital,¹⁴ there has been no coordinated program to reduce viral transmission among Indigenous Australians.

The development of strategies for controlling HTLV-1 transmission in Australia is hampered by limitations of the epidemiological data. Indeed, although the HTLV-1c subtype is thought to be endemic to central Australia, this conclusion is based on laboratory data for Indigenous adults admitted to Alice Springs Hospital,² and these data may substantially underestimate the prevalence of HTLV-1 infections in some Indigenous communities. Conversely, only two studies have reported community-based seropositivity rates, for 36¹³ and 13¹⁷ Indigenous people from undefined populations. In endemic areas, such as southwestern Japan, mother-to-child transmission is thought to be the primary mode of transmission,¹⁴ and this is also assumed to be the case in central Australia.¹⁵ Nevertheless, HTLV-1 testing is not currently included in routine antenatal screening.¹⁶ Modes of transmission other than breastfeeding may be important for Indigenous Australians, among whom infection rates are highest for hospitalised men.¹⁰ Community-based studies are essential for defining the epidemiological associations of HTLV-1 infection in Australia and for accurately determining its prevalence. Such work is complicated by the historical burden of mistrust associated with research in Indigenous communities.¹⁷ Here we report the results of a

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community-based survey of HTLV-1 infection using a culturally safe model that integrated clinical research with a health literacy program; it is the first such community-based survey to be reported. In addition to determining HTLV-1 seroprevalence and its clinical associations, we quantified the number of infected peripheral blood cells with a recently developed HTLV-1c proviral load (PVL) test. A higher HTLV-1 PVL is associated with ATLL and peripheral blood cells with a recently developed HTLV-1c proviral load (PVL) test. A higher HTLV-1 PVL is associated with ATLL and

Methods

A single remote Northern Territory Indigenous community (estimated resident population [2015], 138) was selected for our pilot study, conducted during two visits, 25–29 August 2014 and 15–19 June 2015.

Phase 1: community engagement

A knowledge translation process and health literacy resources were developed during visits to the community by an Aboriginal research officer (CP) and a non-Indigenous academic (KT). These resources were used by a clinician (LE) during two subsequent visits for discussing (through an interpreter, CP) the major disease associations and the risk of HTLV-1 transmission by sexual contact or exposure to infected blood. Given current uncertainties about the predominant mode of transmission and the clear benefit of breastfeeding in remote Indigenous communities, mother-to-child transmission was not discussed. Health messages were provided separately to men and women.

Phase 2: clinical survey

Male and female Aboriginal team members again provided health literacy information. Individuals were then invited to participate in the study, and consent was obtained in their primary language. The clinical survey incorporated a health questionnaire and a limited physical examination. Data collected included self-reported co-morbid conditions and respiratory, gastrointestinal, dermatological and neurological symptoms. All surveys were performed while blinded to the HTLV-1 serostatus of the participants. Clinical records were subsequently reviewed to confirm comorbidity data. Physical examination was restricted to a respiratory examination and limited neurological (gait and lower limb tone, power, reflexes and sensation) and dermatological examinations (generally restricted to the head, back, limbs and abdomen).

Whole blood samples were collected into EDTA-coated tubes. Samples were processed at Alice Springs Hospital and forwarded for *Strongyloides* serological testing (Western Diagnostic Pathology, Perth). Peripheral blood buffy coats were recovered and stored at −70°C for HTLV-1 studies. Blood was not collected from children under 2 years of age.

Community residence was determined from the community health clinic registry. Chronic lung disease was defined as a daily productive cough (lasting at least one month) with inspiratory crackles on auscultation of the chest. Diarrhoea was defined as the passage of several loose stools each day for more than 2 days.

HTLV-1 serologic and molecular studies

Analyses were performed at the National Serology Reference Laboratory, Melbourne, blinded to the clinical state of participants. Plasma HTLV-1 antibodies were detected by enzyme immunoassay (Murex HTLV I + II, DiaSorin) and titres determined with a twofold endpoint dilution method by particle agglutination (Serodia-HTLV-1, Fujirebio). All samples reactive on either screening assay were confirmed by western blot (WB) (HTLV-I/II Blot2.4, MP Diagnostics). HTLV-1 infection was defined by a positive WB test result.

HTLV-1 PVL was determined by polymerase chain reaction (PCR) using primers and probes that targeted a highly conserved region at the 5′ end of the gag gene in the p19 coding region of HTLV-1c (Mel5; accession number, L02534). SP cells18 containing a single integrated, full-length copy of HTLV-1 and one copy of the albumin gene were used to generate a standard curve for determining HTLV-1 copy numbers and cell numbers. The number of HTLV-1 copies per peripheral blood leucocyte (PBL) was then calculated. PVL was expressed as HTLV-1 copies/10⁷ PBL. The lower limit of detection was 6.5 copies for HTLV-1 (95% confidence interval [CI], 5.4–8.4) and 15.6 for albumin (95% CI, 12.9–20.0).

Statistical analysis

Categorical variables were compared in χ² or Fisher exact tests as appropriate. Continuous variables were assessed for significant departures from normality. Normally distributed variables were summarised as means and standard deviations, and compared in t-tests. Variables with skewed distributions were summarised as medians and interquartile ranges (IQRs), and compared in Wilcoxon rank-sum tests. All analyses were performed in Stata 14.0 (StataCorp).

Ethics approval

The study was developed in collaboration with Primary Health Care Remote, Central Australia Health Service, Alice Springs. All participants with a clinical condition were referred for appropriate follow-up and treatment. The study was approved by the Central Australian Human Research Ethics Committee (reference, HREC-14-242).

Results

One hundred and four people (75% of the estimated resident population) consented to participate in the study. Blood was not collected from four children, one sample was lost in transit, and a 68-year-old man with chronic lung disease and ataxia declined to give blood. HTLV-1 test results were discordant (PCR-positive, WB-negative) for an 11-year-old boy with crusted scabies whose mother and maternal grandmother were infected with HTLV-1, and he was excluded from the study. The final analysis therefore included 97 participants (70% of the resident population): 23 children (13 boys, 10 girls) and 74 adults (39 men, 35 women).

HTLV-1 seropositivity

HTLV-1 seropositivity rates were significantly higher among adults than among children (30 of 74 v 1 of 23; P = 0.001) (Box 1). Rates were highest among adults aged 35 years or more; ten of the

<table>
<thead>
<tr>
<th>Age category</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (1–14 years)</td>
<td>1 of 13 (7%)</td>
<td>0 of 10</td>
</tr>
<tr>
<td>Adults (15–34 years)</td>
<td>7 of 24 (29%)</td>
<td>6 of 19 (32%)</td>
</tr>
<tr>
<td>Adults (≥ 35 years)</td>
<td>10 of 15 (67%)</td>
<td>7 of 16 (44%)</td>
</tr>
</tbody>
</table>
15 men in this age group and seven of the 16 women were infected with HTLV-1 (Box 1).

Clinical associations
Four adult participants did not wait for clinical review; data are therefore presented for 27 adults infected with HTLV-1 and 43 who were not (Box 2). Although half of all adults reported respiratory symptoms, with eight exceptions these were all acute conditions, without clinical evidence of chronic lung disease. A chronic productive cough with physical signs was found in seven adults (four men, three women), each of whom was HTLV-1-positive (Box 2). Four had never smoked, two were current smokers, and one had a past history of smoking. Bronchiectasis was radiologically confirmed in one 52-year-old man and in two women aged 36 and 54 years by chest high resolution computed tomography (cHRCT); the other four HTLV-1-positive adults with chronic lung disease were not examined with cHRCT. A chronic productive cough with physical signs was found in only one (HTLV-1-seronegative) child; bronchiectasis was not apparent on cHRCT, and a diagnosis was made of chronic supplicative lung disease with reactive airway of uncertain aetiology.

The gait of three adults (two women aged 54 and 71 years and a 48-year-old man) was ataxic. All were HTLV-1-positive and had chronic lung disease. The two women were unable to walk without walking aids. Lower limb power and sensation were normal, and there was no increased muscular tone or hyperreflexia.

All five participants who reported diarrhoea were HTLV-1-positive (Box 2); serological results for Strongyloides were positive in two instances. Rates of Strongyloides seropositivity were not significantly different for HTLV-1-positive and -negative adults (HTLV-1-positive, 6 of 28; HTLV-1-negative, 4 of 44; $P = 0.172$). Three of 15 children tested, including the child with chronic lung disease, were seropositive for Strongyloides and HTLV-1-negative. No participant presented with infective dermatitis, and the only one with crusted scabies was the 11-year-old boy described above.

### HTLV-1 proviral load

The HTLV-1 PVL for one WB-positive participant could not be determined for technical reasons. The median HTLV-1 PVL for the remaining 30 HTLV-1-positive participants was 145 (IQR, 16.3–558) copies/10⁵ PBL. The results for three HTLV-1-positive participants who did not wait for clinical examination and for two with symptomatic strongyloidiasis were excluded from further analysis. There was no sex difference in the median HTLV-1 PVL for nine men and eight women who did not present with chronic lung disease, ataxia or strongyloidiasis (men, 51 [IQR, 39–271] copies/10⁵ PBL; women, 8.6 [IQR, 0.27–179] copies/10⁵ PBL; $P = 0.180$). The median HTLV-1 PVL was significantly higher for the seven adults with chronic lung disease than for 17 asymptomatic participants (chronic lung disease, 649 copies/10⁵ PBL [IQR, 162–2220]; asymptomatic adults, 40 copies/10⁵ PBL [IQR, 0.9–229]; $P = 0.017$) (Box 3). HTLV-1 PVL for each of the three participants with both chronic lung disease and gait ataxia exceeded 1000 copies/10⁵ PBL (1365, 2214 and 3399 copies/10⁵ PBL).

### Discussion

We found high rates of HTLV-1 infection among Indigenous adults in a remote Indigenous Australian community. The adult seroprevalence rate in this community (30 of 74 people) is comparable with that of some villages in southwestern Japan prior to public health interventions in that country.¹⁵ In contrast to the Japanese results for children, only a single Indigenous child was definitely infected with HTLV-1, and we were unable to test his mother or siblings, as they were absent from the community during the survey. Horizontal transmission may therefore be particularly important in central Australia, as in Jamaica²⁰ and some African countries²¹ where sexual transmission is the predominant mode. Although our data were derived from a single, small community, HTLV-1 serostatus was determined for 70% of its residents, and the adult seroprevalence rate was very close to that for hospitalised adults from this region.¹⁰ Published community-based epidemiological data for HTLV-1 infection in Australia are otherwise limited. HTLV-1 seropositivity rates of

---

### 2 Demographic data for 97 Indigenous Australian residents of a remote Northern Territory community, according to HTLV-1 serostatus

<table>
<thead>
<tr>
<th>HTLV-1-positive</th>
<th>HTLV-1-negative</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>31</td>
<td>66</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Adults</td>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>1 boy</td>
<td>12 boys, 10 girls</td>
</tr>
<tr>
<td>Adults</td>
<td>17 men, 13 women</td>
<td>22 men, 22 women</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical survey findings (adults only)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any history of smoking</td>
<td>13/30</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>12/30</td>
</tr>
<tr>
<td>Asthma</td>
<td>1/30</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2/30</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>0/30</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>6/30</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>21/27</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5/27</td>
</tr>
<tr>
<td>Dermatological</td>
<td>5/27</td>
</tr>
<tr>
<td>Possibly HTLV-1-associated conditions</td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>7/27</td>
</tr>
<tr>
<td>Ataxia</td>
<td>3/27</td>
</tr>
<tr>
<td>Strongyloides seropositivity**</td>
<td>6/27</td>
</tr>
<tr>
<td>Symptomatic strongyloides††</td>
<td>2/27</td>
</tr>
</tbody>
</table>

* Three HTLV-1-positive participants and one HTLV-1-negative participant provided blood but did not wait for medical review. † Wheeze, dry cough or dyspnoea. ‡ Loose bowel actions several times per day for longer than 2 days. § Pruritus or rash attributed to scabies (three participants), impetigo (one), tinea corporis (one) or pityriasis versicolor (one). ¶ Daily productive cough with inspiratory crackles audible on auscultation of the chest. ** Strongyloides serological results were not available for all participants. *** Loose bowel actions several times per day for more than 2 days, together with positive Strongyloides serological result.
The burden of HTLV-1-associated inflammatory diseases has not previously been studied in a community setting. The reported lifetime risk of strictly defined HAM/TSP in people who are HTLV-1-positive ranges between 0.25% for cases solicited from Japanese medical institutions to 1.9% based on data provided voluntarily by medical staff to registries in the Caribbean. In contrast, neurological and dermatological abnormalities respectively affect more than 30% and 70% of infected persons followed up in Brazilian outpatient clinics. The true burden of HTLV-1-associated inflammatory disease in a community setting may therefore be far higher than suggested by a strict application of the HAM/TSP case definition to hospitalised patients. Skin diseases were less common among HTLV-1-infected participants in our study than in Brazil. This may reflect selection bias in the hospital-based Brazilian cohort, but genetic factors may also contribute to the risk of HTLV-1-induced inflammation in particular organ systems.

Notwithstanding the success with which we were able to engage with residents of the remote Indigenous community, the study design had a number of limitations. For example, the small sample size precluded a detailed epidemiological analysis that could identify the major modes of HTLV-1 transmission. We were also unable to develop a multivariable model that included other factors that contribute to chronic lung disease, such as smoking and age. A further limitation was our inability to determine the pathological basis for most cases of chronic lung disease and gait ataxia; this would require investigations that are unavailable in a remote community. Similarly, strongyloidiasis was diagnosed serologically because we were unable to collect stool samples prior to treatment. Nevertheless, even if 18 adult residents not recruited to our study were not infected with HTLV-1, the adult HTLV-1 seroprevalence rate in this community would exceed 30%. Moreover, clinical examinations and HTLV-1 studies were performed without knowledge of HTLV-1 serostatus, and our findings are consistent with studies that have found a strong association between HTLV-1 infection and chronic lung disease in Indigenous Australians.

In summary, we found very high HTLV-1 seropositivity rates among adult residents of a remote Indigenous community, and evidence for disease potentially attributable to HTLV-1 in nearly one-third of HTLV-1-positive participants. The project integrated clinical research with a health literacy program, using both Indigenous and non-Indigenous expertise to decolonise research practice. Further investigations will apply the lessons learned from this pilot project to other communities, in order to identify the major modes of HTLV-1 transmission and the associated disease burden in remote Australia.

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Microgeographic factors and patterns of aeroallergen sensitisation

Andrew W Kam1, Winnie WY Tong2, Jenna M Christensen3, Constance H Katelaris4,5, Janet Rimmer6, Richard J Harvey3,7

The known Socio-economic and geographic factors influence allergic sensitisation.

The new Coastal proximity, climate, and environmental (urban v regional) factors affect allergy patterns in the Greater Sydney area. A selected ten-aeroallergen skin prick test (SPT) panel identified 98.5% of atopic patients in our sample. 72.4% of grass-sensitised patients were co-sensitised to both temperate and subtropical grasses.

The implications The identified patterns of allergic sensitisation can inform more effective aeroallergen avoidance strategies. The high level of co-sensitisation to temperate and subtropical grasses suggests that existing immunotherapy is suboptimal in the Australian setting. Our selected Australian SPT panel may assist clinicians screening for allergy.

Allergic sensitisation is the first step in the pathogenesis of allergic disease. Socio-economic and geographic factors, including rural environment and climate, affect patterns of allergic sensitisation.1,2 Recognising sensitisation patterns may inform more effective allergen avoidance strategies, and help guide approaches to testing for and treating allergies. In particular, it may influence the choice of immunotherapy, a treatment modality that reduces symptoms and medication use, and which modifies disease in the long term.3

Our study explored airborne allergen (aeroallergen) sensitisation patterns in the Greater Sydney area, and their relationships with climate, proximity to the coast, and environment (urban or rural). As co-sensitisation patterns may be important when making choices about allergy testing and immunotherapy, we also explored patterns of co-sensitisation to temperate and tropical grasses, and to house dust mite (HDM) species, Dermatophagoides farinae and Dermatophagoides pteronyssinus.

