Rheumatic fever as an indicator of child health

Medication-related patient harm in New Zealand hospitals

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Emm type distribution of group A streptococcus isolates from the throat swabs of children living in areas with a high (Northland and Gisborne) or low (Palmerston North) incidence of acute rheumatic fever

Noah Mhlanga, Grace Sharp, Mary Nulsen

Group A streptococci (GAS) can cause throat infections in children which can, some days later, often after the GAS have gone from the throat, trigger acute rheumatic fever. GAS can be distinguished by differences in their M proteins encoded by emm genes; there are over 200 emm types. Data from the US suggest that the emm types that cause acute rheumatic fever are distinct from other GAS. Although we did find differences in the emm types of GAS from children living in areas with a high (Northland and Gisborne) or low (Palmerston North) incidence of acute rheumatic fever, there was no obvious correlation between the distribution of GAS emm types known to be associated with acute rheumatic fever in New Zealand and actual disease incidence. We also found that most of the emm patterns circulating among the throat of all three groups of children were either skin specialists or generalists, able to colonise both skin and throat. This is somewhat anomalous since all of the GAS we typed were isolated from the throats of children.

Medication-related patient harm in New Zealand hospitals

Gillian Robb, Elizabeth Loe, Ashika Maharaj, Richard Hamblin, Mary E Seddon

The purpose of this study was to identify the extent of medication-related harm in New Zealand and to use this information to inform decision on where to focus medication safety efforts. The study used a 'trigger tool', which is a method designed to identify harm from reviewing medical records, rather than relying on voluntary reporting. The results show that medication-related harms are common—for every 100 hospital admissions, over 30 patients suffer medication-related harm. While most were minor (61%), more than a third (35%) prompting admission to hospital or prolonging the hospital stay, and 1.6% were associated with permanent harm or death. Opioids and blood thinners were the medication classes responsible for most harm (40%) and the most severe harm. This information helps target medication safety improvement efforts to reduce harm.

What is the relationship between visual impairment and cognitive function in octogenarians?

Denise S de Kok, Ruth O Teh, Avinesh Pillai, Martin J Connolly, Tim J Wilkinson, Robert Jacobs, Marama Muru-Lanning, Anna Rolleston, Simon A Moyes, Dieuwke Schiphof, Ngaire Kerse

With an ageing population, it is projected that the prevalence of dementia will increase. Various modifiable risk factors for dementia have been established and vision loss is of particular interest because it is often treatable. Utilising data from the LiLACS NZ study, this study aims to examine the direct and indirect relationship between vision loss and cognition in more than 600 older adults born between 1920 and 1930. The study found that about one in five older adults have visual impairment and it is not associated with cognition. The relationship between visual impairment and cognition was influenced by one's ability to perform normal daily activities.

Is a rheumatic fever register the best surveillance tool to evaluate rheumatic fever control in the Auckland region?

Diana Lennon, Te Aro Moxon, Philippa Anderson, Alison Leversha, Timothy Jelleyman, Peter Reed, Catherine Jackson

Rheumatic fever is preventable. It causes long-term heart disease in many and can even cause premature death. It is important to count the cases carefully and accurately as there is an important campaign underway to prevent it by treating strep sore throats. We looked at the different methods for case counting. A register is the best way, well established in the Auckland region for several decades and leading to the current MOH campaign.

Mortality within 30 days of systemic anticancer therapy at a tertiary cancer centre: assessing the safety and quality of clinical care

Michelle Wilson, Weng Mak, Melissa Firth, Sanjeev Deva, Michael Findlay

Thirty-day mortality has been proposed to be a useful indicator of avoidable harm to patients from systemic anticancer therapies. As a quality assurance tool, we assessed the 30-day mortality rate at Auckland City Hospital and compared this with international standards. Our local 30-day mortality data compared favourably to international benchmarks of 5% and has not increased over time. Performance of similar studies locally and nationally should be undertaken to continue to assess and improve the quality of our patient care.

Predictors of medical student remediation and their underlying causes: early lessons from a curriculum change in the University of Auckland Medical Programme

Brian Grainger, Jill Yielder, Papaarangi Reid, Warwick Bagg

Most medical students who need remediation are successful in passing the year. We have identified those students who are in greatest need of additional assistance. Interventions to help students are generally seen as helpful, but more could be done to assist students who have academic difficulty. As the cause of academic difficulty is multifactorial, a system-wide approach to addressing inequity, eg, in pre-university education outcomes, may reduce the need for remediation during university.

An in-country model of workforce support for trained mid-level eye care workers in Papua New Guinea and Pacific Islands

Julie Brûlé, Benoit Tousignant, Graeme Nicholls, Matthew G Pearce

Training eye care workers to alleviate the burden of blindness and vision impairment in an under-resourced area is not enough: once trained, the workers need to be integrated and retained in their country's workforce. Their competencies must be upheld, and they need to be introduced to new skills and knowledge. A workforce support programme that addresses all those needs is a powerful tool to improve the delivery of eye care services.

Rheumatic fever as an indicator of child health

Diana Lennon

We should be celebrating as after a half a century we can see signs of making progress. Acute rheumatic fever (ARF) has declined instead of endlessly climbing as it has in the last decade.[1] It is a visible and significant marker of inequality. While we wait for a child-centred society, better housing and a fair wage for all, we have a medical intervention first proven in 1950 to prevent this disease, namely treating streptococcal pharyngitis.[2] Making sure every child and adolescent at risk of ARF has access to adequate healthcare spawned the school clinic idea.

But it is far more than this. ARF, long gone in most OECD countries, signals we have crowded inadequate housing where group A streptococci (GAS) spreads readily and the poorest of our population missing doctors' visits because of costs (debts at the doctors will put off taking up the free child visits) (www.health.govt.nz–NZ Health Survey 2015). Why so much emphasis on this disease? Like severe respiratory disease in babies leading to bronchiectasis, adults suffer long-term consequences with a documented shorter life span. This is inhumane but also is economic insanity. Those carrying the burden of ARF are a third of our young. But unlike severe respiratory disease, which is viral and can only be controlled by better housing to limit spread, at least ARF has an identified trigger, GAS pharyngitis, for which we have scientific evidence that it is preventable. We have been sitting on this for a very long time, adding potentially preventable complex rheumatic heart disease cases to our hospital workloads and destroying people's lives (and productivity). Fine tuning how we continue to deliver the sore throat intervention is now the challenge.

There are many other examples of preventable or treatable infectious diseases where we have failed to put the solutions in place. Infectious diseases are historically diseases of the poor and people in crowded circumstances such as armies or slums. Glomerulonephritis in mostly Māori or Pasifika children following skin infection leads to long-term renal failure in some, osteomyelitis is an unequal burden in the disadvantaged, bronchiolitis burdens our hospitals every winter, skin infections are skewed to the poor and so it goes on.[3] Our meningococcal epidemics firmly linked to housing are legendary globally.[4,5] For some of these there have been vaccine solutions.[4,6] Most are diseases of the past in the better off. Unlike non-infectious conditions, the solutions are often well tried and tested; they may be primordial, eg, housing, as was demonstrated by Singapore. We just fail to apply them.

Why the inordinate delay in controlling ARF? The New Zealand Rheumatic Fever Working Party in the 1980's, partnering with the Māori Women's Welfare League, proposed solutions and wrote scientific articles. Secondary prophylaxis was successfully instigated in most areas but primary care said the solution for prevention of first attacks did not lie with them, despite sore throats being in the top 10 reasons for presentation. So a new paradigm of delivery of healthcare was proposed. This was possible because most ARF presents in primary school-aged children. It was intended that this eventually might spawn a whanau ora approach with the school child being the introduction into a family setting. The focus to begin was a randomised trial evaluating the new paradigm, namely school clinics, to better deliver a known modality (penicillin treatment of GAS pharyngitis to prevent ARF) compared to the then current model of care (general practice).[7] The trial demonstrated a modest but insignificant decrease of ARF most likely due to cross contamination.[7] GAS has nearly a 50% chance of spreading to close household contacts. Some children in the clinic schools had siblings in the control schools, so modifications were necessary

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to the model. Māori in Northland elected to commence sore throat management in schools before the end of the trial, citing "too many in the graveyard". ARF in that small community has virtually disappeared. Other Māori communities followed suit outside of Auckland starting before the national programme. A national workshop funded by the Heart Foundation led to a published "Advice to the Ministry of Health" recommended pathway to ARF control. (www.paediatrics.org.nz) A meta-analysis of mostly poor quality community intervention studies corroborated the observed effect in studies in the US armed forces and an inner city population, viz that a 60–80% reduction was possible.[8] Smaller regions and later Auckland introduced prevention programmes centred on primary schools where disease was concentrated, with funding partnerships between the Ministry of Health and DHBs. Guidelines for sore throat management (and ARF care) emerged. Many regions eventually planned improved healthcare access beyond pharyngitis using school clinics.

Internationally, ARF has disappeared in better-off countries since WW2 with improved housing and free access to healthcare such as the UK or in the LBJ Great Society initiatives introducing free primary care through Medicaid for the poor.[8] There have been some notable successes in developing countries where access including medicine is free and careful health promotion messages have been promulgated to communities and healthcare personnel. Evaluation has not been rigorous.

Recently published from New Zealand is the first high-quality evidence supporting control of first presentation ARF in the community.[9] Diagnosis and treatment of streptococcal pharyngitis management in a school clinic setting using oral amoxicillin can reduce first presentation cases of ARF, a global first and a proof of principle. Such evidence has been surprisingly lacking nationally or internationally up until now. The only evidence was from army studies in the 1950's and 1960's using injectable penicillin, which many countries acted on.[2] As rheumatic heart disease (RHD) is now on the WHO agenda, this is an important contribution to the global effort. New Zealand can take some credit for a substantial contribution to this.

Our rigorous evaluation of an enhanced school clinic programme model (year 1–8) with added features to control GAS spread and cross contamination was possible where ARF is most concentrated in New Zealand (south Auckland) and 90% of children at high risk of ARF are in schools with clinics. A multi-variable model relying on the programme rolling out over time produced concrete high-quality evidence, the first globally, that sore throat management in a community setting, namely in a school, reduces ARF by a significant amount (88/100,000 to 37/100,000 p 0.008).[9] Two thirds of ARF in this population are Pasifika.

What are we doing about it? We now have an evidence base for the success of school clinics where ARF is concentrated. Schools identified with a population at high risk of ARF in several DHBs in the North Island still do not have clinics. The MOH funding model for metropolitan Auckland led to less than adequate funds available for the region, especially central Auckland (Auckland DHB), which should be urgently addressed. The enhanced school clinic model in ADHB was not funded adequately and ~50% of schools at high risk do not have any sort of clinic. Two thirds of this population are Pasifika. Acting on evidence is pressing if we are to continue to progress.

Overall though, the extraordinarily good news is that after 50 years, ARF control in young Māori who carry two thirds of the national ARF burden has reduced by a significant amount meeting government targets (www.health.govt.nz). From the perspective of DHBs, most ARF cases (~75%) occur in the north of the North Island viz Northland, Waikato and the Auckland metropolitan region. The former two regions have also met government targets. The remaining third of ARF nationally is carried by Pasifika populations mostly in Auckland where the school clinic model has been incompletely implemented. ARF control in urban Pasifika presents different challenges, but overall success in south Auckland tells us it is possible. We should remember that very high rates of meningococcal vaccine in this population were achieved.[6] There is no doubt more needs to be done to fine-tune control. Research findings suggest ongoing control of cross sectional pharyngeal GAS prevalence is an important marker.[9]

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How do we judge success of the government's investment in the RF Prevention programme? Data has generally been poor from traditional sources such as hospital discharge or the notifiable disease datasets. Despite ARF becoming a notifiable disease in 1986, little attention has been paid until recently. Moxon et al in this week's *Journal* outline the complexity. Every case deserves careful scrutiny by skilled personnel when there are now <100 per year. The case definition is an estimate of probability rather than a laboratory test, so requires special attention.

Are there other solutions? The intriguing question suggesting GAS skin infection may have a role comes from Australian researchers where purulent skin disease in Aboriginal populations is rampant.[10] In our evaluation cohort, skin infection accounted for <10% of antibiotic usage.[9] Thus we suggest a direct role for skin infection appears unlikely in our population. However, types of GAS (*emm* types) associated with ARF suggest diverse types potentially of both pharyngeal and skin origin, unlike those traditionally described as "rheumatogenic" (and solely pharyngeal), described in epidemics in the US armed forces.[11] Further data will be forthcoming with essential controls. There is a latent period of approximately three weeks between the GAS pharyngitis episode and the onset of ARF, so it is difficult to be sure a particular GAS *emm* is indeed the triggering GAS.[12] In this week's *Journal,* researchers highlight more similarities than differences between pharyngeal GAS strains in areas at low compared to high risk of ARF. The *emm*s from published national data temporally associated with ARF, though seen in all three regions contributing strains in the study, did not correlate with the actual ARF incidence rate. The low ARF incidence region had the same number of ARF-associated *emm*s as the high ARF incidence regions.[13] Conversely in the pre-penicillin era, some GAS strains in a residential hospital were found not to cause recurrent ARF even with repeated patient exposure. However, skin seems likely to be a reservoir for GAS in our environment.

There is no doubt vaccines are a better pathway to reducing inequalities.[14] Progress towards vaccines for GAS and also RSV is slow. We have now a top-quality immunisation programme.

Why this disease and not one of many others? Well it seems this relatively uncommon disease has many aspects which tell us about child health in this country. It tells that there are crowded and cold poorly built and maintained houses, repeated infections unattended to, lack of knowledge that sore throats do indeed matter, lack of access to healthcare at appropriate times and places without barriers of debts from other family members, and often insufficient household income to guarantee food on the table and petrol in the car.

If we can make progress with this indicator of child health and not lose our nerve, we have some broader hopes for the future. Only some hope though, because the commonest preventable infection is viral bronchiolitis in babies, most likely only controlled by better housing, and that is another story.

You may say all these issues only affect a minority of New Zealand kids. Well, actually it is a third of all New Zealand children, and they happen to be largely but not entirely Māori and Pasifika. Don't take the foot off the pedal, New Zealand. We need these kids healthy and from the economist's perspective also working to pay for superannuation if nothing else.

The ultimate goal should be progressive or proportionate universalism, as is well recognised by the OECD (2011) as the best pathway to reducing poverty and inequity. Investment in children should be universal and non-partisan as it is for the elderly. It is humane but it is also economic sense.

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Nil.
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Not too much; not too little; just right: remediation during medical school

Phillippa Poole

To remedy something is to put it right. Remediation during medical school is the process by which students identified as having difficulty are identified and given a formal opportunity to improve so they meet the necessary standard. Elements in best practice are detection of a deficiency in competence, feedback, development of an individualised learning plan, followed by reflection, specific learning activities, feedback and re-testing.[1] Confounders such as health or external factors that impact upon the likelihood of success also need to be addressed.[2]

Given the importance and challenges of remediation, surprisingly few medical schools have published reports on the topic.[1] The paper by Grainger et al[3] in this issue outlines the remediation process at the University of Auckland, adding important insights on a number of levels. First, it quantifies the number of students needing some form of remediation, when and why they need it and who is at higher risk; second, it describes the system needed to deliver remediation; third, there are details on the range of remediation options used; finally, we hear views of staff involved in remediation.

Grainger and colleagues report that 18% of students require one or more of a range of remedial interventions. Most are at the less intensive end of the spectrum, with the students being flagged for closer attention in subsequent attachments. Notably, they do not include students who were subject to the parallel Fitness to Practice process, which has been reported upon previously.[4] In that process, around 5% of medical students receive at least one notification for a health or professionalism issue, with almost all eventually graduating. As professionalism is a key curriculum domain, and health issues may impact on academic performance, inevitably some students will be remediating via both processes. An estimate is, therefore, that around a fifth of Auckland medical students need some formal extra help during medical school in order to achieve the required standard.

Is a fifth of students needing formal remediation too low, too high or about right? The proportion undergoing remediation will depend on how it is defined, the sensitivity of the assessment system to detect deficiencies, the capability to provide remedial education, and tolerance for attrition from the programme. A recent paper from the University of Otago found 36% of medical students in their clinical years had deficiencies in one or more of clinical skills, knowledge or professional behaviour.[5] Before recent curriculum changes, similar rates were seen at Auckland.[3] The majority of students progress satisfactorily after one intervention. Furthermore, most of those 'remediating' in clinical years had technically passed, but were being flagged for attention in a subsequent attachment to ensure they met the standards.

Years ago, many of us were subjected to 'big bang' end-of-year assessments with only three possible outcomes: pass, repeat the year or exclude; with decisions made on relatively opaque criteria. There was no systematic, holistic remedial support. Loss from the programme was higher than it is today. Since then, classes have got bigger with cohorts more representative of the population, students have invested more in their education, and procedural fairness more explicit. Advances in educational pedagogy mean that modern programmes define the competencies or outcomes to be achieved in each stage of training. To these are aligned assessments of knowledge, skills and professional behaviours, which inform progression decisions made by a formally-constituted group of examiners.

Students face multiple small assessments, including those in the workplace judged by a range of supervisors. No one assessment is perfectly valid, but an overall picture of student performance over time in all domains is collated longitudinally. A relatively recent addition to the assessment repertoire in New Zealand is progress testing, although it's been around for over 40 years. Questions are set at graduation level, with tests carefully moderated and delivered several times per year. Students must meet minimum levels for their own year, as well as show progress in acquisition of applied knowledge. For these reasons, newer programmes may be more able to detect problems earlier as well as have more confidence around pass/fail decisions.

Most doctors (from L *docere* = to teach) and university educators (from L *educare* = to lead out of), take on the remedial challenge readily, but they only have so much capacity. Medical programmes are growing in terms of numbers and curricular demands. Hospital services are increasingly busy. Among the constraints are supervisor availability and timing—remediation often coming in the busy end-of-year period. For students already experiencing academic or pastoral difficulty, the imposition of extra work within a year may be too much. A decision to be faced is whether or not it'd be better to repeat the year. This brings into play issues such as financial costs, delay in graduating and an extra line on the academic record, which may be a disadvantage when applying for jobs or training schemes. As an aside, should a repeated year be viewed as a negative, as long as the expected standard is reached eventually? Those taking another year may be better able to consolidate their knowledge and skills, learn new approaches for lifelong learning or address any personal or external factors impacting on performance. It would be of interest to get the student view on remedial education.

Deficits in knowledge and professionalism in medical school are associated with a slightly higher likelihood of being subject to a medical board disciplinary procedure later on.[6] Further, concerns about resilience may be expressed by staff.[3] Universities are often asked if we can select 'better' students. Unfortunately, we lack the ideal combination of selection tools which can do all of (i) ration scarce places, (ii) exclude those frankly unsuited for medicine, yet (iii) result in a diverse group of students who (iv) all graduate in the minimum time. In good faith, medical schools use the tools available in an evidence-based way to choose a group with the best hope of progressing through the medical programme and who will go on to practise as good doctors, in all scopes of practice. At the University of Auckland, the minimum prior academic standard is based on predictive validity testing. Neither the aptitude test, UMAT, nor interviews predict academic progression.[7] Students entering via two specific pathways were more likely to need remedial intervention.[3] Yet both groups are important so it behoves us to do as much as we can to support these students to complete their studies. Moreover, it's a call to re-examine assessment systems for any cultural biases, and continue to address inequities in preparation for tertiary education.