Methods

In a retrospective, cross-sectional, multicentre study, we analysed the electronic database records for patients of three Sydney allergy clinics who had undergone aeroallergen skin prick testing (SPT) during the period January 2001 – October 2014. Electronic records were available from January 2001 for one clinic, from January 2009 for the second, and from January 2013 for the third. One author (AWK) reviewed the records and extracted data on sex, date of birth, SPT results, and age and postcode at the time of testing. If patients had undergone multiple SPT, only the most recent results were analysed. Patients were excluded if their postcodes were grouped these allergens according to shared characteristics: HDM species, Dermatophagoides farinae and Dermatophagoides pteronyssinus.

Skin prick testing

Each clinic performed SPT according to the Australasian Society of Clinical Immunology and Allergy guidelines.2 SPT results were reported as the mean diameter (mm) of the wheal reaction to the testing reagent. Criteria for valid tests were that the mean diameter of the wheal induced by the negative (ie, non-allergic) control, phenolated glycerol saline, was no greater than 3 mm, and that the wheal induced by the positive control, 10 mg/mL histamine dihydrochloride (directly elicits a cutaneous wheal and flare response), was more than 4 mm wider than that of the negative control.5 Patients were deemed sensitised to an allergen if the mean diameter of the induced wheal was at least 3 mm if there was no reaction to the negative control, or more than 3 mm larger than that of the negative control if there was a reaction to the negative control.5

The allergens tested were those known to be present in Sydney. We grouped these allergens according to shared characteristics: HDM (D. farinae, D. pteronyssinus); animals (cat, dog); cockroach mix;...
moulds (Aspergillus, Alternaria, Cladosporium, Penicillium); weeds (plantain, Parietaria, Oleaceae mix); trees (plane tree, pine tree mix [Pinus contorta and P. ponderosa], birch tree); temperate grasses (five grass mix [timothy, rye, meadow, sweet vernal, cocksfoot], rye grass, timothy grass); and tropical grasses (Bermuda grass, Bahia grass). HollisterStier Allergy and Stallergenes (Alyostal) reagents were used during testing. Some patients were exposed to different SPT panels, as clinically indicated at presentation.

Definition of coastal habitation
Each patient was assigned to one of three coastal habitation groups according to the distance of their postcode from the coastline (< 15 km, 15–30 km, > 30 km). To assign these groups, a map of ABS postcode areas (vector format) was opened in ArcGIS (ESRI), a geographic information system program. Each postcode area was converted to a point on the map determined by its geometric centroid (a single coordinate representing the average of all points in the postcode area). The distance of the centroid of each postcode from the nearest point on the coastline was then determined.

Climate zone classification
Climate zones were defined according to the Australian Köppen climate classification of the Australian Bureau of Meteorology (Appendix 1, Box 1). Four climate zones were defined in Sydney: subtropical/no dry season; temperate/no dry season (hot summer); temperate/no dry season (warm summer), and temperate/moderately dry winter (warm summer). To determine the climate zone of each postcode, a digitised map (vector format) of ABS postcode areas was overlaid with a digitised map (raster format) of the Australian Köppen climate zones in ArcGIS (ESRI). Postcodes were assigned the predominant climate zone (by area) within their boundaries.

Definition of urban and regional areas
Urban and regional areas were defined according to the Accessibility/Remoteness Index of Australia+ (ARIA+), an Australian government-endorsed geographic measure of remoteness. Two remoteness categories were defined in the Sydney area, “Major cities of Australia” (in this article: “urban”) and “Inner regional Australia” (“regional”).

Data analysis
The proportions of patients sensitised and co-sensitised to the tested Aeroallergens were calculated. To determine the ten-aeroallergen panel that provided the highest detection rate of atopic individuals, descriptive analyses assessed all possible aeroallergen combinations. These analyses were performed in SPSS 22.0 (IBM). Confidence intervals for proportions of patients exhibiting aeroallergen sensitisation were calculated by the Clopper and Pearson method in GraphPad Prism 6.04 (GraphPad Software).

Differences in the proportions of positive SPT results between climate zones, coastal and inland areas, and urban and regional areas were analysed in \( \chi^2 \) tests. \( Z \)-tests (with Bonferroni correction) identified significant pairwise differences between specific climate zones or coastal habitation areas. Analysis of data for coastal habitation areas by \( \chi^2 \) tests was adjusted for climate zone to assess the interaction of their effects. Sub-analysis of the 563 patients aged 16 years or less evaluated the influence of changes of address on results; it was assumed that children were less likely to have moved house as often as adults. These analyses were performed in SPSS 22.0.

Ethics approval
Ethics approval was granted by the St Vincent’s Hospital Human Research Ethics Committee (reference, LNR/14/SVH/88).

Results
A total of 1421 patients met the selection criteria. The mean age at testing was 28.3 years (SD, 21.3); 757 patients were female (53.3%). As expected of tertiary allergy services, there was a high proportion of sensitised patients, with 1092 (76.8%; 95% confidence interval [CI], 74.6–79.0%) sensitised to at least one Aeroallergen. The
distribution of patients between climatic and geographic zones is summarised in Appendix 2.

Across Sydney, the most common sensitising aeroallergens were HDM (63.2% of tested patients; 95% CI, 60.6–65.7%) and grasses (46.3%; 95% CI, 43.6–49.0%). Sensitisation to temperate grasses (44.5%; 95% CI, 41.7–47.4%) was more common than to subtropical grasses (37.6%; 95% CI, 34.7–40.4%; P < 0.001). The most common sensitising aeroallergens are listed in Box 2.

Among the 1092 patients sensitised to at least one aeroallergen, 1057 (96.8%) had undergone both HDM and grass pollen SPT; of these, 995 (94.1%) were sensitised to at least one of these allergen groups, and 484 (45.8%) were sensitised to both HDM and grass pollen.

Of the 901 patients who had undergone testing to all eight allergen groups, 124 (13.8%) were sensitised to only one allergen group (mono-sensitised), of whom 72% were mono-sensitised to HDM aeroallergen (Box 3).

Climate zone influence
There were no climate zone differences in the patterns of HDM and animal aeroallergen sensitisation. A temperate/warm summer climate, however, was associated with a higher proportion of patients sensitised to cockroach, mould, weed, tree, and temperate or subtropical grass allergens than in temperate/hot summer and subtropical climates (Box 4).

A sub-analysis of patients aged 16 years or younger found that HDM sensitisation was more common in temperate/hot summer zones (72.9%) than in temperate/warm summer climates (72.0%) and in subtropical climates (65.7%) than in temperate/hot summer and subtropical climates (58.4%; P < 0.001). There were no significant differences in patterns of sensitisation between climate zones for other allergen groups (data not shown).

Coastal habitation
There was no relationship between coastal proximity and patterns of HDM and cat sensitisation. Lower proportions of patients residing less than 15 km from the coast were sensitised to cockroach and mould in patients living in temperate/no dry season, warm summer zones also lived more than 30 km from the coast, while all in subtropical climate zones lived more than 15 km from the coast. In both temperate/no dry season zones, the pattern of increasing sensitisation further from the coastline remained significant after adjustment for climate zone, with two exceptions: there was no relationship between coastal proximity and sensitisation to cockroach and mould in patients living in temperate/no dry season, warm summer climates (data not shown).

A sub-analysis of tested patients aged 16 years or younger indicated that those residing less than 15 km from the coast were less commonly sensitised to mould, weed, tree and subtropical grass aeroallergens than patients further inland (P < 0.05 for each). Similar patterns were observed for cockroach and temperate grass sensitisation, but were not statistically significant (P = 0.063 and P = 0.055 respectively) (data not shown).

Urban and regional residence
Lower proportions of patients in urban areas were sensitised to cockroach, mould and subtropical grass aeroallergens than in regional areas. There were no differences for other allergen groups (Box 6). Although the differences in a sub-analysis of patients aged 16 years or younger were similar, they were not statistically

<table>
<thead>
<tr>
<th>Allergen group</th>
<th>Number mono-sensitised (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>House dust mite</td>
<td>89 (72%)</td>
</tr>
<tr>
<td>Animals</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Cockroach</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Moulds</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Weeds</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Trees</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Temperate grasses</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Subtropical grasses</td>
<td>0</td>
</tr>
</tbody>
</table>

*This table includes only patients who had undergone skin prick testing for all eight allergen groups (901 patients) and who were sensitised to aeroallergens of only one allergen group.
Aeroallergen sensitisation according to climate zone of residence

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Temperate/moderately dry winter, warm summer</th>
<th>Temperate/no dry season, warm summer</th>
<th>Temperate/no dry season, hot summer</th>
<th>Subtropical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitised (%)</td>
<td>Number tested</td>
<td>Group*</td>
<td>Sensitised (%)</td>
</tr>
<tr>
<td>House dust mite</td>
<td>58%</td>
<td>116</td>
<td></td>
<td>63.2%</td>
</tr>
<tr>
<td>Animals</td>
<td>33%</td>
<td>106</td>
<td></td>
<td>42.1%</td>
</tr>
<tr>
<td>Cockroach</td>
<td>38%</td>
<td>84</td>
<td>α</td>
<td>38.5%</td>
</tr>
<tr>
<td>Mould</td>
<td>29%</td>
<td>102</td>
<td>α, β</td>
<td>36.3%</td>
</tr>
<tr>
<td>Weeds</td>
<td>37%</td>
<td>83</td>
<td>α, β</td>
<td>42.6%</td>
</tr>
<tr>
<td>Trees</td>
<td>13%</td>
<td>85</td>
<td>α, β</td>
<td>24.6%</td>
</tr>
<tr>
<td>Temperate grasses</td>
<td>46%</td>
<td>109</td>
<td>α, β</td>
<td>53.6%</td>
</tr>
<tr>
<td>Subtropical grasses</td>
<td>50%</td>
<td>93</td>
<td>α</td>
<td>52.3%</td>
</tr>
<tr>
<td>All grasses</td>
<td>50%</td>
<td>111</td>
<td>α, β</td>
<td>55.2%</td>
</tr>
<tr>
<td>Total patients tested</td>
<td>483</td>
<td></td>
<td></td>
<td>788</td>
</tr>
</tbody>
</table>

* Z-test (with Bonferroni corrections) for pairwise comparison of proportions of patients sensitised to each allergen group in each climate zone. Significant differences (P < 0.05) are indicated by allocating climate zones different Greek letters: α zones are significantly different from β and γ zones, but not from other α zones. For example, the proportion of patients sensitised to grass allergens in temperate/moderately dry winter, warm summer zones (50%) was significantly different to the proportion for subtropical zones (16%), but not the proportions in the other two temperate zone categories (55.2%, 41.9%). † χ² test. ◆

Aeroallergen sensitisation according to coastal proximity of residence

<table>
<thead>
<tr>
<th>Allergen</th>
<th>&lt; 15 km from coastline</th>
<th>15–30 km from coastline</th>
<th>&gt; 30 km from coastline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitised (%)</td>
<td>Number tested</td>
<td>Group*</td>
</tr>
<tr>
<td>House dust mite</td>
<td>62.6%</td>
<td>621</td>
<td></td>
</tr>
<tr>
<td>Animals</td>
<td>40.5%</td>
<td>612</td>
<td></td>
</tr>
<tr>
<td>Cockroach</td>
<td>15.1%</td>
<td>391</td>
<td>α</td>
</tr>
<tr>
<td>Mould</td>
<td>17.4%</td>
<td>610</td>
<td>α</td>
</tr>
<tr>
<td>Weeds</td>
<td>23.2%</td>
<td>611</td>
<td>α</td>
</tr>
<tr>
<td>Trees</td>
<td>24.8%</td>
<td>613</td>
<td>α</td>
</tr>
<tr>
<td>Temperate grasses</td>
<td>33.9%</td>
<td>496</td>
<td>α</td>
</tr>
<tr>
<td>Subtropical grasses</td>
<td>20.4%</td>
<td>491</td>
<td>α</td>
</tr>
<tr>
<td>All grasses</td>
<td>36.5%</td>
<td>619</td>
<td>α</td>
</tr>
<tr>
<td>Total number of patients tested</td>
<td>676</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Z-test (with Bonferroni corrections) for pairwise comparison of proportions of patients sensitised to each allergen group in each climate zone. Significant differences (P < 0.05) are indicated by allocating climate zones different Greek letters: α zones are significantly different from β and γ zones, but not from other α zones. † χ² test. ◆

significant (cockroach, P = 0.153; moulds, P = 0.456; subtropical grasses, P = 0.190) (data not shown).

Co-sensitisation

A total of 1135 patients underwent both temperate and subtropical grass SPT. Of the 554 sensitised to any grass, 401 (72.4%) were sensitised to both temperate and subtropical grasses; 128 patients (23.1%) were sensitised to temperate grasses only, and 25 (4.5%) to subtropical grasses only.

A total of 496 patients underwent both *D. pteronyssinus* and *D. farinae* SPT. Of the 301 sensitised to HDM, 260 (86.4%) were sensitised to both species, while 32 patients (11%) were sensitised to *D. pteronyssinus* only and 9 (3%) to *D. farinae* only.

**Testing panel**

A ten-aeroallergen testing panel consisting of *D. pteronyssinus*, cat, dog, cockroach mix, *Alternaria, Aspergillus*, plantain, rye grass, timothy grass, and either Bermuda or Bahia grass (the two grasses yielded the same results) identified 98.5% of all sensitised patients (1076 of 1092).

**Discussion**

This study explored patterns of aeroallergen sensitisation in Sydney. Other authors have hypothesised that *D. pteronyssinus* is the predominant HDM allergen in Sydney; indeed, it has been found that *D. farinae* comprises only 5.1% of HDMs found in house dust in Sydney. Other studies of HDM species
prevalence reported that *D. farinae* is rarely found in Australian cities, suggesting the predominance of *D. pteronyssinus* across the nation, an interpretation supported by our results. Only a small proportion of our Sydney sample were sensitised solely to *D. farinae* (3%) and a comparatively higher proportion to *D. pteronyssinus* alone (11%). *D. farinae* and *D. pteronyssinus* allergen cross-reactivity probably explains the high proportion of HDM-sensitised patients who were co-sensitised to both species (86.4%).

A panel of ten aeroallergens — *D. pteronyssinus*, cat, dog, cockroach mix, *Alternaria*, *Aspergillus*, plantain, rye grass, timothy grass, and either Bermuda or Bahia grass — may be a useful screening panel in Sydney, having identified 98.5% of atopic patients in our study. This panel, modified by adding or subtracting aeroallergens according to regional variations in the predominance of allergens, may also be useful elsewhere in Australia.

We found a high proportion of co-sensitisation to temperate and subtropical grasses in the Sydney area (72.4%), consistent with findings by studies in subtropical Australian regions. This differs from findings in Europe and North America, where temperate grasses are predominantly responsible for grass pollen sensitisation. Temperate and subtropical grass pollens have both shared and distinct immunological properties, and the IgE reactivity of residents of temperate and subtropical regions is higher to the grass group of the corresponding climate. This suggests that differences in temperate and subtropical grass immunological reactivity are clinically relevant. As such, the high proportion of patients co-sensitised to temperate and subtropical grasses which we found indicates that both temperate and subtropical grass testing and immunotherapy may be important in Sydney and other temperate and subtropical regions. As most immunotherapeutic agents, particularly newer sublingual immunotherapy tablets, are directed against temperate grass aeroallergens alone, they may not provide adequate coverage in Australia. Treatments directed against both temperate and subtropical grasses may be required. Bermuda grass testing and immunotherapy may be particularly relevant, as it is less cross-reactive with temperate grasses than Bahia grass.

Our results confirmed that sensitisation to *Alternaria*, grass, weed and tree is less common in residents near the coast. Further, cockroach, *Aspergillus* and *Cladosporium* sensitisation is less common in areas less than 15 km from the sea. The climatic conditions of the coast (including increased humidity, thermal stability, and coastal breezes) may offer some protection against these aeroallergens.

Interestingly, regional patients were more frequently sensitised to cockroach than were urban residents. A possible explanation is that our “regional” areas lay on the outskirts of Sydney, and were areas with lower household incomes and socio-economic status, both of which are risk factors for sensitisation to cockroach aeroallergens.

The strengths of our study included the fact that it was the first to examine associations between sensitisation to specific allergen groups and climatic and geographic factors in an Australian setting over distances of tens of kilometres. It is also the first to report the prevalence of aeroallergen sensitisation in the Sydney area in a cohort of this size. Further, by separately analysing sensitisation for those under 16 years of age, who were unlikely to have changed addresses as often as older people, the study provides strong evidence of the effect of coastal habitation on reducing sensitisation rates to mould, weed, tree and subtropical grass aeroallergens. Finally, this study is more likely to reflect patterns of clinically relevant sensitisation because it used SPT results to define sensitisation, rather than allergen-specific IgE blood tests; further, it was restricted to patients who had presented to allergy specialists.

Our study, however, has limitations. Firstly, as postcodes and not exact addresses defined places of residence, microclimate and geographic location could not be precisely allocated for each person. Secondly, the proportion of people with allergic sensitisation in our investigation would be higher than in the general population, as we studied patients attending tertiary allergy clinics. Finally, as some patients were tested with different SPT panels, according to clinical indication at presentation, the prevalence of sensitisation we report may be higher than if all patients had undergone SPT for each of the allergens. This limitation was unavoidable, given the retrospective nature of our study. We also note that clinical reactivity requires both allergen sensitisation and subsequent allergen exposure. As such, sensitisation is clinically relevant only when there is also a risk of exposure to the allergen.

In conclusion, our study yields three major insights. Firstly, allergic sensitisation to a variety of different aeroallergens was less...
common in patients attending allergy clinics who resided less than 15 km from the coast, in temperate/hot summer or subtropical climates, or in urban parts of Sydney. These relationships may affect decisions about allergen reduction and avoidance measures. Secondly, a ten-aeroallergen SPT panel identified more than 98% of atopic patients in Sydney; this panel may assist clinicians when screening for allergy. Finally, currently available immunotherapeutic options, based on northern hemisphere temperate grass allergens, may be inappropriate in the Australian setting in view of the high degree of co-sensitisation to temperate and subtropical grasses; regimens directed at both grass types would be more suitable for treating grass allergy in subtropical regions.

Competing interests: Richard Harvey is a consultant for Medtronic, Olympus and Nelméd, and received grant support from Meda Pharmaceuticals, Stallergenes, ENT Tech and Nelméd. Janet Rimmer has received honoraria from Novartis, Sanofi Aventis, Mundipharma, BioCSL and Stallergenes. Constance Katerlak has received honoraria from Novartis, BioCSL, Stallergenes and Sanofi Aventis.

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Gluten content of imported gluten-free foods: national and international implications

Geoffrey M Forbes1, Kenneth Dods2

Celiac disease (CD) is the only common disease for which strict dietary compliance is the sole treatment. Sensitivity to gluten varies between patients with CD, so that restricting levels in food to under one part per million (ppm) would protect the maximum number of patients.1 In a daily diet of 500 g food, 1 ppm is equivalent to 0.5 mg, the amount in 1/5000 of a slice of wheat flour bread containing 2.5 g gluten.

International food codes require that foods labelled “gluten-free” (GF) contain less than 20 ppm gluten; in Australia and New Zealand, however, a “no detectable gluten” standard applies.2,4 Current laboratory techniques have a reporting limit of 1 ppm, and a detection limit of 0.5 ppm gluten in food. We assessed the compliance of imported GF-labelled foods with the local food standard, as well as the international capacity of industry to comply with Australian standards, given commercially available analytical reporting and detection limits.

A total of 169 GF-labelled food items manufactured overseas were purchased from four retailers in Perth, Western Australia. The countries of origin were in Europe (nine countries), Asia (nine), and North (two) and South America (five); the food categories included crackers, bread and biscuits (41 items), cereals, flour and grains (37), condiments and sauces (30), spices (21), pasta (16), drinks and soups (15), and confectionary and snacks (nine).

We used a sandwich enzyme-linked immunosorbent assay (ELISA) gliadin detection kit (ESGLISS-48, ELISA Systems). Testing complied with strict food chemistry testing protocols: five variable concentration calibration standards and blank solution tests were used, calibration standards performance was confirmed every 15 samples, internal control materials were employed, and duplicate random samples (1 in 10) from each ELISA plate were tested. All positive results were confirmed on a stored original food sample.

Gluten was detected in 24 of 169 products (14%), of which 20 had unquantifiable but detectable levels (<1 ppm) and four had quantifiable levels (three, 1.0 ppm; one, 1.1 ppm). Gluten was detected in products supplied from each of the four continents and from each food category (except pasta and drinks/soups).

Our findings, in conjunction with those of 2008 and 2010 surveys of foods mostly produced in Australia,5 have three important implications. Firstly, people with CD can confidently consume GF-labelled products purchased in Australia. Secondly, a marked tightening of international GF standards is readily achievable by industry, the gluten levels in the foods we analysed were all below 1.5 ppm, less than one-tenth of the standard set by the Codex Alimentarius of <20 ppm.2 Thirdly, we recommend that authorities revise the current Australian GF standard of “no detectable gluten”2 to “<1 ppm”, as it is not practical or reasonable for industry to comply with the stricter standard. In our survey, 14% of products were non-compliant with the current Australian standard, but none contained more than 1.1 ppm gluten.

Competing interests: No relevant disclosures.


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Barrett’s oesophagus: epidemiology, diagnosis and clinical management

David C Whiteman1; Bradley J Kendall1,2,3

In most industrialised countries, including Australia, the incidence of oesophageal adenocarcinoma has increased fivefold in the past 40 years.1 Almost all of these cancers arise from underlying Barrett’s oesophagus,2 a condition described by Australian-born Norman Barrett in 19573 in which the normal oesophageal squamous epithelium is partially replaced by an intestinal metaplastic columnar epithelium. This narrative review discusses the epidemiology of Barrett’s oesophagus and its relationship to cancer, considers recent developments around screening and surveillance, and briefly reviews the management of dysplasia and early adenocarcinoma arising in Barrett’s oesophagus. It is based on comprehensive Australian guidelines recently published by Cancer Council Australia (http://wiki.cancer.org.au/australia/Guidelines: Barrett’s27s).

Definition

In the Australian guidelines (as in most other international guidelines), a diagnosis of Barrett’s oesophagus requires two components: first, endoscopic evidence of a salmon-pink coloured columnar epithelium extending above the gastro-oesophageal junction and partially replacing the normal tubular oesophageal squamous epithelium; and second, biopsies from the oesophageal columnar epithelium showing evidence of intestinal metaplasia, with the presence of mucin-containing goblet cells (Box 1).4-6 Under Australian guidelines, patients with a columnar-lined oesophagus on endoscopy but no evidence of intestinal metaplasia on biopsy do not meet the definition for Barrett’s oesophagus; the significance of this finding is uncertain, and we discuss the management of such patients below.

The length of the columnar epithelium at endoscopy is described using the Prague C (circumferential length) and M (maximal length) criteria (Box 2).7 Barrett’s oesophagus is defined as long segment when maximal segment length is ≥ 3 cm and as short segment when maximal length is < 3 cm.

Prevalence

Because Barrett’s oesophagus is asymptomatic and requires endoscopic examination and histological confirmation to establish the diagnosis, estimates of prevalence in unselected populations are scarce. The arguably best data were derived from a sample of 1000 Swedish residents recruited at random from the community who underwent upper gastrointestinal endoscopy, of whom 16 were identified with Barrett’s oesophagus (5 long segment, 11 short segment).8 Well conducted surveys in comparable populations (the United States and Europe) suggest community prevalence < 5%, with estimates converging around 2%; Australian data are limited to studies of patients referred for endoscopic investigation of symptoms.9-11 There is evidence that Australian detection rates have increased recently, with higher proportions of patients who undergo upper gastrointestinal endoscopy being diagnosed with Barrett’s oesophagus in consecutive surveys (rising from 0.3% in 1990 to 1.9% in 2002).10

<table>
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<th>Summary</th>
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<tr>
<td>• Barrett’s oesophagus is a condition characterised by partial replacement of the normal squamous epithelium of the lower oesophagus by a metaplastic columnar epithelium containing goblet cells (intestinal metaplasia).</td>
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<td>• Barrett’s oesophagus is important clinically because those affected are predisposed to oesophageal adenocarcinoma. Prevalence surveys suggest that up to 2% of the population may be affected; most will be unaware of their diagnosis.</td>
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<td>• Risk factors include age, male sex, gastro-oesophageal acid reflux, central obesity and smoking. Helicobacter pylori infection confers a reduced risk of Barrett’s oesophagus.</td>
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<td>• Risks of cancer progression are lower than originally reported and are now estimated at 1-3 per 1000 patient-years for patients with non-dysplastic Barrett’s oesophagus. Progression rates are higher for patients with long segment (≥ 3 cm) and dysplastic Barrett’s oesophagus.</td>
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<td>• Australian guidelines have been developed to aid practitioners in managing patients with Barrett’s oesophagus and early oesophageal adenocarcinoma.</td>
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<td>• While generalised population screening for Barrett’s oesophagus is not recommended, endoscopic surveillance of patients with confirmed Barrett’s oesophagus is recommended, with surveillance intervals dependent on segment length and presence of dysplasia.</td>
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<td>• New techniques such as endoscopic mucosal resection and endoscopic radiofrequency ablation are now available to treat patients with dysplasia and early oesophageal adenocarcinoma. New screening and surveillance technologies are currently under investigation; these may prove cost-effective in identifying and managing patients in the community.</td>
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Risk factors

Pooled analyses and meta-analyses of high quality epidemiological studies have consistently identified age, male sex, gastro-oesophageal reflux, central obesity and smoking as risk factors for Barrett’s oesophagus. In most populations, Barrett’s oesophagus is twice as common in men as in women,12 and prevalence rises with age.13

The longstanding clinical association between Barrett’s oesophagus and acid regurgitation or heartburn has been confirmed in research studies; a recent meta-analysis concluded that symptoms of gastro-oesophageal reflux increased the risks of long segment Barrett’s oesophagus more than fivefold.14 In addition, factors that promote reflux, such as hiatal hernia, are also observed more frequently in patients with Barrett’s oesophagus than among endoscopy controls with non-erosive reflux disease.15

While obesity is an established risk factor for oesophageal adenocarcinoma, epidemiological studies have reported

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inconsistent associations between body mass index and Barrett’s oesophagus. However, studies measuring abdominal obesity (eg, waist circumference, waist–hip ratio) have identified two- to threefold higher risks for high versus low waist circumference. Strong evidence of a likely causal association between obesity and Barrett’s oesophagus came from a Mendelian randomisation analysis, in which investigators demonstrated that people with a strong genetic propensity to develop obesity have significantly higher risks of Barrett’s oesophagus than those with a weak genetic propensity to obesity. The mechanisms remain speculative, but include mechanical (increased pressure on the lower oesophageal sphincter promoting reflux), metabolic and hormonal pathways. Importantly, the association between abdominal obesity and Barrett’s oesophagus is observed in people with and without reflux symptoms, indicating that mechanical reflux does not explain the whole effect. Metabolic factors are strongly implicated, with recent investigations reporting positive associations with markers of the metabolic syndrome, including insulin resistance and high serum concentrations of leptin. Increasingly, it seems likely that male–female differences in fat deposition and metabolism may account for some of the observed sex-specific differences in the prevalence of Barrett’s oesophagus.

Many other lifestyle exposures have been assessed as possible risk factors for Barrett’s oesophagus, two of which have been consistently implicated. Smoking increases the risk of the condition by about 50%, whereas past infection with Helicobacter pylori reduces risk by about 50%. Previously, it was hypothesised that H. pylori infection inhibits gastric acid production and thus reduces acid-associated damage. Recent studies suggest that, in Western populations, H. pylori infection occurs predominantly in the antrum and likely reduces the risk of Barrett’s oesophagus by disrupting ghrelin and leptin pathways. Aside from the factors described above, no others have been consistently associated with the disease. Thus, despite considerable investigation, there is no evidence that alcohol is a risk factor. Similarly, several well conducted case–control studies have investigated the role of aspirin and other non-steroidal anti-inflammatory drugs, based on strong and consistent inverse associations with oesophageal adenocarcinoma in observational and experimental studies. However, there is no evidence that this class of drugs alters a person’s risk of Barrett’s oesophagus. Relatively few studies have examined dietary factors and no conclusions can be drawn.

In the past 5 years, several large scale genome-wide association studies have identified a number of single nucleotide polymorphisms significantly associated with Barrett’s oesophagus. Moreover, there appears to be considerable genetic overlap between patients with Barrett’s oesophagus and patients with oesophageal adenocarcinoma, lending weight to the notion that these two conditions share similar causal origins. This is a rapidly moving field, but the clinical utility of these findings remains unknown.
Progression to cancer

Clinical interest in Barrett’s oesophagus stems largely from the concern that the condition is a precursor or risk marker for adenocarcinoma of the oesophagus. Most cases of oesophageal adenocarcinoma arise from underlying Barrett’s metaplasia in which there is a histological progression over time from low grade dysplasia (LGD) to high grade dysplasia (HGD) and subsequent intramucosal and invasive carcinoma (metaplasia–dysplasia–carcinoma sequence). Early oesophageal adenocarcinoma refers to invasion of the carcinoma beyond the basement membrane into the lamina propria (T1a on the current tumour–node–metastasis staging system) or superficial submucosa (T1b), but not deeper. Early oesophageal adenocarcinoma represents 6–12% of patients presenting with oesophageal cancer.49,50

The key question relates to the rate at which patients diagnosed with Barrett’s oesophagus progress to cancer. Early studies, largely conducted in tertiary referral centres, suggested rates as high as 1–2 per 100 patients per year. Since the year 2000, a number of large, population-based, record linkage studies have observed considerably lower progression rates for patients with uncomplicated Barrett’s oesophagus, converging at around 1–3 per 1000 patients per year (an order of magnitude lower than earlier reports).41,45 The risk of progression is greater in those with dysplasia52 and those with long segment Barrett’s oesophagus.53

Considerable uncertainty remains about progression rates among Barrett’s oesophagus patients with LGD. In the community, LGD patients progress to HGD or cancer at a rate of about 1.5% per annum, whereas a recent European academic centre-based study reported much higher progression rates to HGD or cancer (about 13% per annum).42,48 The explanation appears to be that patients attending academic centres are reviewed by multiple expert gastrointestinal pathologists, and up to 75% of community referral LGD patients are downstaged to non-dysplastic Barrett’s oesophagus following expert review. Among the downstaged patients, progression rates to HGD or cancer of about 0.5% per year have been observed,46 similar to those reported from community-based studies.42 Studies from other academic centres of progression rates of patients with expert-confirmed LGD are awaited.