Scores at selection or on individual assessments will never be perfect in predicting student success. As well as providing a basic medical education, medical school could be viewed as a long interview for the workforce. While remediation offers students another opportunity and faculty a 'second look', governance must be robust enough to exclude students who fail to meet the agreed standards, even with appropriate remediation. As the authors suggest, long-term follow up is needed to validate decisions after remediation, ie, were students allowed to progress who subsequently had irremediable problems in the workforce? This type of research only looks at those who did progress into the workforce. It doesn't take account of those who withdrew or were excluded along the way, but who might have progressed if they had received more targeted support. Students and many others make a significant commitment to an individual's medical education and training. A portion of system resources must be dedicated to helping students who take longer, or a different path, to achieving competence. When all this is taken into account, a fifth of students needing this support seems about right.

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Emm type distribution of group A streptococcus isolates from the throat swabs of children living in areas with a high (Northland and Gisborne) or low (Palmerston North) incidence of acute rheumatic fever

Noah Mhlanga, Grace Sharp, Mary Nulsen

ABSTRACT

AIM: To assess the circulating *emm* types of pharyngeal isolates of group A streptococcus (GAS) among school children living in Northland, the Gisborne region and Palmerston North, New Zealand.

METHODS: GAS were isolated from throat swabs sent to laboratories in Northland (197 in 2013) and Gisborne (115 in 2014–15) and from children enrolled in the Palmerston North Solar Ventilation Project (70 in 2013–14). The incidences of acute rheumatic fever (ARF) cases in the three regions in 2014 were 9, 19.1 and 0 cases per 100,000 for Northland, the Gisborne region and Palmerston North respectively. DNA sequencing of the N-terminal portion of the *emm* gene was performed at the Institute of Environmental Science and Research Limited (ESR) laboratory (Porirua, New Zealand).

RESULTS: A total of 36 *emm* types were found among pharyngeal GAS isolates from Northland children with *emm*1 predominating (24%), 28 *emm* types from the Gisborne region with *emm*12 predominating (25%) and 20 *emm* types from Palmerston North, again with *emm*12 predominating (36%).

Of these GAS isolates, 38% were *emm* pattern A-C, usually associated with throat infections, 23% were pattern D, usually associated with skin infections, and 39% pattern E or generalists. The most common of the 13 *emm* clusters detected were A-C4 (*emm*12; 18% isolates), A-C3 (*emm*1, *emm*227, *emm*238; 17% isolates), D4 (9 *emm* types; 16% isolates), E4 and E3 (8 *emm* types each; 15% and 10% isolates respectively). A total of 301 of the 376 (80%) isolates were serotypes previously associated with ARF in New Zealand.

CONCLUSION: The only significant differences in distribution between the regions with high (Northland and Gisborne area) and low (Palmerston North) incidences of ARF were the presence of *emm*3 and absence of *emm*41 among GAS isolates from Palmerston North school children.

Acute rheumatic fever (ARF) has long been considered a rare sequela of untreated group A streptococcus (GAS) pharyngitis, thought to result from GAS infection with distinct or rheumatogenic GAS strains, such as *emm*1, 3, 5, 6, 14 and 18, in genetically susceptible individuals.[1,2] However, there is increasing evidence that ARF may also occur after infection by other *emm* types typically associated with skin, but at least in some cases isolated from the throat.[3–7] The most important risk factors for ARF include poverty, over-crowding, nutrition, substandard housing quality and limited access to healthcare.[1] The Ministry of Health aims to reduce acute rheumatic

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fever incidence by two-thirds by the year 2017, and a number of ARF prevention programs are currently underway across New Zealand.[8] These are all directed at detection and treatment of GAS infection of the throats of school children. Unfortunately, recent symptoms of pharyngitis are frequently absent or too trivial to be noticed among ARF patients.[8,9,10]

ARF rates in New Zealand remain among the highest in the world despite the fact that New Zealand is regarded as an economically developed and industrialised nation.[8,11] ARF is a particular problem among the economically deprived Māori and Pacific peoples.[12] According to Milne et al, the New Zealand national ARF data from 2000–2009 for ages five to 14 years showed an annual incidence of 40.2 per 100,000 for Māori children and 81.2 per 100,000 for Pacific children, which contrasts with 2.1 per 100,000 for non-Māori/Pacific children.[11] More recently, Jack et al established the hospitalisation rates for first episodes of ARF for Māori as 12.7/100,000 and 25.9 per 100,000 for Pacific Island peoples between 2012 and 2013.[8] These are similar to those seen in resource-poor nations.[13]

Molecular epidemiological surveillance of GAS serotypes is a crucial component of the ongoing efforts to understand the distribution of ARF disease and in GAS vaccine development. An important part of epidemiological surveillance involves accurate identification and typing of GAS isolates. The *emm* type of a GAS is determined by the highly variable sequence at the 5'-end of the *emm* gene, which encodes the M protein.[14] There are over 200 *emm* types, but these can be grouped into three distinct patterns based on differences in molecular structure of the M proteins.[15,16] Studies indicate that GAS with *emm* patterns A-C are associated with colonisation of the pharynx, pattern D with the skin and pattern E with both pharyngeal and skin colonisation,[4,15,16] although these tissue tropisms may not apply to GAS isolates from low-income countries.[17] More recently, Sanderson-Smith and other members of the M protein Study Group have proposed that GAS with closely related M proteins be assigned to *emm* clusters.[18] Based on the binding and structural properties of whole M proteins, 175 representative *emm* types have been grouped into 48 *emm* clusters. A number of

these clusters contain a single M type but 16 *emm*-clusters contain 143 M proteins. *emm* cluster D4 was the most common cluster among GAS isolated from ARF cases in New Zealand between 2006 to 2014.[6]

A number of approaches to the development of GAS vaccines are underway, but those based on M proteins are the most advanced.[19] A 26-valent vaccine which includes the N terminal peptides of M proteins from GAS serotypes prevalent in North America and Europe has been trialed in healthy humans. This vaccine was subsequently extended to 30 types and found to provoke bactericidal antibodies in rabbits that cross reacted with additional *emm* types not included in the vaccine.[19] The cross opsonisation is thought to be due to the fact that the *emm* types in a single *emm* cluster share structural homology and, hence, also share cross reacting epitopes.[18] This phenomenon may simplify the development of vaccines to protect against the many GAS strains circulating in low-income countries. For example, a type-specific vaccine that incorporates the 10 predominant *emm* clusters circulating in the Pacific region should offer protection against about 90% of GAS strains in the area.[20]

The aim of the present study was to determine the *emm* types of pharyngeal isolates of GAS circulating among school children in Northland and the Gisborne region, areas with a high incidence of ARF and Palmerston North, which has a low incidence of ARF.[24]

Materials and methods

For Northland, throat swabs were collected from school children, aged seven to 17 years, with sore throats living in Whangarei, Kaitaia, Bay of Islands, Hokianga, Kaikohe and Kaeo areas who participated in the Northland Rheumatic Fever Prevention programme between March and May 2013. A total of 200 group A *streptococcus* (GAS) isolates were obtained from samples submitted to Northland Pathology Laboratory (NPL). Ethical approval was granted by the Northland District Health Board (NDHB) Locality assessment through the office of the Chief Medical Officer and the Māori Health Directorate Kaumatua (reference no. 2013–2) and also by the

Massey University Human Ethics Committee (HEC: Southern A 13/22).

For the Gisborne region, throats swabs were collected from children aged three to 16 years with sore throats. In total, 115 samples positive for group A streptococci were taken as part of the Tairawhiti Rheumatic Fever Prevention Project during 2014–2015. Preliminary isolation and identification was done by TLab Gisborne staff. Blood or chocolate agar plates or chocolate agar slants with β-haemolytic colonies resembling group A streptococci were sent to the Palmerston North campus of Massey University. In Palmerston North, 70 samples positive for group A streptococci were collected from the throats of apparently healthy school children enrolled in the Palmerston North Solar Ventilation Project during 2013–2014. Low decile schools, with a high proportion of children from low socioeconomic communities,[8] were selected for this project. Ethical approval for the study of isolates from the Gisborne region and Palmerston North was granted by the Massey University Human Ethics Committee (HEC: Southern A 14/49).

Isolates were typed as Lancefield group A using commercial agglutination kits. After removal of sample duplicates, 197 samples were analysed for Northland and, after removal of non-viable samples, 109 samples were analysed from the Gisborne region. The GAS isolates were sub cultured onto blood agar plates (Fort Richards, Auckland) and grown at 37°C in in 5% CO_2 for 48 hours. Bacitracin disks (0.04 units; BD BBL™ ex Fort Richards, Auckland) were placed onto the inoculated media to check for sensitivity to bacitracin. The purified GAS isolates were stored frozen at -30°C (Whangarei Hospital Laboratory) or -70°C (Massey University) until they were ready to be transported to the Institute of Environmental Science and Research Limited (ESR) laboratory (Porirua, New Zealand) for *emm* typing. PCR and DNA sequencing of the *emm* genes was carried out using previously described methods.[14]

Simpson's index of diversity[21] was calculated for the data from each region as well as a confidence interval.[22] The overall predicted vaccine coverage was also calculated based on the study by Dale et al (2013).[23] Fisher's exact test was used to compare the proportions of the four most common *emm* types overall between the regions.

Results

Three hundred and seventy-six GAS isolates were successfully cultured and *emm* typed from throat swabs from children living in the Gisborne, Northland or Palmerston North regions between 2013 and 2015. A total of 47 different *emm* types were identified overall (Table 1). The four most prevalent were *emm*12 (17.6%), *emm*1 (16.2%), *emm*41 (6.1%) and *emm*11 (4.3%), making up 44% of the total samples. Only 38% of the total isolates were pattern A-C, which is typically associated with throat infections. The rest were patterns considered to be skin specialists (pattern D, 23%) and generalists (pattern E, 39%) (Table 1). The most common of the 13 *emm* clusters were A-C4 (*emm*12; 18% isolates), A-C3 (*emm*1, *emm*227, *emm*238; 17% isolates), D4 (nine *emm* types; 16% isolates), E4 and E3 (eight *emm* types each; 15% and 10% isolates respectively). Thirty-six different *emm* types were identified in Northland with a Simpson's index of diversity of 0.919 (95% CI, 0.894–0.944). The 30-valent vaccine developed by Dale and co-workers[19,23] would protect against 18/36 *emm* types (65% of isolates) or 24/36 *emm* types (76% of isolates) when theoretical cross opsonisation is considered.

There were 28 different *emm* types in the Gisborne region, with a Simpson's index of diversity of 0.912 (95% CI, 0.878–0.947). Vaccine coverage by the 30-valent vaccine would be 18/28 of the Gisborne region *emm* types (77% of isolates). This would increase to 22/28 *emm* types, accounting for 84% of isolates when theoretical cross opsonisation is taken into account.

In Palmerston North, 20 different *emm* types were found, with a Simpson's index of diversity of 0.837 (95% CI, 0.769–0.906). The 30 valent-vaccine coverage would be 10/20 *emm* types (74% of isolates) and cross-opsonisation would increase coverage to 11/20 (76% of isolates).

Overall, 30 of the 47 *emm* types or 78% of the isolates found in this study would have been covered by the 30-valent vaccine. Ten of the *emm* types associated with ARF in New Zealand[6] (amounting to 18% of the isolates) would not have been covered.

The percentage of ARF-associated *emm* types isolated was quite high in all the regions (80% overall) with 85%, 72% and 79% in the

Table 1: Frequency of *emm* types and their corresponding *emm* patterns and clusters of 376 GAS isolates from throat swabs of children in the Northland, Gisborne and Palmerston North regions collected between 2013 and 2015.

emm type	Northland		Gisborne		Palmerston North		Total		*emm* cluster	*emm* pattern
	n	%	n	%	n	%	n	%		
1*	47	23.9%	7	6.4%	7	10.0%	61	16.2%	A-C3	A-C
2	0	0.0%	1	0.9%	0	0.0%	1	0.3%	E4	E
3*	0	0.0%	0	0.0%	11	15.7%	11	2.9%	A-C5	A-C
4	0	0.0%	3	2.8%	0	0.0%	3	0.8%	E1	E
11*	14	7.1%	2	1.8%	0	0.0%	16	4.3%	E6	E
12*	14	7.1%	27	24.8%	25	35.7%	66	17.6%	A-C4	A-C
19*	1	0.5%	0	0.0%	0	0.0%	1	0.3%	Single protein *emm*-cluster clade Y	A-C
22*	4	2.0%	3	2.8%	1	1.4%	8	2.1%	E4	E
28	3	1.5%	3	2.8%	2	2.9%	8	2.1%	E4	E
33*	0	0.0%	0	0.0%	1	1.4%	1	0.3%	D4	D
41*	12	6.1%	11	10.1%	0	0.0%	23	6.1%	D4	D
44	4	2.0%	3	2.8%	1	1.4%	8	2.1%	E3	E
49*	2	1.0%	0	0.0%	0	0.0%	2	0.5%	E3	E
53*	3	1.5%	4	3.7%	0	0.0%	7	1.9%	D4	D
58	3	1.5%	7	6.4%	1	1.4%	11	2.9%	E3	E
59*	6	3.0%	1	0.9%	0	0.0%	7	1.9%	E6	D
65*	5	2.5%	0	0.0%	0	0.0%	5	1.3%	E6	D
66	4	2.0%	0	0.0%	0	0.0%	4	1.1%	E2	E
74*	2	1.0%	0	0.0%	0	0.0%	2	0.5%	Single protein *emm*-cluster clade Y	D
75	5	2.5%	6	5.5%	1	1.4%	12	3.2%	E6	E
77*	3	1.5%	1	0.9%	0	0.0%	4	1.1%	E4	E
78	0	0.0%	0	0.0%	2	2.9%	2	0.5%	E1	E
81*	5	2.5%	4	3.7%	0	0.0%	9	2.4%	E6	D
82	2	1.0%	4	3.7%	0	0.0%	6	1.6%	E3	E
85*	1	0.5%	1	0.9%	0	0.0%	2	0.5%	E6	D
86	1	0.5%	1	0.9%	1	1.4%	3	0.8%	D4	D
87*	1	0.5%	1	0.9%	0	0.0%	2	0.5%	E3	E
89*	9	4.6%	5	4.6%	1	1.4%	15	4.0%	E4	E
90	0	0.0%	0	0.0%	1	1.4%	1	0.3%	E2	E
91*	10	5.1%	3	2.8%	2	2.9%	15	4.0%	D4	D
92*	6	3.0%	5	4.6%	0	0.0%	11	2.9%	E2	E
93*	2	1.0%	0	0.0%	1	1.4%	3	0.8%	D4	D
97	2	1.0%	0	0.0%	0	0.0%	2	0.5%	D5	D
101	4	2.0%	0	0.0%	0	0.0%	4	1.1%	D4	D
103*	3	1.5%	0	0.0%	0	0.0%	3	0.8%	E3	E
108*	1	0.5%	1	0.9%	1	1.4%	3	0.8%	D4	D
111	0	0.0%	1	0.9%	0	0.0%	1	0.3%	single protein *emm*-cluster outlier	D
112	0	0.0%	0	0.0%	3	4.3%	3	0.8%	E4	E
113*	2	1.0%	0	0.0%	0	0.0%	2	0.5%	E3	E
114	1	0.5%	1	0.9%	0	0.0%	2	0.5%	E4	E
118*	4	2.0%	1	0.9%	0	0.0%	5	1.3%	E3	E
218*	0	0.0%	1	0.9%	0	0.0%	1	0.3%	single protein *emm*-cluster clade Y	D/A-C
222	0	0.0%	0	0.0%	1	1.4%	1	0.3%	single protein *emm*-cluster outlier	A-C
225	0	0.0%	0	0.0%	2	2.9%	2	0.5%	D4	D
227	1	0.5%	0	0.0%	0	0.0%	1	0.3%	A-C3	
232*	9	4.6%	1	0.9%	5	7.1%	15	4.0%	E4	E
238*	1	0.5%	0	0.0%	0	0.0%	1	0.3%	A-C3	A-C
	197	100.0%	109	100.0%	70	100.0%	376	100.0%		

*Group A *streptococcus* strains temporally associated with ARF in New Zealand between 2006-2014.[6]

Figure 1: First episode rheumatic fever hospitalisation rate (per 100,000 total population) in Northland, Tairawhiti (Gisborne region) and Midcentral (Palmerston North) DHBs (2005–2015).[24]
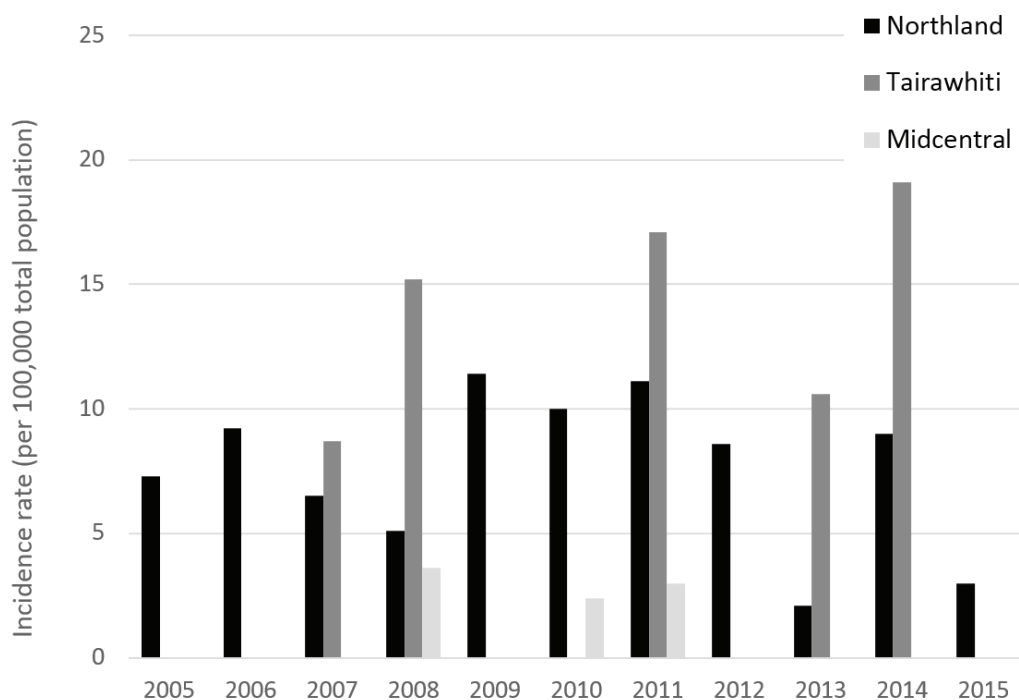
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Northland	7.3	9.2	6.5	5.1	11.4	10	11.1	8.6	2.1	9	3
Tairawhiti	-	-	8.7	15.2	-	-	17.1	-	10.6	19.1	-
Midcentral	-	-	-	3.6	-	2.4	3	-	-	0	-

Northland, Gisborne region and Palmerston North respectively (Table 1). This *emm* type distribution did not correlate with the actual rates of ARF in these regions since Palmerston North has a low rate of ARF compared to Northland and Gisborne (Figure 1).

There was a significant difference between the proportion of *emm*12 and *emm*1 isolates from children living in Northland compared with those from the Gisborne region or Palmerston North. By contrast, the proportion of *emm*41 and *emm*3 isolates was significantly different in children from Palmerston North compared to either the Gisborne region or Northland. For *emm*11, the only significant difference in distribution was in children from Northland versus Palmerston North (Table 2).

Table 2: Comparison of the distribution of *emm*-types 12, 1, 41, 11 and 3 of GAS isolated from the throats of children living in Northland, the Gisborne region or Palmerston North.

emm type	Northland (n)	Gisborne (n)	Palmerston North (n)	Northland vs Gisborne (p)	Northland vs PN (p)	Gisborne vs PN (p)
12	14	27	25	0.000033	0.000000	0.130751
1	47	7	7	0.000073	0.014695	0.404737
41	12	11	0	0.257425	0.040089	0.007335
3	0	0	11	1.000000	0.000000	0.000020
11	14	2	0	0.0596	0.0242	0.52

n: number of isolates; p: probability determined by Fisher Exact Test.

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Discussion

This study examined the *emm* type distribution among pharyngeal isolates of GAS from children living in areas of New Zealand with high and low incidences of ARF. Both the Northland and Gisborne regions are in the upper North Island where there is a high incidence of ARF,[11,13] whereas Palmerston North, a city closer to the southern end of the North Island, has a low incidence (Figure 1).[24] Significant differences in distribution of *emm* types 1, 3, 11, 12 and 41 between Palmerston North and Northland were found (Table 2). However, there was no difference in the distribution of *emm*1, isolated from three ARF cases in New Zealand in 2012,[6] between the Gisborne region and Palmerston North. Another classical rheumatogenic type, *emm* 3, isolated from a single New Zealand ARF case in 2012,[6] was not found among the Northland or Gisborne region isolates, but 11 were isolated from children in Palmerston North. There was also no clear difference in the distribution of all *emm* types that have been associated with ARF between the three regions (Northland 85%, Gisborne 72% and Palmerston North 79%) even though Palmerston North has a much lower incidence of ARF (Figure 1). Simpson's index of diversity was lower for the Palmerston North (0.837) than for the Northland (0.919) and Gisborne (0.912) isolates, but this difference was not significant and less than that reported for the Pacific region (0.979).[25]

Although throat isolates only were examined in this study, the majority were *emm*-patterns considered to be skin specialists (pattern D, 23%) or generalists (pattern E, 39%) for all the regions studied (Table 1). This finding is consistent with other studies, which indicate that skin types have an important role in the development of ARF in New Zealand children.[3,12,] Pattern D and E *emm* types may circulate among children on skin but also cause throat infections.[3,7] The observation that nearly one-third to almost a half of children admitted to hospital for ARF did not have a sore throat during the four weeks prior to admission[8,9] might mean that skin infections play a more direct role in ARF as proposed by Parks, Smeesters and Steer for children

living in a tropical climate.[7] However, the recent report of a 58% reduction in ARF cases in children treated for sore throats in Auckland, New Zealand, confirms the importance of pharyngeal infections in this country.[26] Although structural differences in the M proteins support the allocation of *emm* types into three patterns, A-C, D and E,[27] Bessen and Lizano report that the tissue tropism is not absolute; GAS with pattern D *emm* types were isolated from throat infections in six of the eight countries included in their population-based survey.[16] In addition, skin infections detected in school clinics in Auckland accounted for only 8.8% of total antibiotic prescriptions in 2014,[28] which suggests that GAS infections of skin were relatively uncommon.

emm cluster D4 has been found to contain the majority of ARF-associated GAS in New Zealand,[6] so it was noteworthy that nine different *emm*-types, making up 16% of throat isolates in this study, were in cluster D4 (Table 1). However, three of the *emm*-types in cluster D4 (86,101 and 225) have not been associated with ARF in New Zealand. Although only five *emm* types belonged to an A-C cluster (*emm*1, 3, 12, 227 and 238), these isolates made up 37% of the total throat isolates (Table 1) and all, except *emm*227 have been isolated from patients with ARF between 2006 and 2014.[6]

The most advanced of GAS vaccines are three based on M proteins, two of which are composed of conserved sequences from the C repeat region, while the third contains amino terminal, M-type determinants from 30 M proteins.[19] The latter has been tested in rabbits, which produced antibodies bactericidal for the 30 vaccine serotypes but also for another 43 *emm* types. If these cross opsonic effects can be extrapolated to humans then the 30-valent vaccine developed by Dale and colleagues[19,23] should protect against 78% of the isolates and 30 of the 47 *emm*-types found in the current study.

A limitation of this study is that GAS isolates were obtained from throat swabs of children in Northland and the Gisborne region with uncomplicated pharyngitis and not from those with confirmed ARF. All the children participating in the Palmerston North study had throat swabs taken regardless of clinical symptoms. Most children known to have a pharyngeal

infection with GAS would have been treated with penicillin.[8] Insights into the exact mechanisms of ARF pathogenesis are limited by the fact that patients are typically GAS culture-negative at the onset of the disease, which usually takes place 2–3 weeks after initial infection. The organism responsible for initiating ARF is usually not known and must be inferred from studying GAS isolates cultured from epidemiologically associated individuals.[29]

Another limitation of this study was the time difference between the collection of throat swabs from children in the three regions. It is well established that the GAS *emm*-types circulating among the children change over time.[3,30]

In conclusion, this study found diverse *emm* types among GAS isolated from the throats of children from the Northland, Gisborne and Palmerston North regions. A high proportion of *emm* types of isolates from this study have previously been associated with ARF in New Zealand. As Palmerston North has a low incidence of ARF compared to Northland and Gisborne, these findings support previous studies that show that there are other factors involved in development of ARF such as ethnicity, socio-economics and housing situations.

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Medication-related patient harm in New Zealand hospitals

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ABSTRACT

AIM: The purpose of this study is to identify patterns of medication-related harm from a national perspective, and to use this information to inform decisions on where to focus medication safety efforts. This study updates a 2013 study using the same methodology.

METHOD: District health boards (DHBs) still actively using either the Adverse Drug Event (ADE) Trigger Tool (TT) or the Global Trigger Tool (GTT), submitted two years of anonymised ADE data (1 July 2013–30 June 2015) to the Health Quality & Safety Commission (the Commission) using a standard template. Analyses were conducted using aggregated data only.

RESULTS: Of eight DHBs who submitted data, six datasets were included, representing a total of 2,659 chart reviews. From these reviews, 923 harms were identified in 751 patients, with 28% of patients experiencing one or more harms. Harms occurred at a rate of 34.7 per 100 admissions, 42.5 per 1,000 bed days and 28% of patients experienced one or more medication-related harms. Those harmed were more likely to be older, female and have an increased length of stay.

Most harms (65%) occurred during an inpatient stay, however, a substantial number (29%) originated in the community and precipitated an admission. Across all levels of severity, the most common types of medication harm were constipation, hypotension and bleeding. In the more serious harm categories, bleeding, hypotension and delirium/confusion/over-sedation were most common. Six groups of medicines caused the greatest amount of harm: opioids (including tramadol), anticoagulants/antiplatelet agents, antibiotics, antianginals (beta-blockers, nitrates, calcium channel blockers and others), diuretics and other cardiovascular medicines (angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), centrally acting agents and statins). Opioids and anticoagulants/antiplatelet agents not only accounted for 40% of all harm, they were implicated in the most severe harm.

CONCLUSION: This paper confirms earlier work that medication-related harms are common, occur both in hospitals and in the community, and are a substantial burden for patients and our healthcare system. Work is underway at local and national levels to decrease this harm, with a focus on the high-risk medicines most commonly implicated.

Adverse drug events (ADEs) and adverse drug reactions are major causes of patient morbidity and mortality, and a source of significant costs for both organisations and patients.[1,2] The ability to accurately quantify medication-related harm is therefore important, but there is no gold standard for measuring such harm.

Currently, district health boards (DHBs) in New Zealand rely on voluntary reporting of incidents as the primary method to identify medication-related patient harm. Voluntary incident reporting systems have a number of limitations. Most harm goes unreported[3,4] and most reporting is done by nurses rather than doctors, reflecting only part of the workforce.[5] Incidents relating to the use of medication typically focus on errors, most of which do not result in harm.[6] Furthermore, hospital incident reporting is unlikely to capture medication-related harm originating from the primary care or aged

care sectors. The principal concern with voluntary reporting is that it cannot identify trends in ADE harms, as these may be clouded by trends in reporting rather than trends in events. It is therefore of limited value in quantifying rates of medication-related harm and driving improvement in medication safety.

In 2013, a New Zealand study used a 'trigger tool' (TT) to direct limited chart reviews across three DHBs.[7] This study estimated a rate of 30 ADEs per 100 admissions and identified opioids and anticoagulants as the major medicine classes implicated in harm. While most events were in the lower severity harm scale, 2.5% contributed to death or permanent harm.[7] This work stimulated interest in trigger tools in New Zealand as a practical approach to quantifying harm and identifying patterns of harm to inform improvement.

The trigger tool method is a systematic approach to medical record review that involves the use of pre-defined triggers. The concept was developed by the Institute for Healthcare Improvement (IHI). Initially, an ADE TT was developed in the late 1990's.[8] This was subsequently modified for inclusion as part of the more comprehensive Global Trigger Tool (GTT), which has additional trigger modules (eg, surgery, intensive care).[9]

In 2011, the Commission initiated a trigger tool programme to promote and support the uptake of these tools in New Zealand DHBs. By 2014, 14 of 20 New Zealand DHBs had taken up the ADE TT and/or the GTT. Eight are still actively using the tool. Six DHBs discontinued using the trigger tool primarily due to resource constraints.

The purpose of this study was to identify patterns of medication-related harm from a national perspective, and to inform decisions on where to focus medication safety efforts.

Method

In this study, the same methodology was applied as that used in the first New Zealand trigger tool study, published in this journal in 2013. For a detailed explanation of the trigger tool method, see Seddon et al,[7] and the Commission's Practical Implementation Guide.[10]

In brief, the methodology involves a random selection of 20 medical records per month for review. Participating DHB trigger tool teams, trained and experienced in the IHI trigger tool method, review the selected charts for the ADE triggers outlined in Table 1. These triggers act as 'flags' for possible ADEs and if found, they prompt a standardised review of the chart to confirm if an ADE has in fact occurred. Reviewers were typically senior nurses or pharmacists and applied the same standard definitions and method as outlined by the IHI[9] and the New Zealand Implementation Guide.[10] The steps involved are outlined in Figure 1.

Five DHBs used the extended list of triggers in the ADE TT. One provincial DHB used only the GTT, which includes a subset of 14 of the 21 ADE triggers (see Table 1).

DHBs still active in the trigger tool programme submitted two years of anonymised data (1 July 2013 to 30 June 2015) to the Commission using a standard trigger tool template. Case weight and demographic data for the sample were obtained from each DHB's decision support team.

Inter- and intra-rater reliability were not assessed by the individual review teams, however, the internal consistency of the data was assured to an extent, as the review teams underwent comprehensive training, used standardised definitions and followed the New Zealand Implementation Guide. There were also regular local and national review team meetings where difficult cases were discussed and definitions of harm severity agreed on.

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Figure 1: Trigger tool methodology.

The standard IHI methodology includes the following:
- DHBs randomly select a set of 20 medical records per month that meet the inclusion and exclusion criteria:
  - Inclusion:
    - Patients (age 18 years and older)
    - Length of stay at least 24 hours and formally admitted to the hospital
    - Closed and completed record (discharge summary and all coding is complete).
  - Exclusion:
    - Paediatric/neonatal patients (age <18)
    - Mental health admissions.
- Records are reviewed by a team of two, usually nurses or pharmacists, who independently review each record and then reach agreement about identified harm and harm classification.
- Reviewers apply a systematic approach to the record review, with a time limit of 20 minutes per record.
- Standard triggers for either ADE TT or the medication module of the GTT (Table 1) are used when reviewing the record to flag potential harm.
- Positive triggers initiate a more in-depth record review to determine if harm has occurred.
- Identified harms are classified by severity (Table 2) and type (Table 3) and documented in a database to capture basic patient demographics, location of harm and length of stay data. Where possible, medications involved are recorded.
- Harms are routinely validated by a medical reviewer.
- Trigger tool teams typically meet monthly to discuss the classification of harm to ensure ongoing consistency and reliability of the data.

Table 1: ADE triggers.

ADE triggers (n=5 DHBs)		GTT medication module triggers (n=1 DHB)
1	Vitamin K use	Vitamin K use
2	Antihistamine use	Antihistamine use
3	Flumazenil use	Flumazenil use
4	Naloxone use	Naloxone use
5	Anti-emetic use	Anti-emetic use
6	Over-sedation/hypotension	Over-sedation/hypotension
7	Abrupt medication stop	Abrupt medication stop
8	Raised urea/creatinine (>2 x baseline)	Raised urea/creatinine (>2 x baseline)
9	International normalised ratio (INR) >4	INR >4
10	Activated partial thromboplastin time (APTT) >100 seconds	APTT >100 seconds
11	C. *difficile* positive	C. *difficile* positive
12	Hypoglycaemia: serum glucose <3.0mmol/L	Hypoglycaemia: serum glucose <3.0mmol/L
13	Laxatives	
14	Anti-diarrhoeal	
15	Resonium/calcium/sodium polystyrene sulfonate	
16	White blood count <3 x 10^9/L	
17	Platelet count <50 x 10^9/L	
18	Digoxin level >2nmol/L	
19	Rash	
20	Transferred to a higher level of care/rapid response team/arrest	Code/arrest/rapid response; transfer to higher level of care (cares module GTT)
21	Other	Other

Table 2: Harm severity categories.

Category	Description
Categories A-D	No harm
Category E	Temporary harm to the patient and required intervention
Category F	Temporary harm to the patient and required initial or prolonged hospitalisation
Category G	Permanent patient harm
Category H	Intervention required to sustain life
Category I	Patient death

Definitions

Triggers

Table 1 outlines the triggers in both the ADE TT and the GTT.

Harm

The definition of harm, including medication-related harm, is "unintended physical injury resulting from or contributed to, by medical care that requires additional monitoring, treatment or hospitalisation, or that results in death".[9] This definition includes all harm, whether preventable or not. The authors of the IHI tool justified this decision on the basis that preventability can change rapidly with advances in care (such as the prevention of central-line-associated bacteraemia), and if included, this would interfere with the ability to assess trends over time. Also, to ensure a more consistent measure, the focus in trigger tools is primarily on harm resulting from active care. Harm resulting from the omission of care is not specifically sought, partly because acts of omission are more subjective and less easily defined. For example, a patient with inadequately treated hypertension who subsequently suffers a stroke could be an act of omission and therefore not counted, but giving a high dose of warfarin causing bleeding would.

Definitions relevant to medication harm have been previously described.[7] In brief, types of medication-related harm include unintended harm caused by the drug itself at normal doses (an adverse drug reaction) or from a medication error. While most medication errors do not result in harm,[11] approximately 25% of ADEs are caused by medication errors.[6]

Table 3: Types of medication harm.

Events related to medication/intravenous fluids
1. *Clostridium difficile* medication-associated infection
2. IV volume overload/electrolyte imbalance
3. Kidney damage due to contrast dye
4. Medication-related cardiac event/arrhythmia
5. Medication-related renal insufficiency
6. Medication-related allergic reaction
7. Medication-related bleeding
8. Medication-related delirium, confusion or over-sedation
9. Medication-related diarrhoea
10. Medication-related glycaemic events
11. Medication-related hypotension
12. Medication-related nausea and vomiting
13. Medication-related constipation
14. Other

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Table 4: Where harm occurred.

Code	Definition	Example
Inpatient	Medication-related ADE occurred during this hospital admission.	Patient had anaphylactic reaction to chlorhexidine.
Re-admission	Medication-related ADE present on admission, related to a prior discharge, within 30 days of the index admission.	Patient admitted with constipation after being discharged on morphine.
Non-inpatient	Medication-related ADE that occurred in the community and precipitated an admission.	Patient on metoprolol admitted with a fracture due to a fall resulting from a hypotensive episode.

The DHB reviewers classified the type of harm in three different ways: using the NCC MERP (National Coordinating Council for Medication Error Reporting and Prevention Index) (Table 2); the Florida Harm Classification table adapted for the New Zealand setting (Table 3); and where on the patient journey that the harm occurred (Table 4).

Analysis

The Commission Health Quality Intelligence team undertook the analyses using aggregated data only. Confidentiality of data was assured and no individual DHBs were to be identified.

Results

Of eight DHBs who submitted data, six datasets were included: four large hospitals in main centres across both the North and South Islands, and two provincial North Island hospitals. Two of the original eight datasets did not include all the data items required for analysis and were therefore excluded. The data reported cover the two-year period 1 July 2013 to 30 June 2015.

Data from 2,659 chart reviews were included. There were 751 patients identified with medication-related harm and 1,908 with no medication-related harm. Table 5 compares the demographics between these two groups.

Table 5: Comparison across variables between those with an ADE and those with no ADE.

Variable	Patients with no ADE (N=1,908)	Patients with ADE (N=751)	Difference	P-value
Length of stay (LOS) days (mean)	4.6	8.7	4.1	0.01
Age years (mean)	49.9	57.2	7.3	<.001
Gender (F)	49%	60%	11%	<.001
Case weight	1.5	2.3	0.8	0.14
Māori	11.7%	9.9%	-1.8%	0.21
Pacific Islander (PI)	12.1%	13.1%	1.0%	0.31
Non-Māori/Non-PI	76.3%	76.9%	0.6%	0.41

Table 6: ADEs by harm severity and status.

Harm type	Inpatient	Non-inpatient	Readmission	All
E	484	72	4	560 (61%)
F	98	185	42	325 (35%)
G	6	7	0	13 (1.4%)
H	15	5	2	22 (2.4%)
I	1	0	1	2 (0.2%)
Total	604 (65.5%)	269 (29%)	49 (5.5%)	922

For all harm categories, those harmed were more likely to be older, female and have an increased length of stay (LOS). There were no significant differences between groups for case weight and ethnicity. A similar pattern was noted for patients with more serious harm (Categories F, G, H and I).

Across all categories (inpatient, non-inpatient and readmissions), 923 harms were identified, with 28% of patients experiencing one or more medication-related harms. Harm occurred at a rate of 34.7/100 admissions and 42.5/1,000 bed days.

Harms occurred during an inpatient stay in 65.5% of patients (n=604) and 5.5% (n=49) were associated with an inpatient stay that resulted in a readmission. Events originating in the community and precipitating a hospital admission contributed 29% (n=269).

Minor harms (Category E) accounted for 61%, however, 35% (n=325) were category F, contributing to an admission or excess LOS. Serious harm occurred in 4% (n=37), with 1.6% (n=15) contributing to permanent disability or death (Category G and I), while harm that required an intervention to sustain life accounted for 2.4% (n=22) (see Table 6).

Across all harm severity levels (excluding the 'other' category), the top five harms, representing 70% of the burden of medication-related harm, were: constipation, hypotension, bleeding, nausea/vomiting and delirium/confusion/over-sedation (see Figure 2).