Little is known about lifestyle factors that increase or decrease the rate of progression to cancer. The literature underpinning this area is limited in scope and challenged by methodological issues such as small sample sizes, losses to follow-up, possible selection bias and confounding. Notwithstanding these limitations, it would seem that men with Barrett’s oesophagus progress to cancer at about twice the rate of women,46,49 and smokers progress at twice the rate of non-smokers.50,51 While prospective observational studies suggest that non-steroidal anti-inflammatory drugs,52,53 proton pump inhibitors54 and statins52,55 might retard progression to cancer, to date there are no randomised trials to support such conclusions and caution is warranted. Clinical factors associated with high rates of progression include longer segment length,45,46,50,52 and the presence of nodules,56 ulceration57 and strictures57 on endoscopy.

Screening

Screening is the process of identifying new cases of disease in an unselected population. Endoscopic screening for Barrett’s oesophagus in an unselected population with gastro-oesophageal reflux symptoms is not recommended, as it is not cost-effective. Focused endoscopic screening programs in those at greatest risk for Barrett’s oesophagus improve cost-effectiveness.58 Guidelines published by the British Society of Gastroenterology in 2014 recommend that endoscopic screening be considered in patients with chronic gastro-oesophageal reflux symptoms and multiple risk factors for Barrett’s oesophagus (at least three of aged 50 years or older, Caucasian background, male sex, and obesity). They suggest that the threshold of multiple risk factors should be lowered in the presence of a family history including at least one first-degree relative with Barrett’s oesophagus or oesophageal adenocarcinoma.59

For more widespread Barrett’s oesophagus screening to be considered, the costs of detection need to be reduced substantially with no compromise in accuracy. Studies of less costly screening methods (eg, ultrathin endoscopes, cytoscopes) have yielded promising results but it is too early for these to be recommended at a population level.60,61

Endoscopic surveillance

Endoscopic surveillance is the strategy of systematically following up patients with a known precursor condition to reduce (or prevent) the harms of cancer progression. The aim is to detect progression early, so that disease can be treated with the least invasive method, thereby reducing morbidity and mortality from cancer. The decision to commence endoscopic surveillance should be individualised for each patient, after considering factors such as age, comorbidities and the patient’s wishes and ability to participate in a long term surveillance program.

Endoscopic surveillance in Barrett’s oesophagus involves careful and meticulous examination of the Barrett’s segment with a high resolution white light endoscope, followed by biopsies from the segment. It is recommended that biopsies be taken according to the Seattle protocol, with biopsies of any mucosal irregularity (labelled separately) and quadrantic biopsies every 2 cm, unless there is known or suspected dysplasia, in which case quadrantic biopsies should be taken every centimetre. In the presence of erosive oesophagitis, it is recommended that acid suppression be maximised and surveillance endoscopy repeated in 2–3 months. This allows the oesophagitis to heal, thereby permitting underlying (masked) lesions to be identified and further biopsies to be taken.

The interval between surveillance endoscopies depends on segment length and the presence of dysplasia (Box 3). In patients with Barrett’s oesophagus with no current or past dysplasia, follow-up endoscopy is recommended every 2–3 years in those with long segment disease, and every 3–5 years in those with short segment disease. Follow-up and management of patients with dysplasia is discussed below.

In some patients, a columnar-lined oesophagus is found at endoscopy but no intestinal metaplasia or dysplasia is seen histologically. The biological implications of this finding remain uncertain. The Australian guidelines recommend follow-up intervals based on segment length: < 1 cm, no endoscopic follow-up; 1–3 cm, 3–5 years; and ≥ 3 cm, 2–3 years.4

Although endoscopic surveillance in Barrett’s oesophagus is the current recommended practice, there is no direct evidence from randomised trials for its effectiveness or cost-effectiveness. Economic modelling studies suggest that current surveillance practices are unlikely to be cost-effective, and that identifying patients at high risk of progression to oesophageal adenocarcinoma substantially improves cost-effectiveness.39,52,63 The future hope is that a combination of clinical, endoscopic, blood or tissue markers might be used to develop risk stratification tools for identifying high risk patients most likely to benefit from surveillance and early intervention.64
Management of gastro-oesophageal reflux disease

In patients with Barrett’s oesophagus and gastro-oesophageal reflux symptoms, proton pump inhibitor treatment is recommended at a dose titrated to control symptoms and heal reflux oesophagitis. If proton pump inhibitors fail to control gastro-oesophageal reflux symptoms or heal reflux oesophagitis, surgical fundoplication can be considered. There is no strong evidence to suggest that medical or surgical therapy of gastro-oesophageal reflux disease leads to any substantial regression in segment length or influences progression to cancer.

Management of low grade dysplasia

Management of low grade dysplasia patients is currently uncertain, as new data suggest cancer progression rates are higher in patients whose LGD has been confirmed by an expert pathologist. A recent multicentre European randomised study of radiofrequency ablation in patients with expert-confirmed LGD found that control patients undergoing intensive endoscopic surveillance had a progression rate to cancer of 8.8%, while patients in the intervention arm had a progression rate to cancer of 1.5%. The Australian guidelines recommend that those with LGD be either closely monitored with frequent endoscopic assessment and biopsies every 6 months or referred to an expert centre for ongoing follow-up and consideration of ablative therapy of the Barrett’s segment. The decision regarding management of patients with LGD needs to take into account the features of the Barrett’s segment and histology as well as patient age, fitness and preference.

Management of indefinite for dysplasia

Indefinite for dysplasia is reported when biopsies from the Barrett’s segment show some histological features of true dysplasia but other processes (e.g., inflammation) cannot be excluded as a cause for the changes. As with LGD and HGD, such biopsies should be reviewed by a second pathologist, ideally an expert gastrointestinal pathologist. If indefinite for dysplasia remains the diagnosis, then Australian guidelines recommend that the patient be placed on maximal acid suppression and undergo repeat endoscopy with dysplasia protocol biopsies in 6 months.

Management of high grade dysplasia and early oesophageal adenocarcinoma

Patients with HGD or early oesophageal adenocarcinoma should be referred to an expert centre that has integrated expertise in endoscopy, imaging, surgery and histopathology. This allows the initial diagnosis to be confirmed by a second pathologist (ideally an expert gastrointestinal pathologist) and allows assessment and management by a multidisciplinary team.

Until a decade ago, the only definitive management option for patients with HGD or early oesophageal adenocarcinoma was...
oesophagectomy. Because of the low risk of metastatic disease in cancers confined to the mucosa (1–2% for T1a lesions), the past decade has seen a number of endoscopic techniques developed to manage these conditions. These techniques can be divided into two groups: resection (endoscopic mucosal resection [EMR] and endoscopic submucosal dissection); and ablation (radiofrequency ablation [RFA], argon plasma coagulation, photodynamic therapy and cryotherapy). In Australia, EMR and RFA are the most commonly used resection and ablation techniques, respectively (Box 4 and Box 5). In EMR, the oesophageal mucosa is aspirated into a cap on the end of the endoscope, a band applied and the captured mucosa and submucosa resected and retrieved endoscopically. In RFA, thermal injury delivered by an endoscopically placed device is used to destroy the oesophageal mucosa. Although these endoscopic methods do carry a small risk of complications (pain, bleeding, perforation and stricture formation), they are substantially less morbid, less expensive and more organ-preserving than surgery.

Initial management of patients with histologically confirmed HGD and early oesophageal adenocarcinoma involves detailed endoscopic assessment and staging of the Barrett’s segment, with EMR of any visible lesions and biopsies of the Barrett’s segment according to the Seattle protocol. EMR of visible lesions enables accurate histological staging of the depth of invasion; studies have shown that EMR can change staging assessments in 48% of patients.

**Endoscopic treatment of high grade dysplasia**

In patients with HGD without adenocarcinoma, further endoscopic treatment of the remaining Barrett’s segment is advised because of the risk of metachronous lesions. Treatment options for the residual flat segment vary from patient to patient, depending on factors such as segment length, the presence of a circumferential segment or the presence of an oesophageal stricture and involve EMR and/or endoscopic ablation. Follow-up studies of endoscopic therapy in HGD have shown promising long-term results, with complete eradication of dysplasia and metaplasia in 89% of patients at 2 years. Longer term outcome studies are awaited. Post-treatment oesophagitis may be associated with decreased success rates of endoscopic therapy. It is therefore recommended that endoscopically treated patients receive ongoing medical therapy with a proton pump inhibitor to control gastro-oesophageal reflux symptoms and to prevent and heal oesophagitis. If medical therapy is unable to achieve these goals, surgical fundoplication may be considered. Long-term, frequent endoscopic surveillance following treatment is recommended because of the risk of recurrence and metachronous lesions.

**Endoscopic treatment of early oesophageal adenocarcinoma**

In patients with early oesophageal adenocarcinoma and favourable histology (T1a; size, <2 cm; well-differentiated grade; no
Barrett’s oesophagus describes a metaplastic change to the epithelium of the lower oesophagus that predisposes the person affected to oesophageal adenocarcinoma. While risks of progression are not as high as previously assumed, they are not insignificant, posing a challenge for clinical management. Australian guidelines have been developed to assist practitioners in this area. New endoscopic techniques for treating dysplasia and early adenocarcinoma are now available that have markedly lower morbidity than older approaches. In the future, it is possible that new screening and surveillance technologies may prove cost-effective for identifying and managing patients with Barrett’s oesophagus in the community.

Conclusion

Barrett’s oesophagus describes a metaplastic change to the epithelium of the lower oesophagus that predisposes the person affected to oesophageal adenocarcinoma. While risks of progression are not as high as previously assumed, they are not insignificant, posing a challenge for clinical management. Australian guidelines have been developed to assist practitioners in this area. New endoscopic techniques for treating dysplasia and early adenocarcinoma are now available that have markedly lower morbidity than older approaches. In the future, it is possible that new screening and surveillance technologies may prove cost-effective for identifying and managing patients with Barrett’s oesophagus in the community.

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Competing interests: No relevant disclosures.

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Narrative review

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Primary amoebic meningoencephalitis in North Queensland: the paediatric experience

Claire L Nicholls, Fiona Parsonson, Lawrence EK Gray, Adele Heyer, Steven Donohue, Greg Wiseman, Robert Norton1

Primary amoebic meningoencephalitis (PAM) is a rare but fulminant disease leading to diffuse haemorrhagic necrotising meningoencephalitis, and has a very poor prognosis.1 Naegleria fowleri is the causative agent. At Townsville Hospital, our first confirmed case of PAM was an 18-month-old girl from a rural location in North Queensland who presented with fever, seizures and an altered level of consciousness.2 Organisms resembling Naegleria spp. were seen on microscopy of cerebrospinal fluid (CSF). Despite aggressive therapy with multiple antimicrobial agents, the patient died within 72 hours of presentation. An older sibling of the patient had presented with a similar syndrome several years earlier and had died of an undifferentiated meningitic illness. The sibling was retrospectively suspected to also have had PAM.2

Our second confirmed patient presented in early 2015. A previously well 12-month-old boy from a nearby West Queensland cattle-farming area had had a 36-hour history of fevers, rhinorrhea and frequent emesis, which progressed to lethargy and irritability. Before arrival at the local rural hospital, he had a tonic–clonic seizure lasting 3–5 minutes. On arrival he appeared drowsy, had mottled skin, a blanching maculopapular rash, which may not necessarily have been related to PAM, and a central capillary refill of 3–4 seconds. He was treated with intravenous antibiotics for presumed bacterial meningitis. Given the remote location and clinical suspicion of elevated intracranial pressure, lumbar puncture was not performed. On arrival at Townsville Hospital, his Glasgow Coma Scale score was 8/15, he was increasingly febrile, and had an evolving maculopapular rash. Broad spectrum antimicrobial therapy was subsequently started for presumed meningoencephalitis. Within 18 hours of leaving home, he had no spontaneous respiratory effort, reduced tone, up-going plantar reflexes and fixed pupils.

Neuroimaging showed diffuse cerebral oedema with progressive dilatation of the ventricular system on sequential studies. An external ventricular drain was placed because of clinical instability, and CSF microscopy showed motile trophozoites on a wet preparation and Giemsa stain, consistent with N. fowleri. The patient was commenced on intrathecal amphotericin, with no improvement in his clinical state. The organism seen in the CSF was confirmed after the patient’s death by polymerase chain reaction (PCR) analysis as being N. fowleri. When reviewing the patient’s history, it was noted that, as in previous cases, he lived on a property that used untreated and unfiltered bore water domestically, to which he had multiple potential exposures, including via water play with hoses and bathing.

Summary

- Primary amoebic meningoencephalitis (PAM) is a fulminant, diffuse haemorrhagic meningoencephalitis caused by Naegleria fowleri, with an almost invariably fatal outcome.
- In Australia and the developed world, PAM remains a rare disease, although it is very likely that large numbers of cases go undetected in developing countries. N. fowleri is a thermophilic, free-living amoeba with a worldwide distribution. It is acquired when contaminated fresh water is flushed into the nose and penetrates the central nervous system via the cribiform plate.
- Clinical features are similar to those of bacterial meningitis, but it does not respond to standard therapy and rapid progression to death occurs in most cases. Some survivors have been reported; these patients received early treatment with amphotericin B in combination with a variety of other medications.
- Our review describes the local and worldwide experience of this disease and its clinical features, and discusses the associated diagnostic challenges. We hope that by detailing the local response to a recent case, and the outcomes of our public health campaign, we can improve the knowledge of this rare disease for doctors working in rural and remote Australia.

We also searched the Queensland Health Communicable Diseases Branch and the Communicable Diseases Network Australia databases for Australian cases, but, as N. fowleri infection is not a notifiable disease, this returned a low yield.

History of Naegleria fowleri

In 1899, the Austrian scientist Franz Schardinger published the first description of an amoeba that transforms into a flagellate, with drawings of the amoeba, cysts and flagellates. In 1912, Alexeieff coined the name Naegleria, but physicians at the time thought that the genus did not cause disease in humans.3 It was not until the late 1960s that Naegleria was implicated as the cause of PAM by the work of Adelaide pathologists Malcolm Fowler and Rodney Cooter, and of South Australian rural general practitioner Robert Cooter. In 1965, it was first proposed that the organism entered the CSF through the cribiform plate after Fowler isolated the organism in autopsy specimens. Following communication of his findings, Cooter and colleagues were able to directly observe the live amoeba in a CSF sample from a 10-year-old boy who presented with meningoencephalitis.4,5

Pathophysiology

N. fowleri lives and multiplies in warm freshwater areas, and acquisition is often associated with water-based recreational activities.6 Infection may occur when contaminated water is flushed into the nasal cavity. After penetrating the nasal mucosa and passing through the cribiform plate, trophozoites migrate along the olfactory nerve directly into brain tissue. Cases are almost

Literature review

We searched the PubMed database using the terms “Naegleria”, “fowleri” and “menigitis”. No time period was specified. The James Cook University ejournal database was searched for historical information.