Figure 2: Types of medication-related harm (all harm categories).
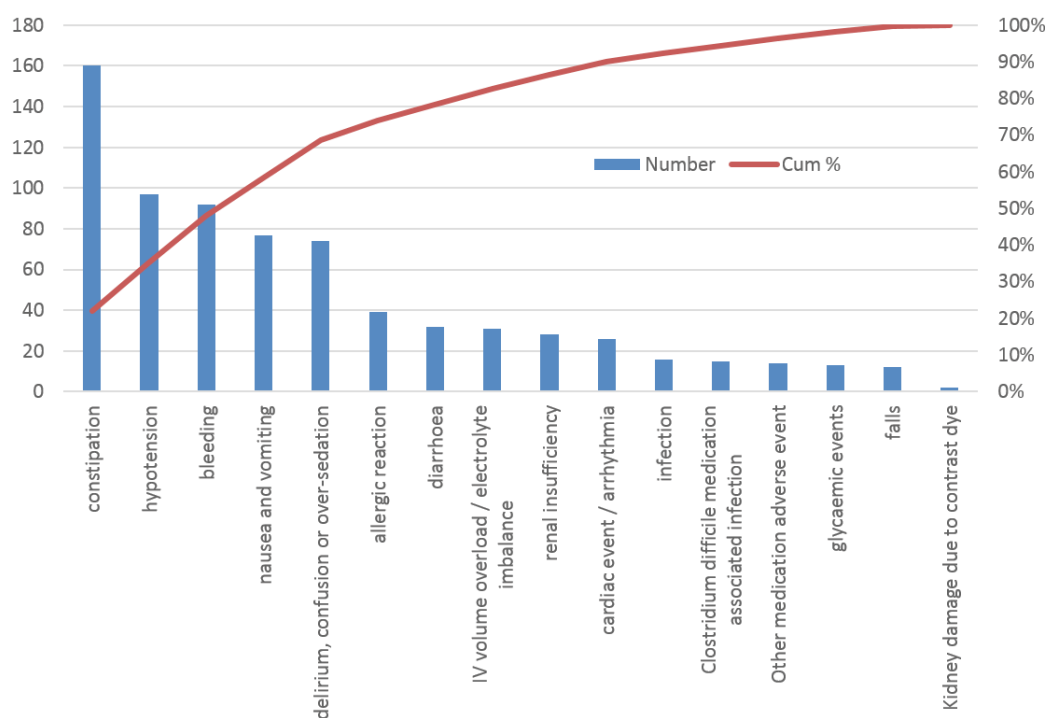
Table 7: Top 10 individual medicines implicated in harm.

1	Morphine	149	16.1%
2	Fentanyl	44	4.8%
3	Oxycodone	38	4.1%
4	Aspirin	34	3.7%
5	Furosemide	28	3.0%
6	Codeine	25	2.7%
7	Amoxicillin; amoxicillin/clavulanic acid	23	2.5%
8	Metoprolol	22	2.4%
9	Tramadol	20	2.2%
10	Warfarin	17	1.8%

The top five serious harms (categories F, G, H, I) were: bleeding, hypotension, delirium/confusion/over-sedation, constipation and IV volume overload/electrolyte imbalance. Cardiac event/arrhythmias were a close sixth cause of the more serious harms. Together these six harms represented 66% of the burden of the more serious medication-related harm.

When considering individual medicines implicated in harm (see Table 7), morphine caused 16% of harm, and other opioids (fentanyl, oxycodone, codeine and tramadol) account for a further 14%. Together these medicines account for 30% of harm and are implicated in three of the five most common harms identified in Figure 2 (constipation, nausea/vomiting and delirium/confusion/over-sedation).

Aspirin ranked fourth in the top 10 medicines (predominantly harm from bleeding). Warfarin contributed a further 1.8%. Although not in the top 10, enoxaparin (ranked 11th) added a further 1.6%. So anticoagulation/antiplatelet agents together account for 7% of harms and are the most common cause of serious harm.

Furosemide and metoprolol, implicated in hypotension-related harm, account for 5.4% of medication-related harm. The antibiotics amoxicillin and amoxicillin/clavulanic acid accounted for 2.5% of all harm (see Table 7).

Medicines identified by the trigger tool process were grouped into categories to identify those contributing most harm overall and the more severe harms (Table 8). We devised six broad categories of medicines. Cardiovascular medicines were separated into different groupings to provide more granular information for clinicians.

Table 8: Medication implicated in patient harm by harm severity.

Medicine classes	E	F	G	H	I	Total	%
Opioids (includes tramadol)	250	33		9		292	31.64%
Anticoagulants/antiplatelet agents	25	52		6	1	84	9.10%
Antibiotics	40	30		1		71	7.69%
Beta-blockers, nitrates, calcium channel blockers and other antianginal agents	33	27		1		61	6.61%
Diuretics	14	23				37	4.01%
Other cardiovascular medicines (ACE inhibitors, ARBs, centrally acting agents, lipid lowering agents	18	15	1	2		36	3.9%
Not recorded/name queried	70	56	4		1	131	14.19%
Other (groups of medicines with less than 30 harms recorded)	112	88	8	3		211	22.9%
Total	562	324	13	22	2	923	100.00%

Discussion

This study reports on a systematic approach to measuring medication-related harm and reveals significant rates occurring both in the community and in hospitals. The study analysed results from four major metropolitan DHBs and two provincial DHBs that used the trigger tool method.

The results show that 28% of patients experienced one or more medication-related harm, the rate per 100 admissions was 34.7 and there were 42.5 adverse drug events per 1,000 bed days. ADEs were more common in older female patients, and also increased with length of hospital stay. Nearly 30% of the identified harm originated in the community, and was identified because the harm precipitated a hospital admission.

Most harm (61%) was minor in nature, however, in 37 (4%) of the cases the harm was serious, requiring life-saving interventions in 22, causing permanent harm for 13, and contributing to the death of two patients. In a further 35% the harm either precipitated or prolonged hospital stay.

The top five harms across all categories were constipation, hypotension, bleeding, nausea/vomiting and delirium/confusion/over-sedation, accounting for 70% of the burden of medication-related harm.

However, for the more serious harms, a different pattern emerged, with bleeding, hypotension, delirium/over-sedation, constipation and IV volume overload/electrolyte imbalance representing the top five.

There were six groups of medicines that caused the greatest amount of harm: opioids, anticoagulants/antiplatelet agents, antibiotics, antianginal agents (beta-blockers, nitrates, calcium channel blockers and others), diuretics and other cardiovascular medicines (ACE inhibitors, ARBs, centrally acting agents and statins).

Opioids and anticoagulants/antiplatelet agents not only accounted for 40% of all harm, they were also implicated in the most severe harm.

Compared with similar international studies,[13–19] our rate of harm was in the high range, although there is wide variation in all three measures between studies: ADE as a percentage of admissions (3.4–31%), ADE/100 admissions (11.5–47.2%); and ADE/1,000 inpatient days (7–61.3%). It should be noted that study design can dramatically alter these percentages (eg, a study of elderly patients taking multiple medication is likely to dramatically increase the rates). For this reason, it is most useful that we compare our results with the previous New Zealand study,[7] which had a very similar design, and reported data from 2010 to 2011.

Compared with the previous study,[7] the degree and severity of ADE harm observed is consistent, although the previous study identified 15% of harm that occurred in the community, as compared with 29% in the current study.

Across both studies the classes of medicines implicated were remarkably similar. Opioids remain the medicine class responsible for most harm, accounting for 33% of all harm in the previous study compared with 32% in the current study. Anticoagulants and antiplatelet agents were also significant, accounting for 10% in the previous study and 9% in the current study. Likewise, antibiotics were similar at 9% in the previous study and 8% in the current study. In contrast, the top 10 medicines implicated in harm did vary from the previous study. While morphine was similar in both studies, warfarin dropped from 6.1% in the previous study to 1.8% in the current study.

Although unknown, we speculate that the reduction in warfarin-related harm could be associated with the increased availability and use of alternative oral anticoagulants, for which there was no trigger during the study period. Two harms associated with dabigatran were identified and in the last six months, idarucizumab has been introduced as an antidote to dabigatran-associated bleeding. The prescription of this medicine could potentially be included as an additional trigger in the future.

Fentanyl increased from 2.9% of harms in the previous study to 4.8% in the current study, and tramadol decreased from 5.2% to 2.2%. We note from the New Zealand Atlas of Healthcare Variation[20] that while use of fentanyl varied 12-fold between DHBs, there was a significant overall increase in the use of fentanyl between 2011 (an average of 0.8/1,000 received fentanyl)

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and 2015 (average of 1.7/1,000). This may account for the increased harm seen. We cannot speculate about the reduction in harm from tramadol.

The finding of increased ADEs in females is similar to that previously reported (62% in the earlier study vs 60%). However, the mean age for women in the current study was considerably younger at 57 years compared with 65 years in the previous study.

The presence of an ADE increased the average length of stay (LOS) in both studies, however, the increase was less dramatic in the current study (4.6 days vs 7.06 days). Interestingly, the LOS of patients without an ADE was also less in the current study (8.7 days vs 10.6 days).

The major strength of our study relates to the number of patients reviewed in diverse areas of the country. The DHBs providing data included major metropolitan hospitals and smaller provincial hospitals. An additional strength was that teams involved in reviewing charts had all undergone rigorous training and had been using the method for a number of years.

Like all studies in this area, our study suffers from the subjectivity inherent in the trigger tool itself (which we attempted to mitigate with regular training and reviewing of difficult cases) and the lack of a true gold standard for medication-related harm. The change of reviewers over time can also represent a threat to reliability, although this is less likely where at least one reviewer remains consistent,[21] which was the case for most of the participating DHBs.

The GTT has a more limited list of medication triggers compared with the ADE TT and may have under-reported ADEs. However, only one provincial DHB was using the GTT alone and it was unlikely to significantly impact on the rate of ADEs reported, and if anything, this would be in the direction of undercounting.

We also noted that in 14% of harms, the name of the medication was either omitted or queried. While this is a relatively small number, it highlights the importance of accurate documentation if we are to fully understand which medicines are most commonly implicated in harm.

The sheer magnitude of this unintended harm from medicines should be of interest to decision makers in two main areas. The first is economic. Although most of the harms were minor, they contribute to extended hospital stays and therefore DHB costs. The finding that a substantial number of ADEs occurred in primary care and precipitated a hospital admission is also an important economic consideration. Our data is likely to be an underestimate of the true rate of medication-related harm in primary care as we were only identifying these ADEs if they contributed to an admission. Further research is needed on ADE trigger tools in primary care to understand the factors that contribute to medication-related harm in the community, so that improvement efforts can be appropriately targeted. Preliminary work has begun on the use of trigger tools in primary care with the development of a set of triggers for the New Zealand setting[22] and a trial of the trigger tool methodology as part of a primary care 'Safety in Practice' improvement collaborative in the Auckland region.[23]

The second policy area is in the type of medicines that caused harm: the high-risk medicines. If we know that these medicines cause most of the harm, then it is reasonable to concentrate our efforts nationally on understanding why, and putting resources and energy into making them safer for our patients. Following on from the results of the previous New Zealand ADE study, the Commission recently supported a national approach to decreasing harm from opioids in hospitals. This was a formative collaborative involving all DHBs and one private hospital, which ran for 18 months (November 2014 to June 2016). An independent evaluation reported positive results, with many of the participating hospitals reducing opioid-related harm between 13–74% in the targeted wards.[24] This work is continuing in an effort to sustain and spread improvement.

There is potential for a similar approach to be directed at improving the management of anticoagulants and antiplatelet agents, which were identified by this and the previous ADE study, as major causes of serious patient harm.

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Whether to continue with the ADE trigger tool is a question for individual DHBs. The ADE TT offers an alternative and more systematic approach to measuring medication-related harm. The first requirement for improving the 'drug delivery process' Bates et al wrote in 1995 is an 'effective mechanism for systematically collecting and feeding back data about ADEs'.[25] The authors also emphasised the importance of focusing on system changes to address preventable ADEs.[25] This advice still applies more than 20 years on.

Concerns have been raised about the resource implications of using trigger tools, yet no DHB has questioned the cost of the voluntary reporting system, a system that misses most if not all medication-related harm[7] and that has a poor record in improving care. DHBs could consider alternative approaches to use trigger tools more efficiently. A targeted approach has been used successfully to identify medication-related harm in a surgical service[26] and in a selected cohort of patients over 65 years of age on five or more medicines.[27] This approach provides a snapshot at a specific point in time that can engage staff and inform local improvement work.

How best to measure medication safety remains a challenge.[28] Perhaps the most important message comes from a recent systematic review:[29] counting numbers of ADEs is perhaps less important than understanding and characterising the types of medicines that cause harm, and using this to prioritise quality improvement activity.

Considerable work is currently underway in New Zealand to mitigate harm from medication, ranging from high-tech electronic prescribing, administration and medication reconciliation systems, to increasing partnerships of clinical pharmacists with clinical teams, and the specific programmes around high-risk medication.

Conclusion

This paper reports on medication-related harm from six DHBs across New Zealand. It confirms earlier work that such harms are common, occur both in hospitals and in the community, and are a burden for patients and our healthcare system. Considerable work is underway at local and national levels to decrease this harm, with a focus on the high-risk medicines most commonly implicated. Part of such an approach should include an effective mechanism for measuring and monitoring medication-related harm, so that changes can be assessed for their ability to lead to improvement.

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What is the relationship between visual impairment and cognitive function in octogenarians?

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ABSTRACT

AIMS: To examine direct and indirect pathways between visual and cognitive function in advanced age.

METHODS: We analysed cross-sectional baseline data from *Life and Living in Advanced Age: A Cohort Study in New Zealand,* which recruited equal sample sizes of Māori (n=421) and non-Māori (n=516) octogenarians. The Modified Mini-Mental State Examination assessed cognitive function. Vision was assessed with self-report and measured distance visual acuity. Associations between visual and cognitive function were explored using general linear models and structural equation modelling.

RESULTS: Both Māori (mean age 82) and non-Māori (mean age 85) had good visual acuity [Māori: mean (standard deviation) 0.18 (0.20) logMAR; non-Māori 0.20 (0.17) logMAR] and cognitive function scores [Māori: median (interquartile range) 3MS=90 (11), non-Māori: 94 (8)]. Self-reported visual impairment was present almost 25% of the sample. Adjusting for confounders, no direct association was found between visual and cognitive function. For non-Māori, the path diagram showed the association between vision loss, and cognitive function was mediated by functional status.

CONCLUSION: Findings indicate that cognitive function is a multifactorial entity; rather than a direct effect of vision loss, mediating factors appear to contribute to cognitive decline in advanced age.

With the world population ageing rapidly, healthy ageing becomes a global priority. Cognitive function is one of the main factors defining how successfully we age.[1] The prevalence of dementia is projected to increase dramatically in the near future.[2] Various modifiable risk factors for dementia have been established, such as depression, physical and cognitive function, engagement in social and productive activities, and medical conditions including diabetes mellitus.[3,4] Of particular interest is vision loss, common in old age and often treatable. There is growing evidence for a possible (predictive) association between vision loss and poorer cognitive function in advanced age,[5–8] but the mechanism behind this association remains to be fully understood.

Besides a direct relationship, studies also reported on associations between vision loss and several other risk factors for cognitive decline, including functional status, medical conditions, social relationships and depression.[9–11] This suggests that the relationship between cognitive function and poor vision is to some extent mediated by interrelated factors. Because better understanding of the relationship between vision and cognition could lead to interventions for maximising cognitive function in late life, we aimed to explore the direct and indirect relationships between vision loss and cognitive function in an older New Zealand population, utilising data from Te Puāwaitanga o Nga Tapuwae Kia Ora Tonu - Life and Living in Advanced Age: A Cohort Study in New Zealand (LiLACS NZ).

Methods

Study population and data collection

LiLACS NZ is an ongoing longitudinal population-based cohort study of those in advanced age.[12,13] The study was started in 2010, eligible individuals were those living within the Lakes and Bay of Plenty District Health Board geographical boundaries, aged 80 to 90 years for Māori and aged 85 years for non-Māori. Different age criteria applied between the two cohorts due to a large disparity in longevity for Māori.[14]

Participants were identified from the New Zealand general and Māori electoral rolls; primary care databases; whānau and community networks. The study recruited 421 Māori and 516 non-Māori.

All participants underwent an annual interviewer-administered standardised questionnaire (brief or comprehensive) and physical assessment, conducted by trained interviewers and research nurses during a home visit or at another site as the participant chose. Medical conditions were identified by self-report, general practice and hospital records, physical assessment and blood analysis. A detailed description of LiLACS NZ study design and recruitment strategies has been reported elsewhere.[12,13]

The current study uses the baseline data. The study sample comprises only participants who completed the comprehensive interview, which included cognitive function assessment.

The study was approved by the Northern X Regional Ethics Committee of New Zealand Ministry of Health in December 2009 (NXT 09/09/088). Written informed consent was obtained from all participants before enrolment.

Measures

Cognitive function: The Modified Mini-Mental State Examination (3MS)[15] was used to assess global cognitive status. The 3MS is a screening instrument for dementia, with components assessing orientation to time and place, registration, memory, language and construction. To adjust for vision loss for those who were blind or had self-reported vision loss, we omitted similar items as in the Mini-Mental State Examination—blind version,[16] a validated cognitive test for the visually impaired: naming of the appointed item or body part; following a written command; writing a sentence; copying a drawing; performing a three-stage command. Scores range from 100 (best) to 0 (worst).

Visual impairment: Vision loss was administrated with both self-report and measured visual acuity. Binocular distance visual acuity was measured using the three metre 2000 series revised ETDRS chart. The test conditions were standardised: illumination was measured with a preferred minimum of 350 lux and participants were encouraged to wear corrective glasses during the test if glasses were normally worn. This habitual visual acuity was recorded as the smallest line read correctly plus additional letters read correctly. Acuity scores were converted to the logarithm of the minimum angle of resolution (logMAR) to transform the data to an approximately normal distribution.[17] A single self-reported item, modified from the Cognitive Function and Ageing studies[18] was used to assess subjective disability caused by vision loss. Participants were asked whether their vision loss interfered with normal day-to-day functioning, "yes" or "no".

Covariates

Socioeconomic-demographic information (age, gender, ethnicity, education level and socio-economic deprivation) was determined from the comprehensive questionnaire. Socio-economic deprivation was reflected in the New Zealand Deprivation Index derived from the address at recruitment.[19] Baseline functional status was assessed with the Nottingham Extended Activities of Daily Living scale (NEADL), a self-reported 22-item scale validated as an assessment of functional disability in domestic tasks, mobility, leisure activities and kitchen-related tasks.[20] Participants were asked whether they did perform the activities on their own, with help or were unable to do them. Scores range from 0 at worst to 22 at best. Depression was assessed using the 15-question version of the Geriatric Depression Scale (GDS-15), a screening test for depressive symptoms in older people.[21] The scale consists of 15 items, of which participants were asked how they have felt the past week. Higher scores indicate more depressive symptoms. Comorbidity was determined by summing the number of chronic conditions.[22] Data about participants' engagement in social

activities during the previous month were obtained from an index of nine questions on how often they had: "Attended meetings of any community/neighbourhood or social groups, such as old people's clubs, lectures or anything like that?", "Attended any religious meeting?", " Been a spectator at a sports event?", "Gone to an entertainment or arts event, such as concert, theatre or cinema?", "Gone to a restaurant, café, pub or bar?", "Attended a family event?", "Attended a social occasion, such as a barbeque or hangi?", "Gone to the library or museum?". Answers were dichotomised into participated (those who reported "every day" to "occasionally") or no participation (those who reported "not at all" for all questions).

Statistical analyses

Separate analyses were conducted for Māori and non-Māori, as previous research showed differing health profiles and life expectancies between the two cohorts.[14] Descriptive statistics are presented for all variables. For categorical variables, frequency and percentage are presented. For continuous variables, the mean (standard deviation (*SD*)) or median (interquartile range (*IQR*)) is presented; depending on whether the variable was normally distributed or not.

General linear models (GLM) were used to determine the direct association between visual impairment and cognitive function while adjusting for covariates. Covariates that were associated with 3MS score in univariate models with a *p*-value <0.2 were included in multivariate models. These were social engagement, functional status and depressive symptoms (and comorbidity for Māori). Age was not included in the multivariate models for non-Māori because all participants were 85 years old at baseline. Due to the skewed distribution of 3MS scores, we inversed and log-transformed 3MS scores to establish a normally distributed score (Log (100 - 3MS score)). Back-transformed beta-correlation coefficients are presented in the tables.

In the GLMs, inversed log-transformed 3MS was entered as the dependent continuous variable and visual impairment (either self-reported or visual acuity) as the independent variable. Models were repeated replacing visual acuity (continuous variable) with self-reported visual impairment (categorical variable). A

p-value <0.05 was considered statistically significant. Data were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows (IBM SPSS version 21).

Structural equation modelling (SEM) was used to produce path diagrams modelling direct and indirect pathways between either visual acuity or self-reported vision loss and cognition via intermediate variables. The 3MS scores were entered as the continuous dependent variable. Those covariates significantly associated with 3MS score in the GLMs were included as confounders. The strength of the relationship between two variables was estimated as a standardised regression weight (ie, path coefficient, *Beta*). While there is no established guideline regarding sample size requirements for structural equation modelling, a general rule of thumb is that the minimum sample size should ideally be 20 times the number of variables in the model.[23] The model generated in this study consisted of five variables and thus the non-Maori sample size of sample of 402 was sufficient for path analysis. Model fitness was assessed by the ratio of chi-squared to degrees of freedom (Ratio of Chi-square/df), the root mean square error of approximation (RMSEA), the Tucker Lewis Index (TLI) and the Comparative Fit Index (CFI). The following values indicate a good fit; for the Ratio of Chi-square/df, a value of <3, for RMSEA a value close to 0.05, for TLI a value that approaches 1, for CFI a value >0.95. The product of estimates along each path reflects the total effect of that compound in the path diagram. Then, the total indirect and direct causal effect of vision on cognition is the sum of the estimates of all the separate paths. The path analysis was performed using IBM SPSS Amos version 22.0 (IBM Corp, Armonk, New York, USA). Significant levels were set at p<0.05.

Results

At baseline, 661/937 participants (259 Māori, 402 non-Māori) completed the comprehensive interview, of which 649 (258 Māori, 391 non-Māori) participants had their cognition tested. After excluding four participants from the analysis because of incorrect visual acuity measurement, visual acuity was tested in 554 participants (210 Māori, 344 non-Māori); 650 (253 Māori, 397 non-Māori) reported on their vision loss.

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Table 1: Baseline characteristics of participants.

Variables	Māori n=259	Non-Māori n=402
Gender	**n (%)**	
Male/Female	104 (40)/155 (60)	189 (47)/213 (53)
Education level		
Primary school or no schooling	73 (29)	62 (16)
Secondary school, no qualification	94 (37)	137 (35)
Secondary school qualification	46 (18)	85 (22)
Post-secondary schooling	38 (15)	110 (28)
Socio-economic deprivation (NZ Dep. index)[24,a]		
1–4 (low)	37 (14)	103 (26)
5–7 (medium)	61 (24)	173 (43)
8–10 (high)	161 (62)	126 (31)
Engagement in social activities[e]	234 (93)	377 (94)
Ocular disease		
Cataract	131 (53)	247 (62)
Glaucoma	27 (11)	45 (11)
ARMD	40 (16)	72 (19)
Diabetic eye disease	19 (8)	7 (2)
Measured visual impairment (>0.3 logMAR)[g]	46 (22)	66 (19)
Self-reported visual impairment[h]	69 (27)	95 (24)
Cognitive impairment (3MS≤77)[25]	39 (15)	25 (6)
Mean (SD)		
Age in years	82.3 (2.7)	84.6 (0.5)
Comorbidity (number of conditions)[b]	4 (2)	4 (2)
Distance visual acuity (logMAR)[f]	0.18 (0.20)	0.20 (0.17)
Median (IQR) Min, Max		
Cognitive function (3MS)[i]	90 (11) 1, 100	94 (8) 12, 100
Functional status (NEADL score)[c]	19 (4) 0, 22	19 (3) 1, 22
Depressive symptomatology (GDS-15 score)[d]	2 (3) 0, 14	2 (2) 0, 10

Abbreviations: *SD*, standard deviation; *IQR*, interquartile range; NZ Dep. Index, New Zealand deprivation index; NEADL, Nottingham Extended Activities of Daily Living scale; GDS-15, Geriatric Depression Scale-15 items; ARMD, Age-Related Macular Degeneration; logMAR, logarithm of the Minimum Angle of Resolution; 3MS, the Modified Mini Mental State Examination.

[a] Derived from the address at recruitment.

[b] Derived from an index of 15 selected chronic conditions.

[c] NEADL scores ranging from 0 (at worst) to 22 (at best).

[d] GDS-15 scores, higher scores indicate more depressive symptoms.

[e] Participants who participated in any of nine predefined social activities.

[f] Higher scores indicates worse visual acuity.

[g] The minimum visual acuity required for an unrestricted driver's license in New Zealand.[26]

[h] Participants who reported their vision interfered with normal day-to-day functioning.

[i] 3MS scores ranging from 0 (at worst) and 100 (at best).

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Table 2: Association between cognitive function and visual impairment using general linear models.[a,b]

Variables	Beta[c]	95% CI	p-values	Back transformed Beta
Māori				
Distance visual acuity (logMAR)	0.103	-0.217, 0.422	0.526	-1.267
Self-reported visual impairment[d]	0.110	-0.030, 0.251	0.123	-1.289
Non-Māori				
Distance visual acuity (logMAR)	0.197	-0.120, 0.515	0.223	-1.574
Self-reported visual impairment[d]	0.065	-0.056, 0.187	0.290	-1.163

Abbreviations: 95% *CI*, 95% confidence interval; logMAR, logarithm of the Minimum Angle of Resolution.
[a] Models were adjusted for: gender, education level, socio-economic deprivation, social engagement, functional status and depressive symptoms (and age, comorbidity for Māori).
[b] A *p*-value of less than 0.05 (two tailed test) was considered statistically significant.
[c] Estimates from the inversed log transformed 3MS scores.
[d] Reference group are participants who reported that their vision did not interfere with day-to-day functioning.

Baseline characteristics of Māori and non-Māori participants are presented in Table 1. Among Māori, 40% were male; mean (*SD*) age was 82.3 (2.7) years. Non-Māori participants had a mean (*SD*) age of 84.6 (0.5) years; 47% were male. Median (*IQR*) 3MS scores were 90 (11) and 94 (8) for Māori and non-Māori, respectively.

More than one-quarter (n=69) of Māori participants and 24% (n=95) of non-Māori participants reported their eyesight interfered with their normal day-to-day functioning. The majority of participants had good visual acuity, with mean (SD) visual acuity scores of 0.18 (0.20) logMAR for Māori and 0.20 (0.17) logMAR for non-Māori. In addition, 22% (n=46) Māori and 19% (n=66) non-Māori could be regarded as having measured visual impairment; a visual acuity <0.3 logMAR is an often used cut-off point and the minimum visual acuity required for an unrestricted driver's license in New Zealand.

In unadjusted GLM, self-reported visual impairment was significantly associated with 3MS scores in the Māori (*Beta*=0.150, *CI*=[0.012, 0.289], *p*=0.033). A non-significant trend was found for non-Māori (*Beta*=0.118, *CI*=[-0.002, 0.239], *p*=0.054). Visual acuity scores were not significantly associated with 3MS scores in both cohorts (Māori: *Beta*=0.202, *CI*=[-0.104, 0.509], *p*=0.194; non-Māori: *Beta*=0.285, *CI*=[-0.031, 0.602], *p*=0.077).

Table 2 shows associations between vision and cognition for each cohort after adjusting for multiple covariates. Both self-reported vision loss and measured visual acuity were no longer significantly associated with 3MS scores in both Māori and non-Māori.

Since certain conditions may play more of a role than others on cognitive decline, we repeated analyses replacing comorbidity by hypertension, diabetes, stroke and cardiovascular disease, all known risk factors for dementia.[3,27] However, no significant associations between these health conditions and cognitive function were found in the final models for both cohorts (data not shown).

In contrast to visual impairment, some other variables of interest were independently associated with the 3MS scores in the multivariable adjusted models. Significant predictors of poorer cognitive function in Māori included male gender and more depressive symptoms; post-secondary education level was associated with better cognition (Tables 3 and 5). For non-Māori participants, more education and better functional status were significantly associated with better cognitive function (Tables 4 and 6). The role of these variables in the relationship between vision and cognition was further explored using SEM to produce corresponding path diagrams.

Cognition was placed in the structural equation model as the outcome variable. Vision loss (either measured or self-reported), education, and for Māori only gender, were modelled with direct effects. The indirect effect of either self-reported or measured distance visual acuity on cognitive function was mediated through functional status in the non-Māori cohort (Figures 1A, 1B) and through depressive symptoms in the Māori cohort (Figure 2A, Table 4).

Figure 1A: [a]Path diagram for the direct and indirect relationship between self-reported vision loss and cognitive function in the non-Māori cohort.
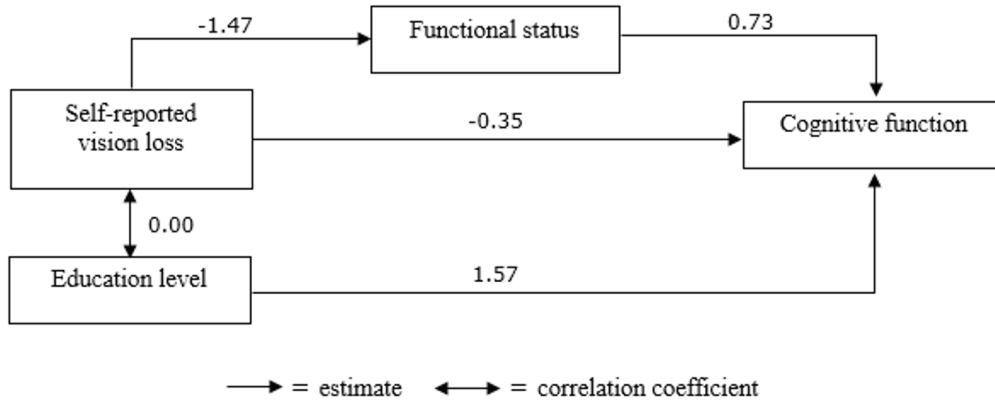
Total indirect effect via functional status: -1.07, total indirect and direct effect: -1.42. No correlation between vision and education level.
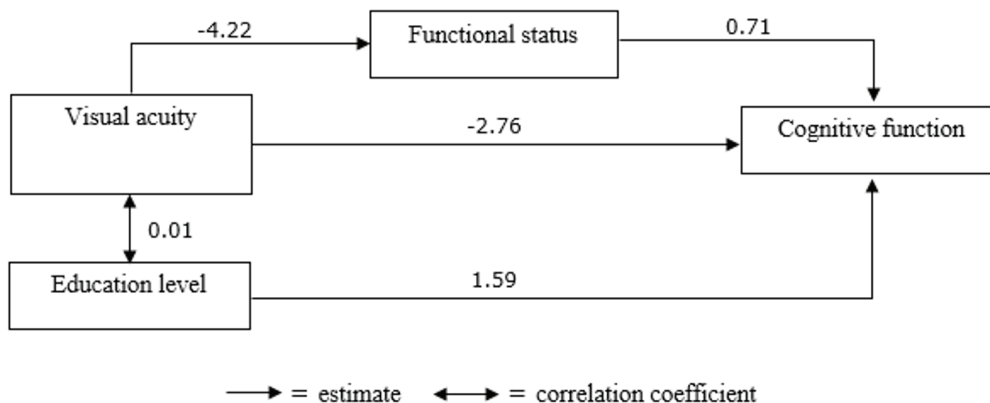[a] Ratio chi-squared degrees of freedom (*Chi-square*/df) = 0.113, root mean square error of approximation (RMSEA)= 0.000, Tucker Lewis Index (TLI)= 1.108, comparative fit index (CFI)= 1.000.

Of the path diagrams produced, only the path diagrams including non-Māori did fulfil all assumptions for fitness of the model (Figures 1A, 1B).

Both path diagrams illustrated that the relationship between cognitive function and poor vision is to some extent mediated by functional status. Self-reported vision loss was directly associated with a decline of 0.35 points on the 3MS; measured visual acuity with a decline of almost three points. The indirect pathway from self-reported vision loss to cognitive function via functional status was associated with a total decline of 1.07 points on the 3MS and with a total decline or 3.00 points in the path diagram with measured visual acuity. Together, self-reported vision loss decreases 3MS scores through indirect and direct pathways with 1.42 points; measured visual acuity demonstrated a total combined direct and indirect effect of almost six points (6%) decline on the 3MS. However, higher education was independently associated with an increase of 3MS scores; vision loss was not correlated with education level in this path diagram.

Figure 1B: [a]Path diagram for the direct and indirect relationship between measured visual acuity and cognitive function in the non-Māori cohort.

Total indirect effect via functional status: -3.00, total indirect and direct effect: -5.76. No correlation between vision and education level.
[a] Ratio chi-squared degrees of freedom (*Chi-square*/df) = 0.248, root mean square error of approximation (RMSEA)= 0.000, Tucker Lewis Index (TLI)= 1.162, comparative fit index (CFI)= 1.000.

Discussion

This study aimed to examine the impact and pathways by which vision loss affects cognitive function in advanced age. In line with previous cross-sectional and longitudinal studies, we found neither self-reported nor measured visual impairment was independently associated with cognition.

However, the path analyses confirmed that the relationship between vision loss and cognitive function was explained by functional status in the non-Māori cohort. This may be best explained by 'the common cause hypothesis' (common age-related factor is responsible for both vision loss and cognitive decline), where functional status serves as the age-related common cause. The SEM findings can also be explained by 'the sensory deprivation hypothesis' (assumes that cognitive decline is caused by changes in the brain as a result of diminished sensory input; sensory loss reduces the opportunity to engage in cognitively stimulating activities).[28] Note that the path diagram does not provide information on the direction of associations. Persons with poor functional status may be less likely to see an optometrist. They also may be less able to participate in social and cognitively stimulating activities, suffer from more depressive symptoms and be less physically active. Baseline disability in activities of daily living have been linked to dementia incidence, and vice versa, dementia also may predict functional disability.[29,30]

In the cross-sectional survey of the Blue Mountains Eye Study (BMES) with participants aged 50+, visual impairment was associated with higher odds of cognitive impairment.[31] However, no association observed between visual impairment and cognitive decline at five and 10 years follow-up in this BMES population.[32] Similarly, the Hispanic Established Populations for Epidemiologic Studies of the Elderly found no relationship between distance visual impairment and change in MMSE-blind scores over a seven-year period; only near vision impairment conferred an increased 0.13 points annual decline in MMSE-blind scores compared to those with adequate near vision.[7] In a six-year follow up of a cohort of older Dutch people (baseline mean age 65), Valentijn et al (2005) concluded that the deterioration of visual acuity was associated with deterioration in cognitive measures and attributed the positive relationship to the reduced ability of participants with sensory impairments to perform well on executive function domain on the cognitive test.[33] Elyashiv, Shabtai and Belkin (2014) found an attenuated association between vision and cognition with advanced ageing and postulated that increased impact of other risk factors for cognitive decline mask the impact of visual impairment on cognitive function in older age.[5] Both propositions comply with the previously hypothesised explanations for the relationship between vision and cognition.[28,33]

The high median 3MS scores in the LiLACS NZ cohort may have reduced the power to observe a direct relationship with visual impairment. Using a cut-off point of 3MS ≤77 to define cognitive impairment, only 15.1% (n=39) of Māori and 6.4% (n=25) of non-Māori would have been considered cognitive impaired.[25] Other limitations of this study include its reliance on the inclusion of only those participants who completed the comprehensive questionnaire; this could have introduced a selection bias towards a healthier sample.[14] It is unclear if omitting items not independent of vision will lead to under or overestimation of cognitive performance among those with visual impairment contributing to a type II error. The study by Busse et al reported that the validity of the vision-adjusted MMSE (MMSE-blind) is comparable to the full MMSE.[16] We assume similar observation between the full and vision-adjusted 3MS; future studies are needed to examine this. Lastly, causal inference cannot be established from this cross-sectional analysis. The strengths of this study derive from its large collection of comprehensive health and social data; the separate analyses for indigenous people, which strengthened generalisability to older Māori; and the assessment of both measured and self-reported visual impairment. These results address the literature gaps on vision and cognitive function in older indigenous people and octogenarians.

In conclusion, we found that rather than a direct effect of vision loss, mediating factors appear to contribute to cognitive decline in advanced age. Further longitudinal research is needed to examine the role of sensory function and mediating factors, on cognitive function over time. Findings from this research are able to inform policies on health and social living of older people, particularly extending relevant information to people of advanced age.

Appendix

Table 3: Adjusted association between cognitive function and self-reported visual impairment in the Māori cohort (n=187).[a,b]

Variables	Beta[c]	95% CI	p-values	Back trans-formed Beta
Self-reported visual impairment[d]				
No	Reference category			
Yes	0.110	-0.030, 0.251	0.123	-1.289
Age	0.011	-0.013, 0.036	0.373	-1.026
Gender				
Male	Reference category			
Female	-0.216	-0.344, -0.089	0.001	0.608
Education level				
Primary school or no schooling	Reference category			
Secondary school, no qualification	-0.121	-0.276, 0.034	0.126	0.757
Secondary school qualification	-0.145	-0.334, 0.043	0.131	0.716
Post-secondary schooling	-0.402	-0.610, -0.193	<0.001	0.397
Socio-economic deprivation (NZ Dep. index)[34,e]				
1–4 (low)	Reference category			
5–7 (medium)	-0.031	-0.246, 0.184	0.774	0.930
8–10 (high)	-0.108	-0.298, 0.083	0.268	0.781
Comorbidity (number of conditions)[f]	0.009	-0.021, 0.039	0.552	-1.021
Engagement in social activities[g]				
No	Reference category			
Yes	-0.022	-0.312, 0.269	0.883	0.951
Functional status (NEADL score)[h]	0.001	-0.017, 0.020	0.896	-1.003
Depressive symptomatology (GDS-15 score)[i]	0.046	0.009, 0.083	0.016	-1.111

Abbreviations: 3MS, modified mini-mental state examination; SE, standard error; 95% CI, 95% confidence interval.
[a] Models were adjusted for: age, gender, education level, socio-economic deprivation, comorbidity, social engagement, functional status and depressive symptoms.
[b] A p-value of less than 0.05 (two tailed test) was considered statistically significant.
[c] Estimates from the inversed log transformed 3MS scores.
[d] Participants who reported their vision interfered with normal day-to-day functioning.
[e] Derived from the address at recruitment.
[f] Derived from an index of 15 selected chronic conditions.
[g] Participants who participated in any of nine predefined social activities.
[h] NEADL scores ranging from 0 (at worst) to 22 (at best).
[i] GDS-15 scores, higher scores indicate more depressive symptoms.