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Narrative review

universally fatal, although survival has been reported in the literature following early diagnosis and management.\textsuperscript{7,8}

Epidemiology

The worldwide incidence of PAM is not accurately known,\textsuperscript{9} and the disease is likely to be under-diagnosed and under-reported. In the developing world, numerous factors affect accurate identification, including a lack of resources or expertise in microbiological diagnosis; prioritising management of other infections that are more common; and cultural beliefs that prevent autopsies.\textsuperscript{9} Higher water temperatures, inadequate sanitation, unsafe water sources, and religious ablution practices, such as the use of Neti pots for nasal cleansing, could potentially increase the risk for acquiring PAM.\textsuperscript{10,11} \textit{N. fowleri} is a thermophilic organism and would therefore be expected to occur more frequently in tropical areas; however, the majority of cases are reported from subtropical or temperate regions.\textsuperscript{12} In a study in Karachi, Pakistan, \textit{N. fowleri} was recovered from 8\% of 52 domestic water taps that were sampled.\textsuperscript{13}

An epidemiological review of PAM cases in the United States showed that \textit{N. fowleri} infections are rare and primarily affect younger males exposed to warm recreational freshwater in the southern states.\textsuperscript{14-16} There are two case reports of patients who acquired \textit{N. fowleri} from using treated municipal water for nasal irrigation,\textsuperscript{17} and another patient who contracted the disease from inadequately treated municipal water.\textsuperscript{18}

In Australia, Dorsch and colleagues reported 20 cases of PAM, 13 of which occurred between 1955 and 1972 in South Australia. These cases were attributed to household water that was piped overland for long distances,\textsuperscript{19} allowing it to be heated to temperatures that promoted growth of the amoeba.\textsuperscript{5} After the introduction of continuous water chlorination in 1972, only one further case was reported in South Australia in 1981.\textsuperscript{19} In Queensland, only three previous patients have been described in the literature: one from Mount Morgan who survived, one from Charters Towers,\textsuperscript{19} and one referred from North West Queensland to Townsville Hospital.\textsuperscript{2}

Clinical challenges

Patients with PAM present with the same symptoms as those with bacterial meningitis, and clinical differentiation between the two conditions is impossible. Patients often have a history of recent exposure to warm fresh water, although the definite exposure event is not always identified.\textsuperscript{9} The incubation period ranges from 2 to 15 days, and presenting symptoms may include meningism, fever, confusion and signs of elevated CSF pressure, such as seizures or coma.\textsuperscript{14}

Diagnosis is made more difficult in North Queensland by the vast distances between remote towns in the western part of the state. Townsville Hospital services an area of nearly 150,000 km\textsuperscript{2} and has the only dedicated paediatric intensive care unit north of Brisbane. Patients with PAM inevitably require intensive care unit management and tertiary level investigations. Obtaining CSF samples for formal microscopic diagnosis is often impossible in small clinics with limited medical imaging or local laboratory services, and where performing a lumbar puncture is contraindicated by symptoms of raised intracranial pressure. Because of the rarity of the infection, greater awareness of PAM among primary health care professionals is required in order to increase suspicion in a clinically compatible case. Most importantly, education about prevention is essential for the continued health of rural communities, of which local medical professionals are a vital part. To this end, recent guidelines for the management of encephalitis\textsuperscript{20} include assessing risk factors for this condition and performing appropriate testing, as described below.

Diagnostic challenges

Diagnosis requires identification of motile trophozoites in CSF or characteristic morphology in stained specimens by a trained microbiologist (Box 1), with confirmation using molecular methods (PCR) or culture (\textit{Escherichia coli} lawn culture). The trophozoites are visible in a wet unstained preparation of CSF (magnification, $\times$ 400), exhibiting sinusoidal movement by means of lobopodia; however, specimens need to be examined very soon after collection, as the amoebae degenerate rapidly in vitro and can be easily mistaken for leucocytes.

CSF chemistry is not diagnostic and will usually reveal a similar pattern to that of bacterial meningitis (Box 2). PCR analysis is performed using in-house methods at reference laboratories, and confirmation is often posthumous due to the rapid decline experienced by most patients. The US Centers for Disease Control and Prevention has developed a multiplex real-time TaqMan PCR assay to simultaneously identify three free-living amoebae (\textit{N. fowleri}, \textit{Acanthamoeba spp.} and \textit{Balamuthia mandrillaris}) in clinical specimens.\textsuperscript{21} In Queensland, the pathology laboratory which performs all \textit{N. fowleri} molecular testing uses primers and probes in line with the method of Qvarnstrom and colleagues.\textsuperscript{21} Culture may take several weeks and is difficult to perform.

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>White cell count (10\textsuperscript{9}/L)</th>
<th>Polymorphonuclear leucocytes</th>
<th>Protein (mg/L)</th>
<th>CSF: blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No organisms</td>
<td>&lt;1</td>
<td>0</td>
<td>&gt;0.4</td>
</tr>
<tr>
<td>Patient 1</td>
<td>Motile trophozoites</td>
<td>7200</td>
<td>91%</td>
<td>3900</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Motile trophozoites</td>
<td>240</td>
<td>54%</td>
<td>2700</td>
</tr>
</tbody>
</table>
Treatment

Given the limited data available, there are no set guidelines for antimicrobial therapy; however, it can be extrapolated from cases of patients who have survived that combination therapy with multiple anti-parasitic agents is required.

In 1969, Carter was able to demonstrate the sensitivity of the organism to amphotericin B (AMB) and it has remained the mainstay for treatment of PAM to this day. AMB has been used in all patients who have survived the illness. N. fowleri is highly sensitive to AMB in vitro with a minimum amoebicidal concentration of 0.01 µg/mL, and no resistance has been reported. Conventional AMB is preferred to liposomal forms as it can be given intrathecally as well as intravenously. Despite this, only a few patients have survived.

Other antifungal drugs, such as miltefosine and the azoles, have all shown in vitro activity against N. fowleri. Miconazole has synergistic activity when combined with AMB, and fluconazole is used as first line in combination therapy.

Miltefosine is a protein kinase B inhibitor that was originally developed as an antineoplastic agent. It also has anti-parasitic activity and is used for the treatment of leishmaniasis. Schuster and colleagues reported that miltefosine showed in vitro activity against free-living amoebae, including N. fowleri, Acanthamoeba spp. and B. mandrillaris. Recently, miltefosine has been used in the treatment of Acanthamoeba granulomatous amoebic encephalitis and PAM. Linam and colleagues described the case of a child treated for PAM with combination therapy including amphotericin, miltefosine, fluconazole and rifampicin, who survived with no significant neurological sequelae.

Rifampicin is commonly used in the treatment of PAM; however, it has variable central nervous system penetration and poor efficacy in vitro. It may also reduce the efficacy of the azole drugs due to cytochrome P450 interactions. Although azithromycin has shown some in vitro and in vivo activity against N. fowleri, the other macrolides are less effective. Atypical agents such as the diamidines and chlorpromazine have been studied in animal models but have yet to be utilised clinically.

Public health

As described, our patient was probably the third child to die with PAM in 14 years in a small area with a tiny population on remote Queensland cattle stations. As a response to the third death, a public health investigation found large numbers of N. fowleri at the patient’s homestead. In this district, water was sourced from deep artesian bores at about 60°C (Box 3) and cooled in open surface dams before being piped hundreds of metres on the surface to households, keeping water temperatures high. It was noted that the cases described in North Queensland were of children too young to be swimming in surface waters, the assumption being that they contracted the disease in the home environment. There had never been water treatment or filtration in the homesteads for generations; the clarity and taste of the bore water had often been a source of pride for owners. The difference in the present era of rural life was the advent of modern facilities, allowing the heated bore water to be pressurised via taps, hoses, toys and showerheads and delivered directly into the homestead.

The public health hypothesis was that:

- Hot artesian bore water and long surface pipelines promote large concentrations of N. fowleri, which can be sucked into water pipes from sediments, particularly in drought years.
- There had been no form of treatment for apparently clean water.
- In recent years, among young families with modern water facilities, there were many more opportunities for water to be forced into a vulnerable (non-immune) child’s nose at pressure.
- Simple filtration and disinfection of all water for washing and playing would prevent child deaths on these properties.

The public health dilemma was whether health promotion for a single, rare disease could be cost-effective or gain traction among
rural people possibly reluctant to accept an expensive treatment of their water. Untreated surface water can also lead to a whole spectrum of gastrointestinal diseases, even if these were not familiar to the remote communities. It was decided that a health promotion campaign about domestic water filtration and treatment could protect not only from PAM but also from a range of other diseases.

The family of our second confirmed patient embarked on a rural education campaign of their own to prevent any further deaths from PAM or other waterborne diseases, culminating in an episode of the television series Australian Story in November 2015.29 To coincide with this story, public health physicians gave a series of talks to communities and health staff across a wide area of outback Queensland. To follow up the face-to-face campaign, Queensland Health released a safe water booklet with advice on cost-effective filtration and disinfection.30 As a result, many rural properties and some small towns are installing water treatment equipment for the first time. The South Australian and Western Australian governments have online education resources specifically targeting rural communities at risk of amoeba acquisition,31,32 with the primary focus on prevention. The aim of the Queensland public health booklet was to provide a more comprehensive education document for water treatment in rural communities.33

Conclusion

We hope an increased awareness of N. fowleri and its association with warm, non-chlorinated water provides an opportunity for counselling families about safe water use: avoiding diving or jumping into or squirting untreated water, and disinfecting or filtering water used for washing and playing, as well as for drinking. In particular, bore water at warm or hot temperatures and other warm water sources should be considered ideal reservoirs for this organism. In the clinical setting, difficulties with analysing CSF make it unlikely that an accurate diagnosis could be provided in a remote environment. The presentation of an acutely unwell child with a history of bore water exposure and signs of meningitis or encephalitis should, however, prompt consideration of PAM as a potentially life-threatening diagnosis. Our experience with this disease clearly demonstrates the crucial role of medical professionals working in rural and remote Australia in primary prevention of this almost universally fatal condition.

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Sarcopenia: a potential cause and consequence of type 2 diabetes in Australia’s ageing population?

David Scott1, Barbora de Courten2,3, Peter R Ebeling1

Obesity epidemics have developed concurrently with population ageing worldwide. More than 40% of adults who were aged 25–29 years in 2000 will be obese by the time they reach the age of 60–64 years. The increasing prevalence of type 2 diabetes has mirrored obesity epidemics. There are about one million people living with type 2 diabetes in Australia, and more than 90% of these individuals are aged 40 years or older. Worldwide, the highest age-specific prevalence of any diabetes (19%) is observed in those aged 60–79 years, and this age group will also have the greatest proportional increase in patients with any diabetes by 2035.

A characteristic of ageing that has been under-investigated as a potential contributor to the risk of type 2 diabetes, and functional deficits common to this condition, is sarcopenia. We performed a non-systematic search of the MEDLINE and Embase databases using search terms including (but not limited to) “sarcopenia”, “muscle mass”, “physical performance”, “diabetes” and “insulin resistance”, with additional review of our personal reference libraries, to identify recent scientific literature investigating the effects of sarcopenia on the risk of type 2 diabetes, the progression of sarcopenia in older adults with existing type 2 diabetes, and potential therapies beneficial for both conditions.

Defining and diagnosing sarcopenia

The term sarcopenia, from the Greek for “poverty of flesh”, was first proposed in 1989 as a descriptor for age-related muscle wasting by Irwin Rosenberg, who commented that “no decline with age is more dramatic or potentially more functionally significant than the decline in lean body mass”. Although this decline in muscle mass with age has consequences for health, subsequent research has found that loss of muscle strength during ageing outpaces loss of muscle mass by up to five times, and that low muscle strength is more consistently associated with functional decline than low muscle mass. Accordingly, experts now describe sarcopenia as a multidimensional condition requiring assessment of muscle mass, muscle strength and physical performance.

The development of clinically relevant operational definitions for sarcopenia and the recent establishment of an International Classification of Diseases, 10th revision, (ICD-10-CM) code for the condition have provided the first real impetus for clinicians to diagnose sarcopenia in a systematic fashion. Box 1 summarises three current operational definitions and their appropriate measurement techniques and thresholds. Although the lack of consensus on a single operational definition of sarcopenia is a barrier to its clinical assessment, the condition can be diagnosed using relatively inexpensive equipment requiring minimal time and expertise. For example, the European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as the presence of low appendicular lean mass (generally assessed by dual-energy x-ray absorptiometry, but can also be assessed by portable bioelectrical impedance analysis equipment) in addition to low hand grip strength (measured by hydraulic hand grip dynamometer) or gait speed over a short (4 m) walkway. The International Working Group on Sarcopenia30 and the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium Sarcopenia Project31 state that sarcopenia can be assessed using the same equipment, but with different thresholds.

There is justification for sarcopenia case finding in health care. Although sarcopenia prevalence estimates are influenced by the operational definition applied, as many as 30% of community-dwelling older adults may have the condition, depending on demographic characteristics including age and ethnicity. Sarcopenia is consistently a predictor of poor quality of life, difficulties with activities of daily living, mobility disability, falls, fractures, institutionalisation and mortality, independent of other comorbidities. The costs of sarcopenia to health services in

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Australia are likely to be substantial, given that annual health-related costs for older Dutch adults were about three times higher for individuals with sarcopenia than for those without the condition.13

Sarcopenia in the pathogenesis of type 2 diabetes

The metabolic outcomes of sarcopenia have received less attention than the functional consequences in the research literature, but they are no less relevant clinically. There are several pathways by which age-related changes in skeletal muscle may contribute to insulin resistance (Box 2). Skeletal muscle is the largest insulin-sensitive tissue in the body and accounts for 80% of glucose uptake under euglycaemic hyperinsulinaemic conditions. Skeletal muscle insulin resistance is a key process in the development of type 2 diabetes, which may be observed decades before β-cell failure and hyperglycaemia develop.14 It is likely that significantly lower skeletal muscle mass results in reduced capacity for glucose disposal in older adults with sarcopenia.

In addition to a loss of mass during ageing, muscle undergoes numerous composition changes that are often described as declines in muscle quality. These declines in quality partly explain the faster rate of loss of muscle strength compared with loss of mass, and may also increase the risk of insulin resistance. Ageing skeletal muscle has reduced oxidative capacity, resulting in increased production of reactive oxygen species, which contributes to oxidative mitochondrial DNA mutagenesis and pro-inflammatory processes.15 Both mitochondrial dysfunction and chronic low-grade inflammation are associated with insulin resistance.15 Also, during ageing, there is an increase in infiltration of skeletal muscle by ectopic fat, including intramyocellular lipids (IMCL) and adipocytes located between muscle groups (intermuscular) and between muscle fascicles (intramuscular). Both IMCL and intramuscular and intermuscular adipose tissue (IMAT) have been implicated in insulin resistance.16 Paradoxically, high levels of IMCL are reported in endurance athletes, suggesting that high levels are beneficial for some individuals. IMAT-derived adipocytes may deleteriously affect muscle metabolism and insulin sensitivity through increased local secretion of pro-inflammatory adipokines, and intermuscular fat may also impair insulin action through reducing blood flow to muscle.16

### 1 Suggested measurement techniques and thresholds for components of sarcopenia according to current consensus definitions

<table>
<thead>
<tr>
<th>Component</th>
<th>Thresholds</th>
<th>Method and equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Working Group on Sarcopenia in Older People6</td>
<td><strong>Low muscle mass</strong>&lt;br&gt;Appendicular lean mass adjusted for height (m²):&lt;br&gt;Men: &lt; 7.26 kg/m²&lt;br&gt;Women: &lt; 5.50 kg/m²&lt;br&gt;Skeletal muscle mass adjusted for height (m²):&lt;br&gt;Men: &lt; 8.87 kg/m²&lt;br&gt;Women: &lt; 6.42 kg/m²</td>
<td>Whole-body DXA and stadiometer &lt;br&gt;BIA and stadiometer</td>
</tr>
<tr>
<td><strong>Low muscle strength</strong>&lt;br&gt;Hand grip strength:&lt;br&gt;Men: &lt; 30 kg&lt;br&gt;Women: &lt; 20 kg</td>
<td>Hydraulic hand grip dynamometer</td>
<td></td>
</tr>
<tr>
<td><strong>Poor physical performance</strong>&lt;br&gt;Gait speed: ≤ 0.8 m/s</td>
<td>4 m walkway and stop watch</td>
<td></td>
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</tbody>
</table>

International Working Group on Sarcopenia10

<table>
<thead>
<tr>
<th>Component</th>
<th>Thresholds</th>
<th>Method and equipment</th>
</tr>
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<tbody>
<tr>
<td><strong>Low muscle mass</strong>&lt;br&gt;Appendicular lean mass adjusted for height (m²):&lt;br&gt;Men: &lt; 7.23 kg/m²&lt;br&gt;Women: &lt; 5.67 kg/m²</td>
<td>Whole-body DXA and stadiometer</td>
<td></td>
</tr>
<tr>
<td><strong>Poor physical performance</strong>&lt;br&gt;Gait speed: &lt; 1.00 m/s</td>
<td>4 m walkway and stop watch</td>
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</tbody>
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Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project11

<table>
<thead>
<tr>
<th>Component</th>
<th>Thresholds</th>
<th>Method and equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low muscle mass</strong>&lt;br&gt;Appendicular lean mass adjusted for BMI (kg/m²):&lt;br&gt;Men: &lt; 0.789&lt;br&gt;Women: &lt; 0.512</td>
<td>Whole-body DXA, stadiometer and weight scales</td>
<td></td>
</tr>
<tr>
<td><strong>Low muscle strength</strong>&lt;br&gt;Hand grip strength:&lt;br&gt;Men: &lt; 26 kg&lt;br&gt;Women: &lt; 16 kg</td>
<td>Hydraulic hand grip dynamometer</td>
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BIA = bioelectrical impedance analysis. BMI = body mass index. DXA = dual-energy x-ray absorptiometry.
Using peripheral quantitative computed tomography imaging of calf muscles, we have observed that overweight and obese women aged 50–89 years with type 2 diabetes have a 70% larger IMAT cross-sectional area and 4% lower muscle density (indicating higher levels of intramuscular adipose tissue) than women without type 2 diabetes matched by age and body mass index (both $P < 0.05$, our unpublished data) (Box 3). In the Look AHEAD trial of middle-aged to older adults in the United States, participants with type 2 diabetes had 0.5 kg more IMAT than did controls without diabetes. IMAT, but not subcutaneous adipose tissue, is positively correlated with insulin resistance in type 2 diabetes, despite constituting a much smaller proportion of total body fat.

Leg muscle mass, strength and functional performance are significantly lower in older patients with type 2 diabetes compared with healthy controls, but few prospective studies have investigated the risk of incident type 2 diabetes in older adults with sarcopenia. Among obese participants in the English Longitudinal Study of Ageing, there was a more than threefold increased risk of self-reported incident type 2 diabetes over 6 years for those whose baseline hand grip strength was in the sarcopenic range according to the FNIH definition. In the Osteoporotic Fractures in Men study, older men in the highest quartile for insulin resistance (among those without type 2 diabetes), defined by the homeostasis model assessment of insulin resistance, had a twofold increased likelihood of a 5% decline in total lean body mass over almost 5 years. An 11-year follow-up of the Health, Aging and Body Composition (Health ABC) Study found a 40–60% decrease in the risk of incident type 2 diabetes among normal-weight women with greater abdominal and thigh muscle area, but greater muscle mass predicted an increased risk in overweight and obese women. It is possible that larger IMAT depots in the muscles of obese women explain this controversial finding.

Factors including inflammation, comorbidities and low levels of physical activity also predispose patients with type 2 diabetes to an increased risk of sarcopenia. In the Health ABC Study, thigh muscle size declined twice as fast over 6 years in older women with type 2 diabetes compared with women without diabetes, and strength declined by one-third more over 3 years in older patients with type 2 diabetes compared with those without diabetes.

Patients in the US over the age of 60 years with type 2 diabetes were found to have poorer balance and increased likelihood of falls in the previous 12 months compared with patients without diabetes. In a prospective analysis of the Study of Osteoporotic Fractures, older women with insulin-treated type 2 diabetes at baseline had an almost threefold increased risk of falling more than once a year over an average of 7 years, compared with patients without diabetes. Conditions common to type 2 diabetes, such as hypoglycaemia, poor vision and peripheral neuropathy, undoubtedly contribute to the increased risk in older adults with diabetes, but poor physical function is also clearly important. In a secondary analysis of the North Carolina Established Populations for Epidemiologic Studies of the Elderly and Women’s Health Initiative trials, a one-third higher risk of incident fracture was observed for older women with type 2 diabetes, but this association was mediated by poor physical function. Thus, poor muscle function may partly explain why older patients with type 2 diabetes have more fractures than those without diabetes, despite generally having higher bone mineral density. Furthermore, the increased mortality risk for normal-weight compared with overweight patients with type 2 diabetes appears to be mediated by their smaller relative muscle size.

**Concurrent therapies for type 2 diabetes and sarcopenia**

There is little evidence that common pharmacological therapies for type 2 diabetes are beneficial in preventing or reversing sarcopenia in older adults. On the contrary, metformin, the first-line pharmacological therapy for diabetes, is an AMP-activated protein kinase agonist and may cause autophagic muscle cell death, while insulin stimulates muscle protein synthesis in young but not older adults, suggesting it provides no protection from age-related muscle wasting.

Lifestyle modification, particularly weight loss, is a key therapeutic component for type 2 diabetes, with modest weight loss (5–10% of bodyweight) contributing to improved glucose control. However, weight loss can include declines in muscle mass and may result in undesirable metabolic and functional consequences, particularly in patients with type 2 diabetes and sarcopenia. For this reason, exercise that promotes gains in muscle mass and function should be a component of lifestyle modification for older adults with type 2 diabetes. A 6-month randomised controlled trial of high-intensity progressive resistance training plus moderate weight loss versus moderate weight loss alone in 36 overweight older adults showed threefold greater decreases in glycated haemoglobin levels in the resistance training group. Furthermore, this group had significantly higher lean body mass and muscle strength at follow-up compared with the weight loss-alone group, despite similar reductions in fat mass. Similarly, in postmenopausal women with obesity, glucose infusion rates increased significantly after 16 weeks of aerobic plus resistance (involving weight machines) exercise, but not aerobic exercise alone.

Clearly, resistance training requiring access to large equipment such as weight machines is not feasible in most clinical settings. Nevertheless, exercise programs requiring minimal equipment may improve physical performance in older adults with type 2 diabetes. In the US Lifestyle Interventions and Independence for Elders...
required to achieve a success in enhancing adaptations to exercise.36
regulators of the transcription of these genes may therefore have effects of 5 months of aerobic or resistance training on physical function in overweight and obese women aged 65–79 years, 13%, 30% and 30% showed no improvement in aerobic capacity, knee extension strength and physical performance, respectively.27 It has been hypothesised that poor exercise responsiveness within skeletal muscle occurs as a result of attenuated expression of key fuel metabolism genes, including peroxisome proliferator-activated receptor γ coactivator-1α, peroxisome proliferator-activated receptor β/δ and pyruvate dehydrogenase kinase. Studies investigating regulators of the transcription of these genes may therefore have success in enhancing adaptations to exercise.28
Inflammation, low 25-hydroxyvitamin D (25(OH)D) status and poor muscle quality are all common in people with type 2 diabetes and may contribute to poor exercise responsiveness. Almost 20% of sedentary adults with elevated plasma C-reactive protein (CRP) concentrations have no improvement in fasting insulin levels after an endurance training program.38 We have found that older adults with high baseline levels of both 25(OH)D (> 50 nmol/L) and physical activity (≥ 10 000 steps/day) gained 2 kg less body fat over 5 years compared with those who had low 25(OH)D levels but high levels of physical activity, suggesting that adequate 25(OH)D levels enhance the benefits of physical activity for body composition in older adults.39 In support of this, the greatest improvements in physical performance in frail Japanese older adults after 3 months of exercise were observed in those with higher baseline 25(OH)D levels (> 67.5 nmol/L).40 Older women with adequate vitamin D status also demonstrated greater fat oxidation during exercise.41
We have previously proposed that low vitamin D status promotes adipogenesis, leading to increased IMAT deposition.42 Given older adults with high baseline IMAT levels have blunted improvements in muscle function after exercise,43 it is possible that increased IMAT and associated skeletal muscle inflammation is a mechanism through which low vitamin D status contributes to poor exercise responsiveness. Vitamin D supplementation has, to date, shown few benefits for metabolic health and physical function, although studies have been limited by inadequate sample sizes, doses and durations, and by inclusion of vitamin D-replete participants.44 This therapy is only likely to be effective in those who achieve replete 25(OH)D levels from initial low levels. A 12-month weight loss intervention combined with 2000 IU/day of vitamin D showed no effect on body composition compared with placebo.45 However, participants whose 25(OH)D levels reached ≥ 75 nmol/L lost 3 kg more bodyweight and 2% more body fat than did those whose 25(OH)D levels were < 75 nmol/L.

Although Australian guidelines currently recommend dietary protein intake of 1 g/kg/day for adults aged over 70 years, intakes of 1.2 to 1.6 g/kg/day may be most effective for enhancing exercise-induced muscle gains, and there is no evidence of renal disorders with these intakes.46 Managing weight loss in older patients with type 2 diabetes while increasing the proportion of energy from protein may be best accomplished by reducing carbohydrate intake.47 High protein intakes may also support weight loss by increasing satiety. A 4-month cluster randomised controlled trial of 100 female nursing home residents found that progressive resistance training combined with 1.3 g/kg/day of red meat resulted in greater gains in muscle mass and strength and decreases in fat mass, relative to resistance training alone.48 Muscle protein synthesis in response to protein supplementation in older adults may also be enhanced by adequate vitamin D status. Daily supplementation of 2 g β-hydroxy β-methylbutyrate (a metabolite of leucine), 5 g arginine and 1.5 g lysine for 12 months in older adults resulted in significant improvement in knee extension strength only for those whose baseline 25(OH)D levels were ≥ 75 nmol/L.49 Similarly, in older adults with sarcopenia, exercise plus daily whey protein (22 g), essential amino acids (11 g, including 4 g leucine) and vitamin D (100 IU) resulted in almost 2 kg greater gain in lean mass compared with exercise alone, as well as significant gains in hand grip strength and declines in CRP levels.50 Nevertheless, further research is required to confirm the effects of dietary supplementation in patients with type 2 diabetes and sarcopenia.

Conclusions
The prevalence and socio-economic burden of sarcopenia will increase in Australia in coming years, but sarcopenia presently receives little attention in clinical settings, likely due in large part to a lack of clarity about its definition and assessment. Expert groups have attempted to reduce this confusion by providing clinical guidelines and, while further work is required to achieve a consensus operational definition of sarcopenia, diagnosis can now be easily integrated into clinical practice. The establishment of the ICD-10-CM code will enable improved reporting of the condition. Through integrating sarcopenia case finding into clinical practice, this previously under-appreciated risk factor for type 2 diabetes in older adults can be systematically monitored, and lifestyle modification for primary and secondary prevention much better targeted. The evidence presented here shows that older adults with sarcopenia are at risk of developing type 2 diabetes, and those with prevalent type 2 diabetes show an accelerated loss of muscle mass and function that may increase the risk of further metabolic and functional declines. Interventions that reverse or halt progression of sarcopenia in patients with type 2 diabetes are likely to have important health benefits, given that the evidence suggests poor muscle mass and function substantially mediate associations of type 2 diabetes with incident fractures and mortality.

Including progressive resistance training in lifestyle modification programs should be considered for older patients with sarcopenia, type 2 diabetes or both. Clinicians need to be cognisant that individual responses to exercise vary considerably in patients with type 2 diabetes, and beneficial metabolic and functional outcomes are more likely to be obtained when adherence and responsiveness to the therapy are closely monitored, as with pharmacotherapy.
Exercise programs should also be regularly adapted to support ongoing improvements in muscle mass and function. Ensuring adequate vitamin D status and maintenance of dietary protein intake during energy restriction may optimise the effects of exercise interventions targeting type 2 diabetes and sarcopenia in older adults, thereby delaying onset of morbidity and loss of independence related to both conditions.

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Provenance: Not commissioned; externally peer reviewed.

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Using opioids in general practice for chronic non-cancer pain: an overview of current evidence

TO THE EDITOR: We note with interest the recent article by Currow and colleagues, discussing the use of opioids for the management of non-cancer pain. This piece highlights increased opioid use occurring in Australia and elsewhere. As large scale providers of residential medication management reviews (RMMRs) in the residential aged care facility setting, we write to provide a different insight into the use of these analgesics among older people. We recently analysed aggregated, de-identified data from 15 178 RMMR reports — provided in response to general practitioner referrals from 2014 to 2016 — examining the use of potent oral analgesics. We found that there was little use of methadone or hydromorphone, and the subsequent analysis was limited to addressing only oral morphine, oxycodone and tramadol. Unlike the data from the Australian statistics on medicines, the RMMR represents a snapshot picture of all medicines prescribed, regardless of whether these were subsidised by the Pharmaceutical Benefits Scheme.

In 4474 cases (29.5%), residents who received an RMMR were treated with at least one of the three agents. Oxycodone alone accounted for 3356 cases (22.1%), followed by morphine (n = 611, 4.0%) and tramadol (n = 500, 3.3%). The World Health Organization stipulates a defined daily dose (DDD) for pharmaceutical drugs, specified as the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is set at 75 mg daily for oxycodone, 100 mg daily for morphine and 300 mg daily for tramadol. For 2014 and 2015, each drug was prescribed below the DDD in more than 99% of cases, but for 2016 until May, oxycodone doses above the DDD have increased to 9.1%. Data reveal that, although prescribing rates for morphine and tramadol have remained stable, prescribing rates for oxycodone have increased rapidly (738 cases in 2014, 1512 in 2015, and 1106 for the first 5 months of 2016). As older people are more susceptible to direct and indirect effects of potent analgesics, these preliminary data suggest that closer examination of opioid prescribing in the residential aged care facility setting appears warranted.

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In reply: The letter by Alderman and colleagues is a timely reminder of the continued importance of post-marketing surveillance, especially for medications with frequently encountered and well characterised harms. As outlined, such surveillance must include all medications, whether or not they are subsidised or sold over the counter, in order to account for drug–host and drug–drug interactions.

Pain is prevalent in the elderly and when residents in residential aged care facilities (RACFs) are asked to rate pain themselves, up to two-thirds of them confirm its presence. Pain is a symptom encountered frequently in this clinical care, is mostly multifactorial and requires a response that decreases its intensity and hence reduces suffering.

It is unlikely that many residents of RACFs are ever referred for assessments by chronic pain services in Australia. The responsibility for management of chronic pain in the frail elderly falls almost entirely on general practitioners, nurses, care workers and pharmacists. Reducing pain in RACFs requires a whole-of-systems response that promotes clinician capacity building (such as audit and feedback, education, training and coaching); non-pharmacological and pharmacological interventions tailored to each resident’s unique pain needs, including the World Health Organization analgesic ladder step 3 opioids, such as morphine or oxycodone, for some carefully selected residents; and ongoing pharmacovigilance studies.
The real-world mapping of prescribing in groups at particular risk of adverse events needs to be more widespread in the health system. This is even more important when the groups being studied were almost certainly excluded systematically from the phase 2 and 3 studies that formed the basis of current registered indications. Greater investment in high quality pharmacovigilance is an investment in reducing harm and better targeting of therapies — the essence of personalised medicine.

Current evidence for the management of chronic non-malignant pain is being systematically synthesised as it evolves. Bennett and colleagues point to resources that help to inform the excellent practice support offered by the NPS MedicineWise program. By focusing on managing pain, it is hoped that needed suffering can be reduced safely across the whole community.

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Surgical management of low back pain

To the Editor: Atkinson and Zacek stated that chronic low back pain is reaching epidemic proportions for a variety of medical, psychosocial and work-related problems. The direct and indirect economic cost in Australia has been modelled at $9.17 billion. The provision of surgery for non-specific low back pain (NSLBP) has the potential to significantly increase these costs, particularly under the economic cloak of “work cover”. A review of chronic low back pain pointed out that only 15% of cases may be due to significant intervertebral disc prolapse with neural compromise. The remaining cases were placed under the umbrella of NSLBP, which is a negative description of the failure to reach a diagnosis.