Table 4: Adjusted association between cognitive function and self-reported visual impairment in the non-Māori cohort (n=380).[a,b]

Variables	Beta[c]	95% CI	p-values	Back transformed Beta
Self-reported visual impairment[d]				
No	Reference category			
Yes	0.065	-0.056, 0.187	0.290	-1.163
Gender				
Male	Reference category			
Female	-0.052	-0.153, 0.048	0.306	0.886
Education level				
Primary school or no schooling	Reference category			
Secondary school, no qualification	-0.158	-0.309, -0.008	0.039	0.694
Secondary school qualification	-0.288	-0.452, -0.123	<0.001	0.515
Post-secondary schooling	-0.245	-0.403, -0.086	0.003	0.569
Socio-economic deprivation (NZ Dep. index)[34,e]				
1–4 (low)	Reference category			
5–7 (medium)	0.027	-0.098, 0.153	0.668	-1.065
8–10 (high)	0.082	-0.053, 0.217	0.233	-1.207
Engagement in social activities[f]				
No	Reference category			
Yes	-0.130	-0.372, 0.112	0.290	0.741
Functional status (NEADL score)[g]	-0.021	-0.039, -0.004	0.017	0.952
Depressive symptomatology (GDS-15 score)[h]	0.021	-0.009, 0.052	0.170	-1.050

Abbreviations: 3MS, modified mini-mental state examination; *SE*, standard error; 95% *CI*, 95% confidence interval.
[a] Models were adjusted for: gender, education level, socio-economic deprivation, social engagement, functional status and depressive symptoms.
[b] A p-value of less than 0.05 (two tailed test) was considered statistically significant.
[c] Estimates from the inversed log transformed 3MS scores.
[d] Participants who reported their vision interfered with normal day-to-day functioning.
[e] Derived from the address at recruitment.
[f] Participants who participated in any of nine predefined social activities.
[g] NEADL scores ranging from 0 (at worst) to 22 (at best).
[h] GDS-15 scores, higher scores indicate more depressive symptoms.

Table 5: Adjusted association between cognitive function and distance visual acuity in the Māori cohort (n=174).[a,b]

Variables	Beta[c]	95% CI	p-values	Back transformed Beta
Distance visual acuity (logMAR)	0.103	-0.217, 0.422	0.526	-1.267
Age	0.009	-0.016, 0.034	0.482	-1.021
Gender				
Male	Reference category			
Female	-0.155	-0.284, -0.025	0.020	0.701
Education level				
Primary school or no schooling	Reference category			
Secondary school, no qualification	-0.074	-0.235, 0.087	0.366	0.843
Secondary school qualification	-0.108	-0.304, -0.088	0.278	0.780
Post-secondary schooling	-0.281	-0.500, -0.061	0.013	0.524
Socio-economic deprivation (NZ Dep. index)[34,d]				
1–4 (low)	Reference category			
5–7 (medium)	-0.018	-0.241, 0.206	0.875	0.960
8–10 (high)	-0.106	-0.305, 0.092	0.292	0.783
Comorbidity (number of conditions)[e]	0.003	-0.026, 0.033	0.820	-1.008
Engagement in social activities[f]				
No	Reference category			
Yes	-0.008	-0.295, 0.279	0.956	0.981
Functional status (NEADL score)[g]	-0.014	-0.034, 0.005	0.152	0.967
Depressive symptomatology (GDS-15 score)[h]	0.043	0.004, 0.081	0.029	-1.103

Abbreviations: 3MS, modified mini-mental state examination; SE, standard error; 95% CI, 95% confidence interval; logMAR, logarithm of the Minimum Angle of Resolution.

[a] Models were adjusted for: age, gender, education level, socio-economic deprivation, comorbidity, social engagement, functional status and depressive symptoms.

[b] A p-value of less than 0.05 (two tailed test) was considered statistically significant.

[c] Estimates from the inversed log transformed 3MS scores.

[d] Derived from the address at recruitment.

[e] Derived from an index of 15 selected chronic conditions.

[f] Participants who participated in any of nine predefined social activities.

[g] NEADL scores ranging from 0 (at worst) to 22 (at best).

[h] GDS-15 scores, higher scores indicate more depressive symptoms.

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Table 6: Adjusted association between cognitive function and distance visual acuity in the non-Māori cohort (n=337).[a,b]

Variables	Beta[c]	95% CI	p-values	Back trans-formed Beta
Distance visual acuity (logMAR)	0.197	-0.120, 0.515	0.223	-1.574
Gender				
Male	Reference category			
Female	-0.008	-0.113, 0.098	0.885	0.982
Education level				
Primary school or no schooling	Reference category			
Secondary school, no qualification	-0.163	-0.319, -0.007	0.041	0.687
Secondary school qualification	-0.297	-0.466, -0.127	<0.001	0.505
Post-secondary schooling	-0.239	-0.404, -0.074	0.005	0.577
Socio-economic deprivation (NZ Dep. index)[34,d]				
1–4 (low)	Reference category			
5–7 (medium)	0.070	-0.062, 0.203	0.298	-1.176
8–10 (high)	0.095	-0.047, 0.238	0.188	-1.246
Engagement in social activities[e]				
No	Reference category			
Yes	-0.136	-0.422, 0.150	0.350	0.731
Functional status (NEADL score)[f]	-0.019	-0.039, 0.065E^-5	0.049	0.956
Depressive symptomatology (GDS-15 score)[g]	0.024	-0.009, 0.056	0.148	-1.056

Abbreviations: 3MS, modified mini-mental state examination; *SE*, standard error; 95% *CI*, 95% confidence interval, logMAR, logarithm of the Minimum Angle of Resolution.

[a] Models were adjusted for: gender, education level, socio-economic deprivation, social engagement, functional status and depressive symptoms.

[b] A p-value of less than 0.05 (two tailed test) was considered statistically significant.

[c] Estimates from the inversed log transformed 3MS scores.

[d] Derived from the address at recruitment.

[e] Participants who participated in any of nine predefined social activities.

[f] NEADL scores ranging from 0 (at worst) to 22 (at best).

[g] GDS-15 scores, higher scores indicate more depressive symptoms.

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Figure 2A: [a]Path diagram for the direct and indirect relationship between self-reported vision loss and cognitive function in the Māori cohort.
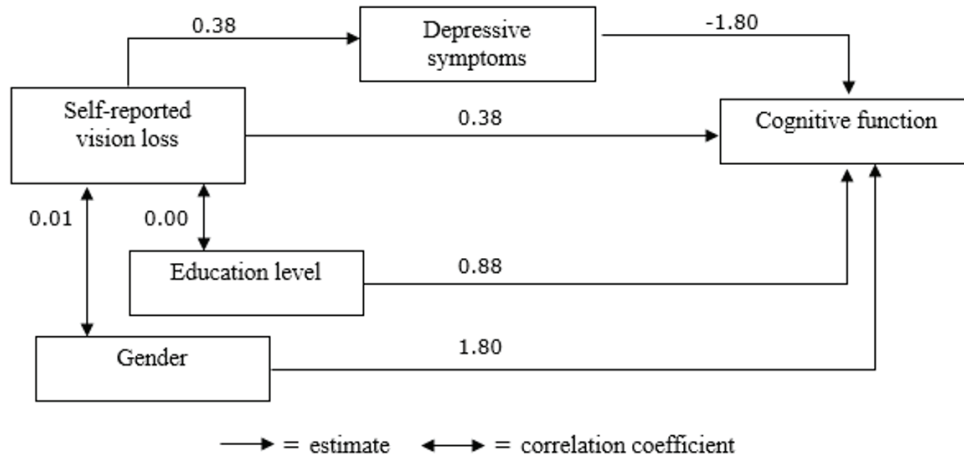
[a]Ratio chi-squared degrees of freedom (χ2/df)=3.493, root mean square error of approximation (RMSEA)=0.100, Tucker Lewis Index (TLI)=0.290, comparative fit index (CFI)=0.787.

Figure 2B: [a]Path diagram for the direct and indirect relationship between distance visual acuity and cognitive function in the Māori cohort.
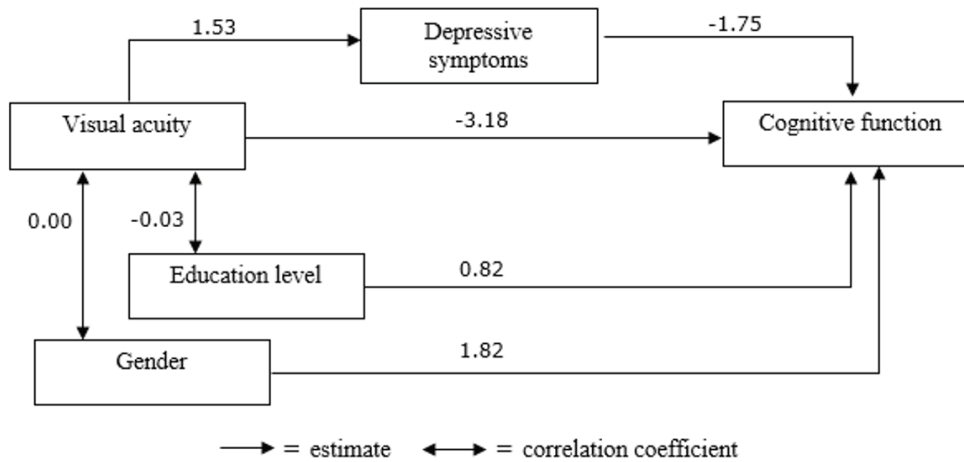
[a]Ratio chi-squared degrees of freedom (χ2/df)=2.954, root mean square error of approximation (RMSEA)=0.089, Tucker Lewis Index (TLI)=0.128, comparative fit index (CFI)=0.826.

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Is a rheumatic fever register the best surveillance tool to evaluate rheumatic fever control in the Auckland region?

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ABSTRACT

AIM: To determine the most accurate data source for acute rheumatic fever (ARF) epidemiology in the Auckland region.

METHOD: To assess coverage of the Auckland Regional Rheumatic Fever Register (ARRFR), (1998–2010) for children <15 years and resident in Auckland at the time of illness, register, hospitalisation and notification data were compared. A consistent definition was applied to determine definite and probable cases of ARF using clinical records. (www.heartfoundation.org.nz)

RESULTS: Of 559 confirmed (definite and probable) RF cases <15 years (median age 10 years), seven were recurrences. Of 552 first episodes, the ARRFR identified 548 (99%), hospitalisations identified 501 (91%) including four not on the register, and public health notifications identified 384 (70%). Of hospitalisation cases, 33% (245/746), and of notifications 20% (94/478) did not meet the case definition and were therefore excluded. Between 1998–2010, eight cases, initially entered as ARF on the ARRFR, were later removed once further clinical detail was available.

CONCLUSION: The ARRFR produced the most accurate information surrounding new cases of ARF (for children <15 years) for the years 1998–2010 in Auckland. This was significantly more accurate than medical officer of health notification and hospitalisation data.

Rheumatic heart disease (RHD), the long-term sequela of acute rheumatic fever (ARF), can persist for life.[1] Despite ARF being preventable, the associated morbidity and mortality continue to be a significant global burden falling largely on low-income countries.[2] However, it remains a significant issue in some indigenous and low-income communities in the industrialised world. The diagnosis of rheumatic fever is an estimate of probability using clinical and laboratory parameters, as there is no single diagnostic test. Internationally, the Jones criteria have been used with modifications made over time to improve specificity at the expense of sensitivity. New Zealand has led the way with the use of echocardiography to support the diagnosis.[3,4] A case definition with precise cut-offs for each criteria have been in place since the 1980's with ongoing modifications[5] (Heart Foundation of New Zealand guidelines www.heartfoundation.org.nz).

In New Zealand by the 197, ARF hospitalisation rates in children and young people had declined.[6] However, the disease persisted and over the last 25 years, until the end of the study period 2010, national ARF hospitalisation rates had not improved.[7] Most (80%) cases occur between 5–14 years of age, predominately in Māori and Pasifika and in lower socioeconomic areas.[4] Rheumatic fever has been a disease legally notifiable to medical officers of health since 1986.[8]

In 2011, the New Zealand Government announced funding of a rheumatic fever prevention programme (RFPP), principally primary prevention of ARF by diagnosis and treatment of group A streptococcal pharyngitis in high-risk populations predominately in schools. A Better Public Services target was announced in 2012 to reduce rheumatic fever by two-thirds to 1.4 cases per 100,000 people by June 2017. Progress towards this target is measured using first episode ARF hospital admissions as the best currently available national estimate of the burden of ARF in New Zealand (http://www.health.govt.nz/about-ministry/what-we-do/strategic-direction/better-public-services/progress-better-public-services-rheumatic-fever-target), (http://www.health.govt.nz/our-work/diseases-and-conditions/rheumatic-fever).

A school-based intervention programme commencing in 2001 in Northland, aiming to reduce ARF rates, was implemented in high-risk communities in the North Island from 2010, including the Auckland region incrementally from 2011/2012. The intervention programme was based on the results of a randomised controlled trial of this alternative form of primary care access and a subsequent meta-analysis.[9,10]

Information from high-quality surveillance is essential to monitor a substantial government investment, comparing the pre-intervention (up to and including 2010) and the post-intervention phases. Currently within the Auckland region (where ~60% of New Zealand ARF occurs), there are three sources of RF surveillance data available.[11] These are the Auckland Regional Rheumatic Fever Register (ARRFR) from 1981, hospitalisation data coded by non-medical staff using International Classification of Diseases (ICD) codes, and the national public health notification database from 1986.[8] ARF notifications were previously recorded by the Auckland Regional Public Health Service (ARPHS) as a paper record and transferred to the national notifiable disease dataset at the Institute of Environmental Science and Research Limited (ESR). The electronic EpiSurv database for notifiable diseases was established in 2006.[12] Data contributing to each rheumatic fever case in public health notifications during the period of the study (up to 2010) did not strictly adhere to the

Heart Foundation of New Zealand guidelines, eg, erythrocyte sedimentation rate of a specific range, age-adjusted PR interval from electrocardiogram, etc. Thus, the application of the ARF case definition could lead to a different decision as to whether or not a case is truly ARF.

Referral of a patient by a clinician to a rheumatic fever register has healthcare advantages, if for example the referral process is appropriately linked to the delivery of penicillin prophylaxis. Building on the New Zealand experience, this has become a worldwide recommendation.[8,13] The ARRFR was established to facilitate delivery of free penicillin prophylaxis in the Auckland region by delegated authority to rheumatic fever patients by community nurses to prevent recurrences and thus further cardiac sequelae.[14] Referrals are predominately made by hospital doctors of both ARF and RHD if penicillin prophylaxis is recommended. Patients/caregivers consent to receiving penicillin by delegated authority (from the prescribing doctor to community nurses) and to allow their anonymised data to be used for prospective surveillance data. Referrals are entered on initial diagnosis of ARF or RHD to ensure prophylaxis once in the community. If information subsequently becomes available (likely to be within weeks) which changes the diagnosis, the record remains on the register but is marked as 'not RF'.

Since 1981, each ARF case referred to the ARRFR has been reviewed against diagnostic criteria and deemed definite, probable or possible cases by a single infectious diseases specialist (DL)[15] (www.heartfoundation.org.nz). Penicillin prophylaxis is delivered to all definite, probable and possible ARF cases, and RHD as requested. Possible cases are those from an at-risk population that fail to meet diagnostic criteria but are considered by a clinician to be highly likely to have ARF and deserving of penicillin prophylaxis.

Consented ARF cases are referred for nurse-delivered penicillin prophylaxis, dental care, and are notified to public health. Notifications to ARPHS are sent by fax or phone and from 2006 entered into EpiSurv, which is housed at ESR under contract to the Ministry of Health.

Prior to 2009, when household contact tracing was introduced, there was no

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immediate public health action in the Auckland region. Thus, time to notification after data cleaning was variable. ARF cases not hospitalised (rare cases) come from general practice or out-patients for free nurse-delivered penicillin prophylaxis. ARF cases unknown to the register from general practitioners have been solicited at intervals with minimal response.[9]

Given the modest case numbers of ARF, accurate diagnosis and population-based surveillance are essential, as minor fluctuations in recorded case numbers can lead to significant changes in the overall rates. The ideal assessment tool provides the application of a consistent case definition over time to provide consistent epidemiology[5] (New Zealand Heart Foundation guidelines www. heartfoundation.org.nz). Presented here is an analysis of the surveillance tools available for ARF and the pre-intervention epidemiology (1998–2010) for the Auckland region.

Methods

Register, hospitalisation and notification data were compared to assess the coverage of the ARRFR during 1998–2010 for children aged less than 15 years. This age group was selected to reflect the population served by children's hospitals and the greatest portion of the case load.[16] The principal focus of the primary prevention intervention is school children enrolled in primary schools (5–12 year olds).

A consistent case definition was applied to all potential first and recurrent cases of ARF from each data source using electronic and paper records as required. The criteria used were the Jones criteria modified for the New Zealand context for this time period as defined by the New Zealand guideline for rheumatic fever diagnosis, management and prevention,[17] (www.heartfoundation. org.nz) and categorised as definite, probable and possible (see Appendix 1). Cases that met the definition of definite and probable are included in this review. 'Possible' rheumatic fever cases were excluded as these cases represent the area of greatest ambiguity in the New Zealand RF classification system. At the time the data extract was obtained, the notification data at Auckland Regional Public Health could not identify

cases of RHD (chronic disease without acute inflammation) separately from ARF and so these cases could not be excluded prior to the formation of the notification dataset. Furthermore, the hospitalisation and notification data could not be defined at first cut as definite, probable or possible cases, and accordingly the exclusion of 'possible' cases could not be applied prior to the formation of the datasets.

Auckland Regional Rheumatic Fever Register (Figure 1)

Definite and probable ARF cases (including recurrences) aged less than 15 years, from 1998 to 2010 (inclusive) were extracted for this study. Scrutiny by the register operator in conjunction with the referring clinician occurs on a case-by-case basis. New information for an alternative diagnosis is likely within weeks of referral. Such cases will cease penicillin prophylaxis and remain on the register as a non-case. Over the study period (n=13 years), eight cases (which did not meet the extraction criteria) were labelled as 'not RF' by this mechanism (see Figure 1 note). The ARRFR encourages clinicians to re-refer suspected ARF recurrences to the register to ensure continuing nurse-delivered prophylaxis.

Auckland hospitalisation data

Hospitalisations for the Auckland region (Auckland District Health Board (DHB), Waitematā DHB and Counties Manukau DHB) with a diagnosis of ARF were identified using the ICD-9 coding system codes 390–392 to identify cases diagnosed prior to January 2000 and the ICD-10 codes I00–I02 (I00, I01, I01.0, I01.1, I01.2, I01.8, I01.9, I02, I02.0, I02.9) to identify cases thereafter. Cases coded with principal and all level diagnoses of ARF were included. Day cases were included; New Zealand non-residents and hospital transfers were excluded. The ICD lists were then compared to the ARRFR listings. Cases with identical National Health Index numbers (NHI's) which had admissions within four months of a known register event were merged and deemed to be the same event. This was considered appropriate given the time course of an ARF episode.[18] Cases unknown to the ARRFR were reviewed using the case definitions (www.heartfoundation.org.nz).

Auckland notification data

In order to compensate for inconsistent recording of admission dates associated with notifications and variable delays in notifications following diagnosis, several data conditions were made. For cases known to the ARRFR, notifications within two years after the register admission date were deemed to have reported the same event (provided there was only one notification and one admission). This was because notifications previously occurred in batches (as there was no public health action associated with notification) and a delay of one to two years was not uncommon in the early stages of notification. If the time lapse was greater than two years, the electronic records for all three DHBs within the Auckland region were reviewed, looking for evidence of a different hospital admission or event (to that known by the register). However, if there was more than one notification for one known register event, the patient's electronic hospital records were also reviewed regardless of the time lapse. Notified cases, unknown to the register extract, then had the case definition applied. This included review for alternative NHIs and comparison to the register for RHD events. If a case was classified as RHD on the register and there was only one notification recorded, these were deemed to be related.

Incidence

Population denominators stratified by age (5–14 years), ethnicity and domicile at time of ARF event were determined using an Excel spreadsheet tool developed within Counties Manukau DHB ("New Zealand 21 DHBs Estimated Resident Population by CAU, 1996–2026", K Wang, personal communication), which is based on New Zealand census and population projection data. Exact Poisson 95% confidence intervals (95% CI) and Poisson regression lines were calculated using StatsDirect V3.0 (StatsDirect Ltd).

Notification to Auckland Regional Public Health Service (ARPHS) from ARRFR

An audit of the notification to ARPHS was also undertaken. A sample year 2010 was reviewed to audit the faxing of notifications to ARPHS, a process in place since 1998.

Results

A total of 559 confirmed (definite and probable) ARF cases less than 15 years (median age 10 years) from 1998–2010 were identified, including seven recurrences (Figure 1). Of the 552 first episodes, the ARRFR identified 548 (99%), hospitalisation data identified 501 (91%), including four not on the register, and the public health notification database identified 384 (70%). Recurrences approximated one case every two years (0.53 cases per year; seven recurrences in 13 years). All seven recurrences were identified on the ARRFR, five were also identified from hospitalisation data and four also from notification data. Three of the seven cases of ARF recurrences were noted to have primary cases of ARF within the hospitalisation data extract. Three other cases were likely to have had primary ARF episodes, which predated our extract, and one case had a primary ARF episode overseas. New primary ARF episodes found from other sources and unknown to the register were added.

Overall review (Figure 2)

On page 53 the three datasets are analysed in turn.

Auckland RF hospitalisations 1998–2010

Inclusions/exclusions

Of the 746 cases listed by the hospitalisation dataset, 501 cases met the stipulated criteria for definite or probable ARF and 245 cases were excluded (Figure 1). Twenty-five percent (62/245) of cases were matched to possible ARF cases known to the register and receiving penicillin prophylaxis. Eleven percent (27/245) represented duplications, ie, more than one recorded hospitalisation for the same ARF episode. No documented record (ie, no electronic or hard copy record could be identified for the reported event) could be located for five cases. The majority of the exclusions (151/245, 62%) were cases that did not meet the criteria and were not referred to the register for penicillin prophylaxis by a clinician. This subset included mostly cases where the diagnosis of ARF was considered but deemed to be very

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Figure 1: Flow diagram for case inclusion for all primary ARF definite and probable cases less than 15 years, 1998–2010 (inclusive).
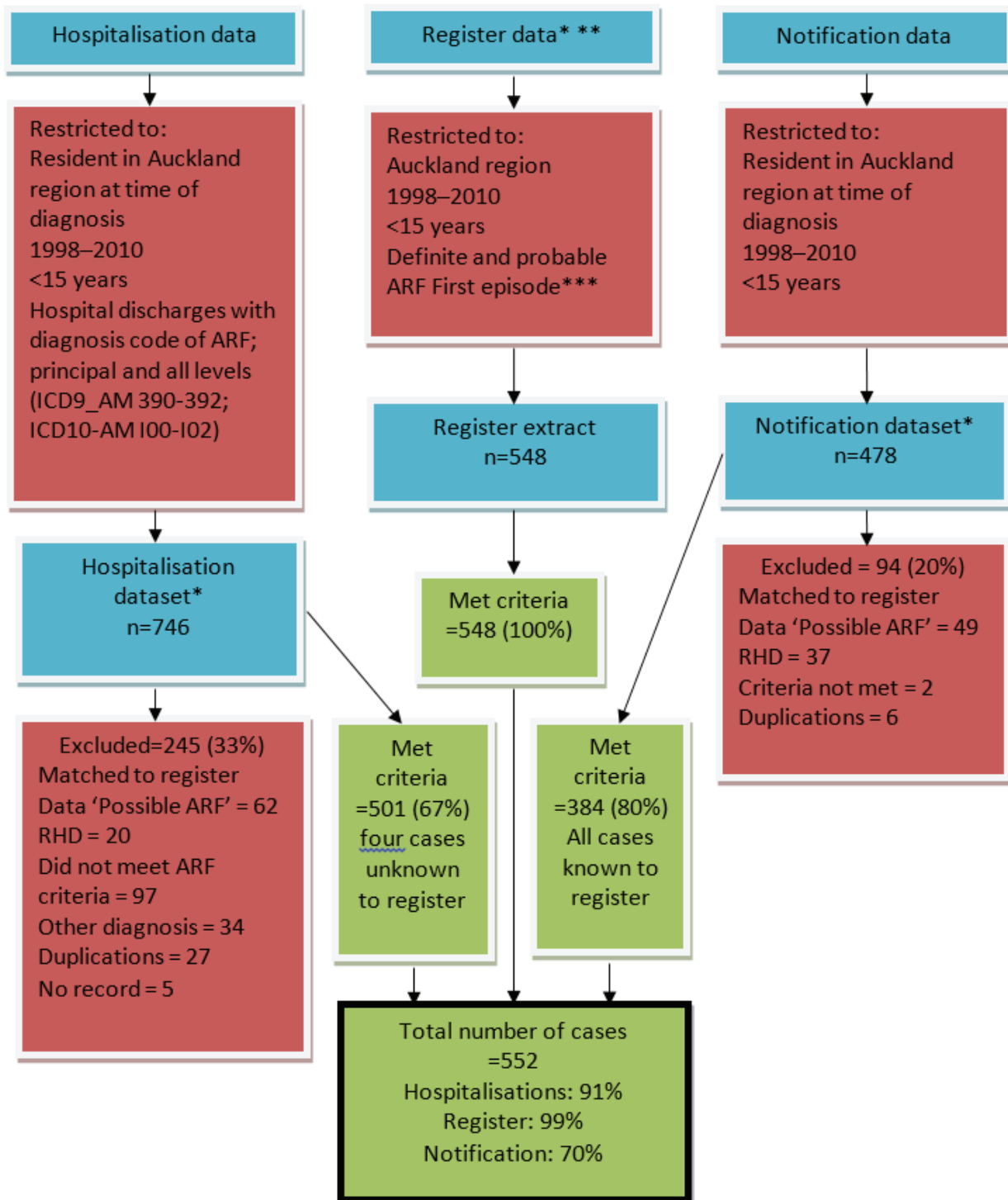
Recurrences excluded from all data sources (n=7).

* Case definition, which was used on the register was applied. All potential cases from all data sources were tested against the case definition.

** Between 1998–2010 for the <15 year age group, eight cases which were initially entered as ARF on the ARRFR were later labelled as 'not ARF' once further clinical detail (which excluded them as ARF) was available. This scrutiny occurs within weeks of initial entry to the register.

*** 'Possible' ARF cases were excluded (n=73).

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Figure 2: Auckland hospitalisation and notification datasets compared to the register extract for first episode ARF, 1998–2010 for under 15 year age group.
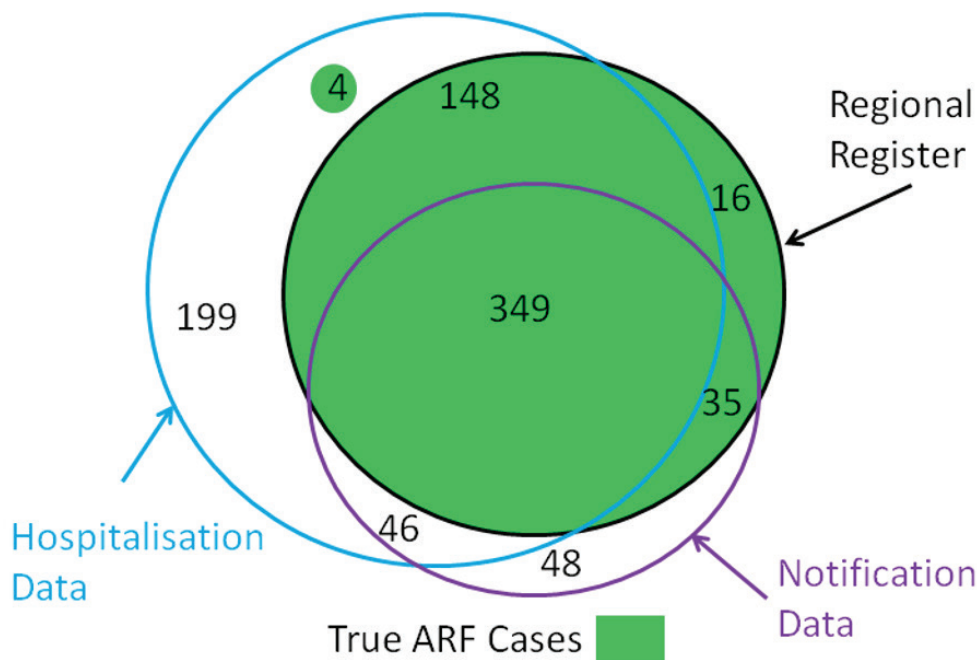
unlikely or data was missing (97/151), RHD (20/151) and a set (34/151) were cases that had no direct association with rheumatic fever, ie, epistaxis, obstructive sleep apnoea, febrile seizures, adenotonsillectomy and counselling (some of these cases had a past history of rheumatic fever).

Accuracy of Auckland RF hospitalisation data 1998–2010 compared to the ARRFR (Figure 3)

The hospitalisation dataset identified 91% (501/552) first presentation cases and identified four cases that appeared to be unknown to the ARRFR. Nine percent (51/552) of the identified total ARF first presentations were not identified by the hospitalisation dataset as ARF, but had a verified admission date on the register. This dataset also comprised 33% (245/746) cases which were not new cases of ARF consistent with our case definition. This subset, even after excluding known possible ARF cases, contains a significant proportion which did not meet the case definition (ie, considered potential ARF but never confirmed) or were duplications (ie, patients with previous ARF events returning for follow up, had duplicate NHI codes or had previous diagnosis of ARF, which was then carried over in the ICD coding).

The four cases unknown to the ARRFR were individually reviewed. The first of these cases was known to the ARRFR from a later date and may have been receiving penicillin prophylaxis from another (but unable to be identified) source, ie, in primary care. Alternatively, this may represent an incorrectly recorded date in the ARRFR database. The second case had declined to proceed with intramuscular penicillin prophylaxis and so opted for oral penicillin prophylaxis through their general practitioner. The third case identified received penicillin prophylaxis while in hospital and then did not attend clinic appointments prior to moving out of the Auckland region, and the fourth was diagnosed in hospital very shortly before moving overseas. In the two cases moving out of region, arrangements were made for penicillin prophylaxis delivery to continue in their respective new areas.

Of the 746 hospitalisation records, 73 (10%) had a secondary diagnosis of ARF. Of the 73, six met the case definition and were known to the register, one was a true case unknown to the register and one was matched to a register 'possible' case. Five cases were RHD, 26 did not meet criteria for ARF (ie, unconfirmed cases), 23 were

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Figure 3: Auckland hospitalisation data compared to register extract for first episode ARF, 1998–2010 for under 15 year age group. Note: The 'Excluded' area includes five cases for which no relevant clinical record could be found.
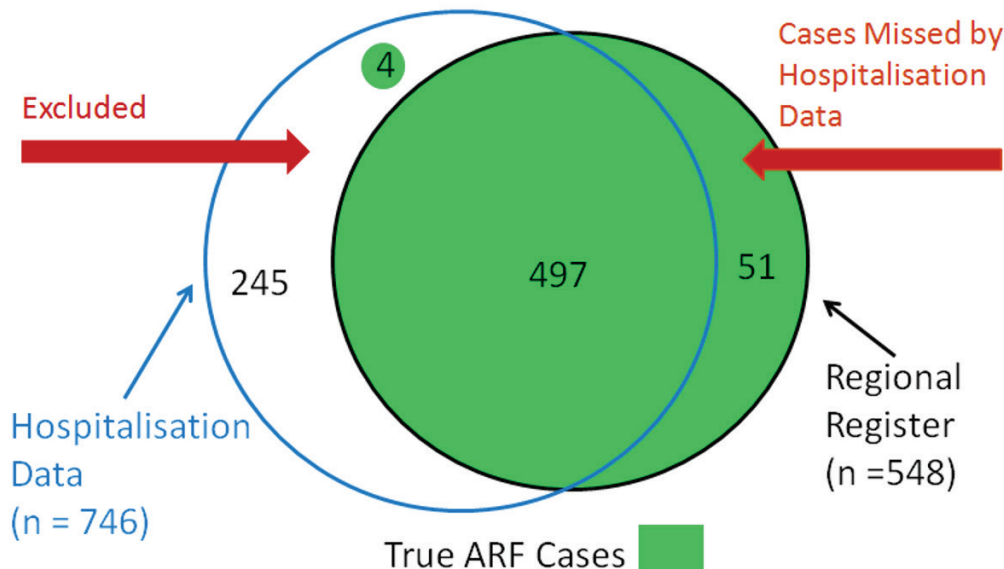
admitted for other diagnoses, eight were duplications and three cases had no identifiable record. Accordingly, of the 501 definite and probable cases identified by the hospitalisation dataset, only seven had ARF coded as a secondary diagnosis.

RF notifications to medical officers of health in the Auckland region 1998–2010

Inclusions/exclusions

The notification dataset identified 478 cases; 384 cases identified represented definite or probable cases of ARF and 94 cases were excluded (Figure 1). Forty-nine (52%) of the excluded cases were matched to register possible cases and 37 cases (39%) were cases known to the register as RHD. Two other cases were excluded as they did not meet the criteria, and six cases represented duplications.

Accuracy of RF notifications to medical officers of health in the Auckland region 1998–2010 compared to the ARRFR (Figure 4)

The notification dataset identified 70% (384/548) of cases known to the register. All cases identified were known to the ARRFR. This dataset also included 20% (94/478) which did not meet the case definition. These were predominantly RHD cases. A

significant proportion, 30% (164/548) of the confirmed ARF cases, were unknown to the notification dataset.

Auckland Regional Rheumatic Fever Register extract

The ARRFR extract identified 99.4% (548/552) of the total ARF cases (Figure 2).

One year audit of faxing information to ARPHS/notification database from ARRFR (2010)

All ARF cases referred to the ARRFR in the study period should have been notified to ARPHS by fax, as ARF is a notifiable disease. This process was audited for this review for 2010. Of the 'missing' cases from the notification dataset, 89% (8/9) had documented evidence of a faxed form for notification sent to ARPHS for the notification database. There was no such evidence for 11% (1/9). There was no process available to verify receipt by ARPHS of faxes.

Incidence of rheumatic fever (ARF definite and probable including chorea and recurrences) in Auckland children aged 5–14 years, for the years 1998–2010

The following results are based on combined data from the ARRFR, notification and hospitalisation data. There was an average of 42 cases per year aged 5–14

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Figure 4: Notification dataset compared to register extract for first episode ARF, 1998–2010 for under 15 year age group.
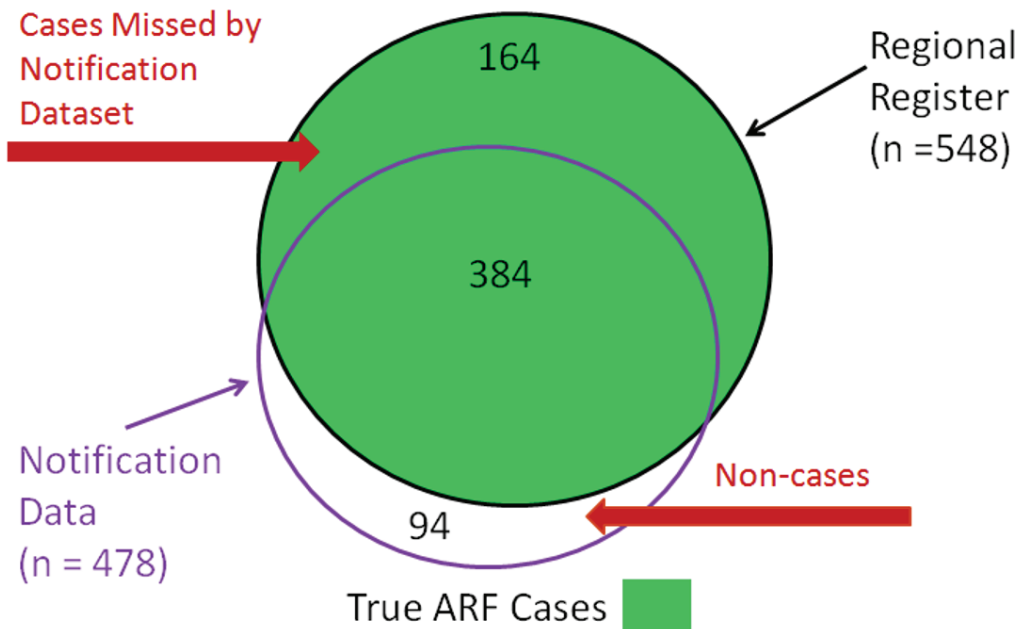
Figure 5: Cases (ARF definite and probable and chorea and recurrences) aged 5–14 years in the Auckland region from 1998 to 2010.
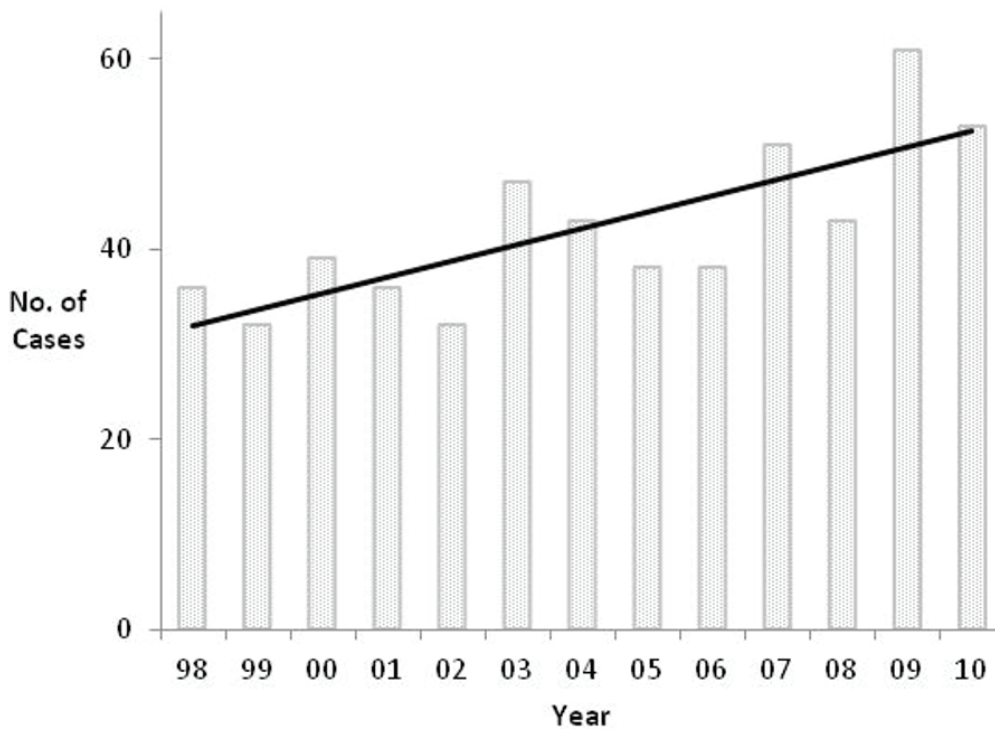
Figure 6: Annual incidence of cases (ARF definite and probable including chorea and recurrences) age 5–14 years in the Auckland region from 1998 to 2010.