Low back pain, which accounts for 25% of cases of NSLBP, may originate in the sacroiliac joint, as in the context of pelvic girdle pain in peripartum women. A northern European study has described patients with such pain arising from dysfunction of the sacroiliac joint in the peri-partum period. Magnetic resonance imaging (MRI) failed to identify these patients, leading to the establishment of clinical criteria for the diagnosis.

The development of a working model of the pathophysiology has assisted in providing appropriate therapy for such patients, which resulted in measurable improvement in 80% of the patients with physiotherapy. A scintigraphic technique, using single-photon emission computed tomography combined with computed tomography, has been developed and validated for diagnosis with high sensitivity and specificity.

Although the role of the sacroiliac joint in lateralising low back pain (pseudo-sciatica) was identified in 1905, it has been lost from medical view since the 1934 study of intervertebral disc prolapse and neural compromise by Mixter and Barr.

The sacroiliac joint may also be injured in trauma (sacroiliac joint incompetence) to the buttocks or low back and, in such cases, MRI scans will invariably be normal, resulting in the patient being classified as having NSLBP with psychological disturbance. Such patients may then be subjected to a variety of questionable treatments including surgery. Appropriate diagnosis and treatment can result in significant clinical improvement in about 25% of cases classified as NSLBP.

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Leslie Cowlishaw (1877–1943): the “bibliophile from the bush”

To the Editor: The article by Roxanas is an excellently researched piece; however, the comments regarding the stewardship of the Cowlishaw Collection by the Royal Australasian College of Surgeons (RACS) and the collection’s public availability should be corrected.

Roxanas states that “it is one of the most significant medical history collections in Australia, but the public has difficulty accessing it, and many items are in disrepair and in urgent need of restoration”. This may give the impression that the RACS does not understand the value of the collection and, possibly, that it is negligent in its custody.

The Cowlishaw Collection, part of the college’s large rare and historic books collection, comprises over 2000 volumes. Most of them are in sound condition, but there are about 120 volumes in need of remedial attention. Twelve years ago, our college curator instituted a program of phase boxing for all our damaged rare and historic books pending permanent repairs and conservation. The program began with the Cowlishaw Collection and is continuing.

The RACS takes seriously its responsibility for preserving these important documents, understanding that they represent the most important collection of historical medical books in Australia, with volumes dating from as early as 1483. Conservation is hampered by the small number of specialists with the necessary skills to whom the volumes can be entrusted.

In 1979, the RACS published a catalogue of its historic books, including the Cowlishaw Collection, written by Professor Kenneth Russell. However, in the 21st century, this is not the most appropriate method of alerting scholars to the collection. Therefore, the Russell catalogue has been digitised and is freely accessible on the RACS website (http://search.surgeons.org/search?getfields=*&client=default_frontend&proxystylesheet=default_frontend&site=default_collection&q=Cowlishaw%20Collection). The collection is a closed one and we welcome requests from scholars — which should be addressed to our curator — to study these volumes.

The RACS fully recognises the historic worth and irreplaceability of the collection and our responsibility to maintain it for posterity.

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Competing interests: I am the president of the Royal Australasian College of Surgeons.
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How are tobacco smokers using e-cigarettes? Patterns of use, reasons for use and places of purchase in New South Wales

To the Editor: Dunlop and colleagues provide valuable insights into the use of e-cigarettes and their potential for improving public health.
Letters

First, e-cigarettes are popular with Australian smokers. Despite legal barriers and restricted availability, 9% of smokers and 7% of recent quitters are currently using e-cigarettes.

The appeal of e-cigarettes to young smokers is important as they have the most to gain from quitting. The study reported that 16% of 18–29 year olds were current e-cigarette users. It also noted the interest from smokers in lower socio-economic groups, who have lower quit rates with conventional therapies.

Second, the study found that smokers are using e-cigarettes principally to quit and to reduce the harm from tobacco and this should be encouraged. Standard smoking cessation therapies have relatively low compliance and success rates and many smokers remain unable to quit smoking in spite of repeated attempts. Evidence from England shows that the availability of e-cigarettes has led to a substantial increase in the number of long term quitters who otherwise would not have quit.

Third, prohibition is not working. The use of e-cigarettes has risen considerably since the New South Wales Population Health Survey in 2014. Some smokers are purchasing nicotine liquid online or “under the counter” and are being criminalised for “quitting the wrong way”. Many others are forced to use nicotine-free solutions, which are significantly less effective.

According to a recent landmark report by the Royal College of Physicians in the United Kingdom, the widespread uptake of e-cigarettes has huge potential to prevent death and disability from tobacco. Current laws allow the widespread sale of deadly tobacco products while perversely banning a safer alternative. Australian smokers have embraced e-cigarettes to reduce the harm from smoking and it is now up to the regulators and health professionals to provide their support.

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Are we optimising outcomes in Australia’s framework for the supply of plasma-derived medicines?

To the Editor: Australian governments endorse a policy for the evidence-based supply of plasma derivatives, which are procured from domestically collected plasma and managed through contracts between the National Blood Authority and the collection and fractionation agencies in Australia, these are the Australian Red Cross and CSL Behring respectively. Historically, these organisations have been granted a sole supplier status by Australian governments and their activities, unlike most arrangements for service provision, have not been subject to the mainstream tender processes for government procurement.

A review conducted by the Australian government in 2006 concluded that the single supplier arrangement for manufacturing plasma in a domestic factory was to stand and would not be subject to possible competition from international organisations. This system generates a potential surplus of other products not needed in Australia. In particular, the government’s decision, in 2004, to fund the provision of imported recombinant coagulation factors used to treat haemophilia has generated a substantial surplus of antihaemophilic factor, which, through discarding the primary cryoprecipitate fraction, is currently not used.

Recent international developments in plasma fractionation arrangements cast some doubt as to whether the system endorsed by the Flood review still represents the best option for Australia. The publicly available information regarding the pricing of contract plasma fractionation indicates that the fractionation services provided by CSL Behring cost the Australian system $420 per kg of plasma. In Italy, in a recent competitive tender for similar plasma fractionation services, the same company won the contract through a bid of €94.6 (about $140) per kg of plasma. In addition, in other countries, such as Canada and Italy, cryoprecipitate surplus is further fractionated to concentrate, which is then donated to humanitarian programs to ensure that altruistically donated plasma derivatives are not wasted. There has been little indication that Australian governments have a policy for a similar program to manage the surplus, particularly for antihaeomophilic factor. Scarce health care resources, including freely donated blood, should be managed with care, and the example of other countries should be noted by Australian decision makers charged with ensuring full value for the health dollar.

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Competing interests: I provide consultancy services to the manufacturers of biotherapies.

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In reply: In his letter about our article, Mendelsohn states that e-cigarettes are popular with Australian smokers. While some groups of smokers in our sample were more likely to be using e-cigarettes, the overall use was relatively low at 9%. Mendelsohn also suggests that the rates of e-cigarette use are increasing, using 2014 data from the New South Wales Population Health Survey as a comparison. However, the samples of our survey and the NSW Population Health Survey are not comparable, with ours being a sample of current smokers and recent quitters and the other a general population survey.

The United Kingdom report from the Royal College of Physicians referenced by Mendelsohn also recognises that there are public health concerns over e-cigarette use because it may be seen as renormalising the act of smoking, acting as a gateway to smoking in young people, and being used for temporary, not permanent, abstinence from smoking. While the UK reports no evidence that these processes are occurring to any significant degree, our research provides the first evidence that Australian adults aged 18–29 years old are in fact dual using tobacco cigarettes and e-cigarettes, and that quitting is not the primary intent of their use. Moreover, emerging research continues to question whether e-cigarettes act as a gateway to tobacco smoking among young people.

The same UK report also recognises that, internationally, the tobacco industry has become involved in the e-cigarette market — which may undermine the tobacco control efforts — and that existing alternative nicotine replacement therapies could be promoted.

Caution and further investigation is warranted, particularly in the Australian context, before lauding e-cigarettes as a potential solution for smoking cessation, particularly among young people.

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do: 10.5694/mja16.00830
Re-invention in China

A gap year spent in China changed the career path of Dr Anna Foley

A YEAR in China before committing to advanced training changed gastroenterologist Dr Anna Foley’s life. After completing her MB BS at Monash University in 2001, Dr Foley did her internship and residency at The Alfred, before moving to Sydney for a stint at Concord Repatriation General Hospital until she earned her fellowship to the Royal Australasian College of Physicians.

“Up until then I was going to do rheumatology,” she tells the MJA. “I had a fantastic mentor in Sydney in rheumatology. He was a great mentor and helped me to formulate my plans.”

But then came her year in China.

“I had almost committed to doing rheumatology but changed my mind during [that] year,” Dr Foley says.

“In China I realised it was time to separate from [my mentor] and meet new people. I also did a bit of general practice there, which put me off a little bit. I saw a lot of chronic back pain and it was a lot of the same thing every day.

“That was misinformed of me, but nevertheless [it shaped my thinking].”

On her return to Melbourne, Dr Foley committed instead to gastroenterology, and went back to The Alfred and Box Hill Hospitals to complete her advanced training.

“I had always been interested in gastroenterology — it’s a nice combination of different skills and there’s lots of communication with the patients.

“The patients are often very challenging. They’ve got long-term illness, and there’s a psychological overlay to much of it.

Dr Foley finished her gastroenterology training in 2009 and started in practice in 2010. She can be found at Brighton Gastroenterology on Melbourne’s bayside, and also has public appointments at both Box Hill and The Alfred, providing services in general gastroenterology and specialist functional gut disorder clinics. She has a keen interest in inflammatory bowel disease and performs gastroscopy, colonoscopy and capsule endoscopy.

“It’s been what I expected,” she says. “I was familiar with the hospital and the people and I had a really good advanced training experience. It prepared me quite well for practice.”

According to Dr Foley, there is no shortage of gastroenterologists. “In fact it’s quite a difficult program to get in to.”

One thing that has changed for the better since she started her advanced training is the gender balance in the specialty.

“It was very male dominated,” Dr Foley says. “It almost seemed like you had to be the son of a top gastroenterologist in order to get in to the training program. I almost shied away from it for that reason.

“But now, pleasingly, that’s been corrected.”

And just as well, as Dr Foley says female gastroenterologists are “absolutely essential for the field”.

“There are plenty of patients who couldn’t say to a man what they can to a woman. Older women with faecal incontinence, for example. Some have been to male gastroenterologists before and never mentioned it.

“A lot of teenage girls with functional gut disorders, irritable bowel syndrome … they’d rather speak to a woman.”

About 30% to 35% of people have a functional gut disorder through their life and it’s more common in women, says Dr Foley.

“It’s incredibly common. Whether the incidence is increasing or if there’s just greater awareness, it’s difficult to say. We’re certainly more interested in treating it than we used to be.”

Despite going in a different direction than the one suggested by her rheumatology mentor, Dr Foley believes mentorship should be an essential part of the support system for students and doctors-in-training.

“Mentors are such a great asset,” she says. “I think we’ve missed the boat in medicine with that a bit. Mentorship needs to be more formalised — matching people with appropriate mentors. A good mentor can have such a great influence, helping young people to make better choices.”

Dr Foley’s next 5 years will be about “reinvention”, she says. “It’s important to have other dialogues, constantly dream of reinvention.

“It’s good to stay engaged and on your toes.”

Cate Swannell
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NHMRC’s “10 of the best” research projects

The National Health and Medical Research Council has announced its “10 of the best” research projects for 2015. Professor Anne Kelso, Chief Executive Officer of the NHMRC, said the projects selected had “achieved results of particular significance for the improvement of human health — whether through advancement of knowledge or the prevention, detection or treatment of disease”.

“Each year when projects are short-listed for this award, we are struck by the extraordinary quality and diversity of research being undertaken in Australia with NHMRC support. This … is an opportunity to showcase some of that research and to honour the brilliant researchers who conceived, planned and delivered it.”

1. Drilling down: discovering the origins of dental anxiety, by Associate Professor Jason Armfield, from the University of Adelaide. “Associate Professor Armfield set out to explain the origins of dental fear and to understand why fear of the dentist is a serious psychological problem for many Australians. He developed a ‘dental anxiety scale’ that will help to identify and treat the condition across the world, leading to more people visiting the dentist and better population level oral health.” A/Prof Armfield was awarded an NHMRC early career fellowship worth $336 561. Team members: Dr Peter Arrow, Associate Professor Donald Chi, Mr Serge Bitzer, Dr Leanne Purins, Dr Trevor Lockett, Mr Charles Lindall, Dr Larry LaPointe, Professor Tony Burgess, Professor Ed Nice, Professor Peter Gibbs, Associate Professor Andrew Ruszkiewicz, Mr James Moore, Dr Michelle Thomas, Associate Professor Rajvinder Singh, Associate Professor Paul McMurrick.

2. Delivering Australia from neurodegeneration. Associate Professor Helen Cooper led a team from the University of Queensland. “[Her] research aims to understand the molecular mechanisms controlling the birth of new neurons in the adult brain. In the long term, it is hoped that these insights will help to design therapeutic approaches to treat neurodegenerative diseases.” A/Prof Cooper and her team were awarded a project grant worth $322 524. Team members: Dr Conor O’Leary, Dr DanaKai Bradford, Dr Min Chen, Ms Amanda White, Associate Professor Zhi Ping Xu, Professor Perry Bartlett.

3. Sanguine advances in detecting colorectal cancers. Associate Professor Leah Cosgrove and her team from the CSIRO (Food and Nutritional Sciences) developed a simple blood test to diagnose colorectal cancer. “A reliable, non-invasive blood test could augment the National Bowel Cancer Screening Program, either as an adjunct primary screen for those unable to do the stool test, or in triaging positive subjects to colonoscopy. This could help drive a significant reduction in colorectal cancer deaths in Australia.” A/Prof Cosgrove and her team were awarded a development grant worth $542 260. Team members: Dr Kim Fung, Dr Tim Adams, Dr Bruce Tabor, Dr Mike Buckley, Ms Ilka Priebel, Dr Leanne Purins, Dr Trevor Lockett, Mr Charles Lindall, Dr Larry LaPointe, Professor Tony Burgess, Professor Ed Nice, Professor Peter Gibbs, Associate Professor Andrew Ruszkiewicz, Mr James Moore, Dr Michelle Thomas, Associate Professor Rajvinder Singh, Associate Professor Paul McMurrick.

4. The scorpion king: lighting the way to defeating brain cancer. Professor David Craik and his team from the University of Queensland set out to make synthetic derivatives of a naturally occurring peptide, chlorotoxin, from the venom of a scorpion to use for brain tumour imaging. “The work was based on a discovery by collaborator, Dr Jim Olson, that through attaching a dye to chlorotoxin it could be used to ‘light up’ tumours. This allows surgeons to pick up small amounts of cancerous tissue during surgery, reducing the risk of the tumour reoccurring.” Prof Craik and his team were awarded a project grant worth $511 299. Team members: Professor Norelle Daly, Dr Jim Olson, Dr Muharrem Akcan, Ms Paola Ojeda, Dr Conan Wang, Dr Richard Clark, Dr Sonia Troeira Henriques, Dr Yen-Hua Huang.

5. Protein: the key to improved kidney functionality. Associate Professor Gordon Doig and his team from the University of Sydney showed that “critically ill patients who received better nutrition were less likely to develop kidney injury. These findings represent an important first step towards global practice change and offers the potential to reduce the need for surgery, dialysis and transplantation.” A/Prof Doig and his team were awarded a project grant worth $845 052. Dr Fiona Simpson, Ms Elizabeth Sweetman, Ms Philippa Heighes, Ms Jennifer Hannam, Professor Carol Pollock, Dr Douglas Cheshire.

6. Gluten for punishment: challenging non-coeliac gluten sensitivity. Professor Peter Gibson and his team from Monash University “set out to determine whether gluten causes problems in people who do not suffer from celiac disease. The team found that short-chain carbohydrates called FODMAPs, not gluten, might be triggering symptoms such as bloating and stomach pain. The results have put some scientifically valid findings in this controversial area.” Prof Gibson and his team were awarded project grant worth $661 496. Team members: Dr Jane Muiir, Dr Jessica Biesiekierski, Ms Simone Peters,
Dr Evan Newnham, Dr Greg Yelland, Dr Jacqueline Barrett, Mrs Ourania Rosella.

7. Mending a broken heart: repairing injured heart cells. Professor Robert Graham and his team from the Victor Chang Cardiac Institute “embarked on their research to understand how the heart develops after birth and why heart muscle cells lose their ability to divide and make new cells. Their research markedly shifted the goal post and showed that heart muscle cells actually retain an ability to divide until adolescence. This discovery holds great promise for new approaches to managing a range of heart conditions.” They were awarded a project grant worth $536 732. Team members: Dr Siiri Iismaa, Dr Ming Li, Ms Amy Nicks, Dr Jianxin Wu.

8. Indigenous health: understanding the health gap. Professor Louisa Jorm and teams from Western Sydney University and the University of NSW “linked and scrutinised the vast data held by modern healthcare systems to understand the factors influencing disadvantage for Indigenous Australians. This important research will translate it into better disease prevention and patient care for Indigenous Australians, as well as more effective health care spending.” Prof Jorm and her teams were awarded a project grant worth $484 697. Team members: Ms Deborah Randall, Professor Alastair Leyland, Professor Sandra Eades, Ms Sanja Lujic, Dr Timothy Churches, Associate Professor Mary Haines, Mr Michael Falster, Dr Kathleen Falster, Mr Holger Möller, Dr Aiden O’Laughlin, Professor Rebecca Ivers, Mr Tim Harrold, Ms Tracie Reinten.

9. Breathing easy: supporting lung development of premature babies. Associate Professor Jane Pillow and her team from the University of Western Australia “sought to understand the respiratory problems of premature babies to help the sickest and smallest babies develop their lungs. This research has contributed a great deal to improving both the quality of healthcare available to premature babies at birth as well as their long-term health prospects.” They were awarded a project grant worth $395 696. Team members: Professor Andrew Bassom, Associate Professor David Tingay, Dr Peter Noble, Dr Clare Berry, Professor Bela Suki, Dr David Kaczka, Dr Jane Kee, Dr Alex Wood, Dr Anna Lavizzari, Dr Elroy Zonnerveld, Mr Jake Hermann.

10. Ectopic pregnancy treatment: a safer way. Professor Stephen Tong and his team from Monash University “are revolutionising the treatment of ectopic pregnancy, meaning most women presenting with the condition could be treated medically, rather than surgically. Not only will this make treating ectopic pregnancies safer, easier and more effective, but it may save many lives across the developing world where surgery is not possible.” They were awarded a project grant worth $228 770. Team members: Professor Terrance Johns, Dr Monika Skubisz, Professor Andrew Horne, Professor Euan Wallace.


Cate Swannell
doi: 10.5694/mja16.0310C2
Calendar of conferences in Australia and New Zealand

This calendar will be updated each month. If you have an event you would like to add, please include relevant details in an email to cswannel@mja.com.au.

The full version of the calendar is available online at www.mja.com.au

OCTOBER 2016

### Careers

#### Program: Advanced, RACGP Clinical Emergency Management

#### American and New Zealand Burn Association 2016 Annual Scientific Meeting, Auckland, NZ

#### Medical Deans Australia and New Zealand Annual Conference, Wollongong, NSW

#### Royal Australian College of Medical Administrators 2016 Annual Conference, Brisbane, QLD

#### RACGP CPR Certification Course, Perth, WA

#### Royal Australian and New Zealand College of Radiologists 67th Annual Scientific Meeting, Gold Coast, QLD

#### RACGP Clinical Emergency Management Program: Intermediate, Sydney, NSW

#### 2016 National Conference, Australian Association of Practice Managers, Melbourne, VIC

#### Inaugural National Educational Conference 2016 ACHSM/ACHS Asia-Pacific Joint

#### 12th Biennial Asia Pacific International Mental Health Conference: Recovered Futures, Sydney, NSW

#### 17th World Sterilization Congress, Brisbane, QLD

#### Surgical Leaders' Forum 2016, Melbourne, VIC

#### Obesity Surgery Society of Australia and New Zealand 2016 conference: Dilemmas in Bariatrics, Sydney, NSW

#### The Australian Melanoma Conference, Sydney, NSW

#### RACGP Skin Cancer Essentials, Sydney, NSW

#### Australasian Professional Society on Alcohol and other Drugs 2016 Conference, Sydney, NSW

#### 11th Annual NHMRC Symposium on Research Translation; Embedding Research into Health Care Delivery: A Culture of Quality, Melbourne, VIC

#### RACGP Grand Round Series 2016 – Session 4, Perth, WA

#### National Primary Health Care Conference, Melbourne, VIC

#### 2016 RACP Northern Territory Annual Scientific Meeting, Darwin, NT

#### RACP WA Rural Physicians' Workshop 2016, Nedlands, WA

#### Australasian and New Zealand Falls Prevention Society Conference 2016, Melbourne, VIC

#### RACP CPR Workshop, Brisbane, QLD

#### RACP Victorian Further Education & Training for Paediatricians & Advanced Trainee (ViFeAT) 2016, Melbourne, VIC

### NOVEMBER 2016

| 2 | RACGP Administering Iron Infusion Intravenously, Adelaide, SA |
| 2-4 | 9th Annual HITH Society of Australasia Conference, Adelaide, SA |
| 5 | RACGP Clinical Emergency Management Program: Intermediate, Brisbane, QLD |
| 5 | RACGP CPR Certification Course, Perth, WA |
| 5 | RACP Continuing Education Program 2016, Melbourne, VIC |
| 5-6 | ACD Dermatological Surgery and Procedures Workshop, Sydney, NSW |
| 8-10 | Lowitja Institute International Indigenous Health and Wellbeing Conference, Melbourne, VIC |
| 9 | National Heat Summit on Obesity Run by the RACGP, Melbourne, VIC |
| 9 | RACP Perform CPR – A Workshop for GPs, Melbourne, VIC |
| 11-12 | 1st Australia and New Zealand Conference on Sarcoptes and Reiters (Australian Institute for Musculoskeletal Science, Melbourne, VIC |
| 11-13 | General Practice Conference and Exhibition, Melbourne, VIC |
| 12 | RACGP Psychodynamic Principles Workshop for GPs (Part 2), Melbourne, VIC |
| 12-13 | RACGP Clinical Emergency Management Program: Advanced, Brisbane, QLD |
| 13 | RACGP Procedural Skills for IMGs Preparing for RMO Roles, Sydney, NSW |

### DECEMBER 2016

#### 1-2 | IK, Perth: Hot Topics in Infection & Immunity in Children – The Perinatal Paradox, Crawley, WA |

### JANUARY 2017

#### 2-5 | 2016 International Indigenous Allied Health Conference, Cairns, QLD |

### FEBRUARY 2017

#### 7-14 | 2016 Australasian College of Sport and Exercise Physicians ASM: Keeping you Active, Gold Coast, QLD |

#### 24-26 | Pathology Update 2017, Sydney, NSW |

### MARCH 2017

#### 12-17 | Sydney International Endoscopy Symposium 2017, incorporating the Westmead Endoscopy Symposium Nurses’ Workshop, Sydney, NSW |

#### 12-18 | International Society of Ocular Oncology Annual Conference, Sydney, NSW |

#### 26-29 | 12th International Congress on Systemic Lupus Erythematosus (LUPUS 2017) and the 7th Asian Congress on Autoimmunity (ACA 2017), Melbourne, VIC |

#### 29 | A day with Dan Siegel: The New Frontiers of Interpersonal Neurobiology, Newcastle, NSW |

### APRIL 2017

#### 3-7 | 15th World Congress on Public Health: Voices, Vision, Action, Melbourne, VIC |

#### 26-29 | 14th National Rural Health Conference: A world of rural health, Cairns, QLD |
DIRECTOR OF EMERGENCY MEDICINE
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• Postgraduate management and/or education qualification or experience desirable.

Swan Hill District Health, ‘My Hospital’
Swan Hill District Health provides a wide range of clinical services including medical and surgical, aged care, community and primary health, renal dialysis, chemotherapy, pathology, radiography diagnostic services and an active and interesting Emergency Department operating 24/7.

Work/life balance is what you get working at Swan Hill District Health. As well as lifestyle comes:
• A professional, committed workforce and highly supportive community
• Variety in work and a sense of achievement
• Top level remuneration and negotiable relocation and accommodation assistance.

SWAN HILL - An ideal place to work and play
We are located on the mighty Murray River, around 3.5 hours from Melbourne. Swan Hill is a safe place where you will be greeted with a warm smile from our friendly local community.
• Our main street boasts a vibrant shopping district with high quality restaurants and no traffic congestion.
• You’ll find affordable housing, safe spaces for kids, swimming pools, quality education options and a healthy lifestyle.
• Imagine breakfast by the riverside, 18 holes at Murray Downs Golf Club, waterskiing at Lake Charm and fishing for the mighty Murray Cod.

Want More Info?
Applications including the names of three referees should be forwarded to: Mr. Steven Wainwright, Human Resources Manager, Swan Hill District Health, PO Box 483, Swan Hill 3585, Victoria or email: hrmanager@shdh.org.au.
Applications will only be accepted if they address the Key Selection Criteria and include an APPLICATION FOR EMPLOYMENT FORM. Email applications are preferred.

VR GENERAL PRACTITIONER REQUIRED
Privately-owned Skin Cancer Clinic in Taree, NSW

We Offer!
• Modern, fully computerised clinic (11 years)
• Digital dermoscopy
• Well stocked operating theater and consulting room
• Training and support available
• Busy well supported clinic and patient database guaranteed

What’s in it for you?
• Need a new challenge or a break from the city?
• Free weekends – family friendly hours
• Full-time or part-time hours available
• Excellent income
• Minimal paperwork

If this sounds interesting or if you would like more information?
Please contact our practice manager: Judy Muscio 02 65501733
OR email you CV to: info@mglskincancerclinic.com.au

Independent Hospital Pricing Authority
Consultation Paper for the Pricing Framework 2017-18
Members of the public and all interested parties are invited to comment on the Independent Hospital Pricing Authority’s Consultation Paper for the Pricing Framework for Australian Public Hospital Services 2017-18.

The Pricing Framework is fundamental to the National Health Reform Agreement and underpins the annual National Efficient Price and National Efficient Cost for Australian public hospital services.

The Consultation Paper for the Pricing Framework 2017-18 includes options to account for safety and quality in the pricing and funding of Australian public hospital services.

Feedback gathered in this public consultation process will be used to help inform IHPA's final Pricing Framework for 2017-18.

Submissions should be emailed as an accessible Word document to: submissions.ihma@ihpa.gov.au or mailed to PO Box 483, Darlinghurst NSW 1300 by 5pm on Monday 31 October 2016.
Help prevent pneumococcal pneumonia in adults with Prevenar 13\(^1,2\)

Community-Acquired Pneumococcal Immunisation Trial in Adults (CAPiTA)

- N=84,496: one of the largest vaccine efficacy trials ever conducted
- Parallel-group, randomised, placebo-controlled, double-blind study in the Netherlands; key eligibility criteria were immune competence and no previous pneumococcal vaccination\(^7\)

Prevenar 13 provided statistically significant reductions in hospital-confirmed cases of vaccine-type (VT) pneumococcal pneumonia and invasive pneumococcal disease (IPD) in adults aged ≥65 years\(^2\)

**Primary endpoint:** Prevention of first episode of VT pneumococcal CAP

\[ \text{Vaccine efficacy } (\%) = \frac{\text{Rate in placebo group} - \text{Rate in vaccine group}}{\text{Rate in placebo group}} \times 100 \]

- \(V=0.001\)

**Secondary endpoint:** Prevention of first episode of VT nonbacteraemic/ noninvasive pneumococcal CAP

- \(V=0.001\)

**46%** (\(P=0.001\))

**45%** (\(P=0.007\))

**75%** (\(P<0.001\))

**Secondary endpoint:** Prevention of first episode of VT IPD

Prevenar 13® Approved Product Information.

PBS Information: This product is listed on the National Immunisation Programme (NIP) for children only and is not listed on the PBS. Refer to the NIP Schedule.

Please review full Product Information before prescribing. Product Information is available on request on 1800 675 229 or at www.pfizer.com.au

**Indications:** Active immunisation for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9N, 14, 18C, 19A, 19F and 23F in adults and children from 6 weeks of age. **Dose:** 0.5 mL I.M. Infants 6 weeks to 5 months: 0.25 mL I.M. at 2 and 4 months; 0.5 mL I.M. at 6 months. Children 2 to 5 years: 0.5 mL I.M. every 5 years. Children ≥6 years: 0.5 mL I.M. every 10 years. Adults ≥65 years: 0.5 mL I.M. every 5 years. Adults >65 years and with chronic medical conditions: 0.5 mL I.M. every 3 years. Children ≥2 years with chronic medical conditions: 0.5 mL I.M. every 5 years.

**Contraindications:** Hypersensitivity to any component of the vaccine, including diphtheria toxoid. Allergic or anaphylactic reaction following prior administration of 7vPCV. Precautions: Do not administer intravenously, intravascularly, intradermally or subcutaneously. Avoid injecting into or near nerves or blood vessels. Do not inject into gluteal area. Postpone administration in acute, moderate or severe headache, rash. Adults >65 years reported fewer adverse effects than younger adults. Adverse effects were generally most common in young adults 18 to 29 years. See full PI for details (V10516).

**Adverse effects:** In adults, injection site reactions (redness, pain, swelling), dizziness, fever, decreased appetite, vomiting, diarrhea, rash. In children, injection site reactions (redness, swelling), fever, pneumonia, pneumonia, decreased appetite, diarrhea, rash, irritability. Children and adults: fever 5 to 7 years: Irritability, injection site reactions (redness, pain, swelling), somnolence, poor sleep quality, injection site tenderness (including impaired movement), fever, decreased appetite, vomiting, diarrhea, headaches, rash. Adults: Diarrhoea, vomiting, nausea, chills, fatigue, injection site reactions (redness, pain, swelling), limitation of arm movement, fever, new or aggravated joint or muscle pain, decreased appetite, headaches, rash. Adverse events generally occurred within 24-48 hours of vaccination.

**Note:** Prevenar 13 is contraindicated in patients with a history of a severe adverse event to Prevenar 7vPCV. Do not use for the prevention of osteomyelitis or for the prevention of meningitis in adults. Do not administer 7vPCV and Prevenar 23vPPV simultaneously. Do not administer DTP vaccine and Prevenar 13 simultaneously. Do not administer Prevenar 13 to children who have received 7vPCV. Prevenar 13 may not protect all individuals from pneumococcal disease. Consider the risks of I.M injection in infants or children with thrombocytopenia or any coagulation disorder. Appropriate treatment and supervision must be readily available in case of a rare anaphylactic event. Prophylactic antipyretic medication is recommended for children receiving concomitant whole-cell pertussis vaccines, and for children with seizure disorders or history of febrile seizures. Consider the potential risk of anaphylaxis when administering to very prematurity infants. Very Common/Common Adverse Effects: Children 6 weeks to 5 years: Injection site reactions (redness, pain, swelling), fever, diarrhea, vomiting, decreased appetite, diarrhea, fever, headache, rash. Adults >65 years reported fewer adverse effects than younger adults. Adverse effects were generally most common in young adults 18 to 29 years. See full PI for details (V10516).