● Pacific ○ Maori ● All ● Non-Maori/Non-Pacific
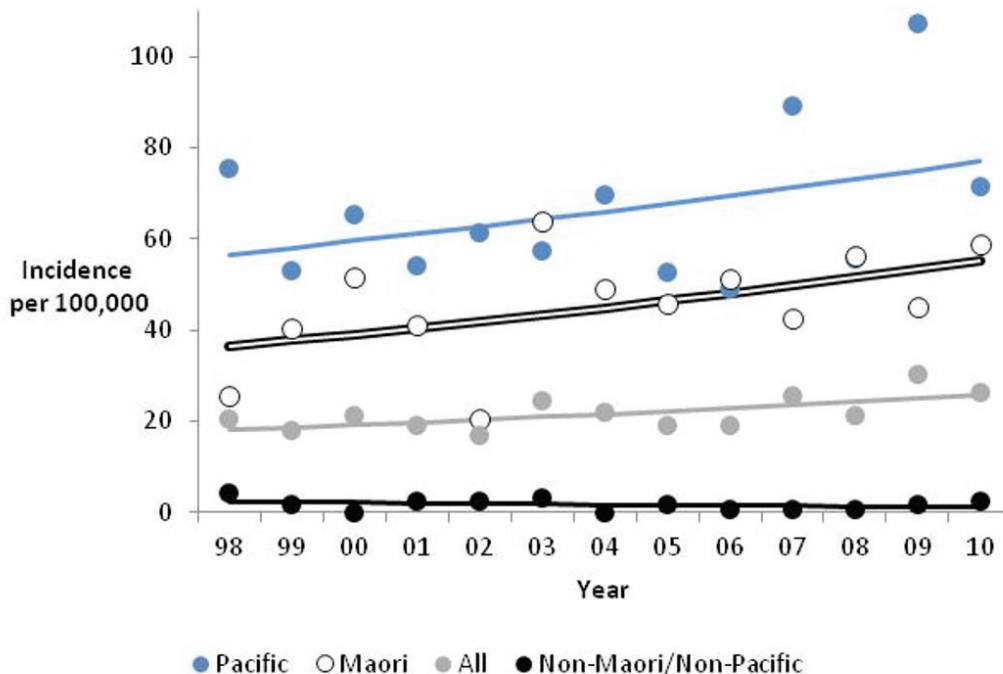
years in the Auckland region from 1998 to 2010, at an overall incidence of 21.9/100,000/ year (95% CI 20.1–23.8). The rates for Māori (45.8/100,000, 95% CI 39.7–52.5) and Pacific (66.6/100,000, 95% CI 59.5–74.4) compared to non-Māori/non-Pacific (1.7/100,000, 95% CI 1.—2.5) had rate ratios of 27 (95% CI 18–42) and 39 (95% CI 26–60) respectively. ARF case numbers (Figure 5) increased over the study period. Incidence of ARF in Māori and Pacific (comprising 18 and 19% of the child population respectively) increased in incidence by 51 and 35% respectively, whereas the incidence in non-Māori/non-Pacific cases more than halved.

Discussion

Key findings and implications

The ARRFR has produced high-quality surveillance data for the pre-primary prevention period for ~60% of New Zealand 5–14 year-old ARF patients over 13 years in this study. Hospitalisation and notification data are not precise tools. Clinicians are motivated to report ARF cases to the register to ensure free penicillin prophylaxis, which is delivered in Auckland by community nurses historically not linked to ARPHS. Nurses network across the region to ensure efficient penicillin prophylaxis delivery across DHB boundaries, as domicile and school may not be in the same DHB.[19] A uniformly applied case definition ensures high-quality data.

Mean annual national hospitalisation data (2000–2009) demonstrated an all-New Zealand rate for 5–14 year olds for Māori of 40.2/100,000 and Pacific of 81.2/100,000.[16] ARRFR data found rates for Māori of 45.8/100,000 and Pacific of 66.6/100,000. With most Pacific children living in the Auckland region, the over-estimate by hospitalisation data could be explained by our study finding. Young Māori with ARF are scattered throughout the North Island; DHB ICD coding practices beyond Auckland were not a feature of this study. Data comparisons for Māori will await further investigations.[20] However, there is no doubt ARF remains significantly disparate, with the disease burden carried almost exclusively by Māori or Pacific children and young people who make up approximately one-third of this age group in New Zealand. Such rates in European children are recorded from the 1920's in Auckland.[21]

Auckland hospitalisation dataset

When compared to the register extract, the hospitalisation dataset identified 91% of the confirmed ARF case load, but over-counted by including n=245 cases (245/746, 33%), which were not definite or probable ARF (http://www.health.govt.nz/system/files/documents/pages/first-episode-rheumatic-fever-hospitalisations-02-14-mar15.xlsx). The Ministry algorithm includes cases with an ARF-related ICD code as the principal diagnosis only, and excludes those with a previous diagnosis from 1998 onwards of ARF or RHD (as searched for case by case in our study) in any of their diagnostic codes. Given these differences, the Ministry algorithm improves accuracy for hospitalisation data, as it is more likely to exclude those with a previous ARF or RHD diagnosis. Under-counting by this method also occurs but is less of a concern. We detected seven confirmed (definite and probable) cases of ARF only coded as a secondary diagnosis.

Why were cases not identified by the Auckland hospitalisation dataset?

In addition, 9% of the total cases of ARF were not identified by the hospitalisation dataset. However, all cases known to the register had associated hospital admission dates recorded in the register database. Accordingly, this discrepancy is most likely attributable to incorrect coding. In some cases the diagnosis may have been suspected but not confirmed until further clinical review (eg, at outpatient clinic) was completed.

Why did cases identified from the Auckland hospitalisation dataset not meet the New Zealand RF criteria?

Coding of hospitalisations that do not meet ARF case definitions has been identified as an important issue. The ICD dataset identified cases of RHD as ARF (a coding error), unconfirmed cases of ARF (ie, ARF was part of the differential, however, the criteria were not met) as well as cases without direct association with ARF. If coding occurs promptly after discharge, missing results, eg, a repeat echocardiogram, may influence the final diagnosis. The cases excluded from the audit comprised 62%, which did not meet the set criteria. This percentage is compa-

rable to the erroneous cases documented by Pennock et al in the Waikato review of all ages using a similar methodology (68%).[22] It is important to note that among the cases excluded from this audit, 25% were known to the register as possible rheumatic fever cases deemed worthy of penicillin prophylaxis. Currently, hospitalisation data does not allow for distinction between definite, probable and possible ARF. Other cases were excluded for not representing a separate ARF event, ie, double-ups of known ARFs who return to hospital for procedures, eg, a repeat echocardiogram or review. This is addressed by the MOH algorithm as above.

The concept of overestimation of the case numbers associated with hospitalisation data has previously been discussed by Oliver et al who also identified a sensitivity of 82%. As there were no chart reviews in the latter study, this is an estimate and does not take into account ARF cases hospitalised but not coded appropriately (highlighted as 9% in our review).[23] This characteristic of dual inaccuracy (elements of over and underestimation of case numbers) of hospitalisation data was confirmed in our audit and also documented by Pennock et al.[22]

Notification dataset

The notification dataset identified a significant number of non-cases (20%) and 30% of total ARF case load was not known to the notification database over the time of this study.

ARF became notifiable in 1986 after advocacy from the Auckland ARF clinicians to improve national data and raise awareness. Initial guidance was to include cases of RHD up to 20 years of age.[8] Unlike most notifiable diseases where data is collected for action, in the absence of household contact tracing there was no ensuing action.

In the time period following this study, RHD has been explicitly excluded from the notification process, the capacity to capture possible ARF cases has been added and the ARF case definition updated to match the modified New Zealand Jones criteria 2015[24] (www.heartfoundation.org.nz). During our study period, as part of the notification process a yes/no question "does the case conform to the Jones criteria?" without a data dictionary was in place. ARF cases were

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not subsequently subject to audit to our knowledge, and therefore we suggest should be viewed with caution.

Why were cases not identified by the notification dataset?

The large number of cases missed by the notification dataset led to our audit of the referrals from ARRFR to ARPHS. The responsibility for notification to public health lies with the clinician responsible for the case.[17] The ARRFR was set up (1981) before ARF became notifiable (1986). Clinicians who referred their patients to the ARRFR for penicillin prophylaxis were aware that registration with the ARRFR would lead to notification to ARPHS, who would then refer on to the national notification database (EpiSurv from 2006). This continued as accepted practice. The audit for 2010 showed that of the cases that were unknown to the notification dataset but known to the ARRFR, the significant majority had evidence of a faxed notification form to ARPHS (90%).

As there was no specific action, eg, contact tracing, by public health in the Auckland region as outlined above, it appears notifications did not necessarily get nationally notifiable. Thus, the notification data is incomplete. This has been rectified from the beginning of the primary prevention programme in 2011.

Why were there cases identified on the notification dataset that did not meet the criteria?

The notification dataset contained 20% of cases which did not meet the criteria. Of this selection, approximately half were possible ARF cases known to the register. The remaining cases were predominantly RHD cases. Until recently, notification guidance still included notification of cases of RHD aged less than 20 years; however, there was at the time of our study no means of distinguishing these from definite acute cases in the national database.[8]

ARRFR

The prime purpose of the ARRFR, free nurse-delivered penicillin prophylaxis, has been highly successful in ensuring prevention of recurrences with high adherence. The first evaluation of the ARRFR revealed 22% of ARF cases on the ARRFR

for 5–14 year olds were for recurrences with the higher likelihood of worsening heart disease.[25] This has been reduced to 1% (7/555) in this current audit.

Limitations and considerations

Within the auditing process there were a number of limitations that were encountered.

The under 15 year age group was selected as a starting point to determine the most effective surveillance data source, as this would capture the majority of first presentation ARF cases. Further work on the over 15 year age group in the Auckland region is underway.

Currently there is no diagnostic test for ARF and so it remains a diagnosis of probability based on criteria specifically modified for the New Zealand context. A consistent case definition has been applied over time in Auckland in the ARRFR with appropriate updates.[4,5,17] As far as possible, information was sought from case files to support or refute the diagnosis of ARF. There may be limitations in the data recorded and available on patient records, which could have prevented some cases from meeting the stipulated criteria. In a small number of cases, patients were awaiting laboratory tests for confirmation of diagnosis, which subsequently did not appear on record. Accordingly, these cases had to be excluded as they did not meet the case definition.

The incomplete recording of admission dates in the notification dataset created difficulty in associating notifications with specific admissions and/or register events. This led to data conditions being imposed as listed in the methodology. As notification on suspicion of a new suspected ARF case is now required by the Ministry of Health within seven days, these difficulties are likely to be less significant moving forward (http://www.nsfl.health.govt.nz/apps/nsfl. nsf/pagesmh/508). Each case is re-reviewed with emerging data to ensure each case is a true case.

A review of the ICD-coded cases of RHD could have potentially increased the ARF case load identified. The inaccuracy of coding raises the possibility that some cases of ARF may have been coded as RHD on the ICD coding system. These cases would not have been identified by the methodology

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implemented in this review. However, a review of RHD-coded ICD cases in the Tairāwhiti region for all ages by Moore et al found that the numbers of cases of ARF miscoded as RHD were minimal (3/122, 2%) over a three-year period.[26]

Relationship to other research

Oliver et al have suggested the use of the notification dataset as a basis for the implementation of a national register.[27] The results of this audit conflict with that recommendation at least for the Auckland region for the time period (1998–2010) of our study. An appropriate and consistent definition (ie, the New Zealand RF criteria) had not been implemented at the time of notification and therefore historical case accuracy remains a significant issue. In 2014, the Ministry of Health reviewed and published updated notification guidelines, which were reflected in modifications in the national notification database, which might lead to higher quality of surveillance data going forward, although the consistent application of the appropriate case definition is not considered in a recent publication.[28] Quality of the retrospective or baseline comparison data for the period prior to the government intervention will remain low unless considerable effort is made to rectify this.

Oliver and others used capture-recapture methodology to assess the accuracy of the currently available New Zealand ARF surveillance data.[23] This approach has been used with many infectious diseases.[29–31] The authors failed to appreciate the difference between their cited examples with clean cut diagnoses, mostly laboratory based, and the complexities of ARF/RHD diagnoses. In addition, allowing for the changing epidemiology by year of age the likelihood of ARF in a patient over 15 years of age is much more likely to be a recurrence of ARF and therefore unable to be prevented by the Government's primary prevention strategy. In addition, they suggested that cases identified by the notification and hospitalisation datasets that are unknown to registers may indicate that register data may be incomplete. Within the Auckland region, (~60% of New Zealand ARF cases), a review of these cases revealed that these 'additional cases' reflected significant inaccuracies of these databases, as a significant number did not meet the case definition even if including ARF cases deemed as possible cases are considered.

Conclusions

In the Auckland region this 1998–2010 audit prior to the primary prevention intervention demonstrates that the ARRFR provided the highest-quality data for monitoring ARF in the under 15 year age group. Notification and hospitalisation datasets were demonstrated to have significant inaccuracies and are not precise surveillance tools. Notification data for this time-period did not identify 30% of the ARF cases. Hospitalisation data included 33% of cases, which were not new cases of ARF in keeping with the case definition (and missed 9% of cases). Historical comparisons pre and post the intervention using these sources will be limited in their estimate of the effect. As ARF case numbers are relatively small, using the most accurate data source for evaluation is imperative.

Appendix

Table 1: New Zealand Rheumatic Fever Criteria adapted from Heart Foundation of New Zealand Guidelines.

Diagnosis categories	
Definite ARF	Two major or one major and two minor manifestations plus evidence of a preceding GAS infection*
Probable ARF	One major and two minor with the inclusion of evidence of a preceding GAS infection* as a minor manifestation (Jones, 1956)[32]
Possible ARF	Clinical suspicion of ARF, but insufficient signs and symptoms to fulfil diagnosis of definite or probable of ARF
Recurrence**	Two major or one major and two minor or several** minor plus evidence of a preceding GAS infection* (Jones, 1992)[33]
Criteria	
Major	Carditis—including ECHO evidence alone*** PolyarthritisⱵ Chorea Erythema marginatum Subcutaneous nodules
Minor	Fever ≥38°C ESR ≥50 CRP ≥50 PolyarthralgiaⱵ Prolonged P-R interval on ECG: age-adjusted definitions#

Source: Lennon et al.[9] Note: ARF: acute rheumatic fever; CRP: C reactive protein; ECHO: echocardiogram; ESR: erythrocyte sedimentation rate; GAS: group A streptococcal.

* Elevated or rising antistreptolysin O or other streptococcal antibody is sufficient for a diagnosis of definite ARF. A positive throat culture or rapid antigen test for GAS alone is less secure, as 50% of those with a positive throat culture will be carriers only. Therefore, a positive culture alone demotes a case to probable or possible ARF.

** Most cases of recurrence fulfil the Jones criteria. However, in some cases (such as new carditis on previous RHD) it may not be clear. Therefore to avoid under-diagnosis, a presumptive diagnosis of rheumatic recurrence may be made where there are several minor manifestations and evidence of a preceding GAS infection in a person with a reliable history of previous ARF or established RHD.

*** Acceptance of ECHO evidence of carditis as a major criterion is a modification to the Jones (1992) update.

Ⱶ Other causes of arthritis/arthralgia should be carefully excluded, particularly in the case of monoarthritis, eg, septic arthritis (including disseminated gonococcal infection), infective or reactive arthritis and auto-immune arthropathy (eg, juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis and sarcoidosis). Note that if polyarthritis is present as a major manifestation, polyarthralgia cannot be considered an additional minor manifestation in the same person.

When carditis is present as a major manifestation (clinical and/or echocardiographic), a prolonged P-R interval cannot be considered an additional minor manifestation in the same person.

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Mortality within 30 days of systemic anticancer therapy at a tertiary cancer centre: assessing the safety and quality of clinical care

Michelle Wilson, Weng Mak, Melissa Firth, Sanjeev Deva, Michael Findlay

ABSTRACT

AIMS: Thirty-day mortality has been proposed to be a useful indicator of avoidable harm to patients from systemic anticancer therapies (SACT). As a quality assurance tool, we assessed the 30-day mortality rate at Auckland City Hospital and compared this with international standards.

METHODS: Clinical characteristics and treatment details of medical oncology patients who died within 30 days of SACT from October 2014–September 2015 were collected and compared with data from a similar series performed from October 2008–September 2009. SACT was limited to chemotherapy or biologic agents.

RESULTS: From October 2014–September 2015, 1,965 patients received 2,145 treatment regimens. Forty-seven patients (2.2%) died within 30 days of SACT. Treatment was given with palliative intent in 42 patients (in 89%) and curative intent in five (11%). Mortality rates did not change with time (2.8% in 2009 vs 2.2% in 2015).

Of the patient who died within 30 days, ECOG performance status at the time of chemotherapy was one in 16 patients (34.0%), two in nine patients (19.1%) and 3/4 in nine of the 47 patients (19.1%). All patients treated with curative intent had a PS of 0 or 1. Most patients who died within 30 days were on first- or second-line therapy (45 and 38% respectively). Two-thirds of patients with a PS of 3/4 were receiving first-line therapy. Approximately half the patients died during their first cycle of therapy (48.9%).

CONCLUSIONS: Our local 30-day mortality data compares favourably to international benchmarks of 5% and has not increased over time. Performance of similar studies locally and nationally should be undertaken to continue to assess and improve the quality of our patient care.

The expertise of an oncologist reflects his/her knowledge of chemotherapy and ability to individualise this to the patient under their care. Over the past 30 years there has been an increase in both the number of chemotherapy agents and additionally the indications for treatment.[1,2] In 2016, 45 new drugs were approved by the Food and Drug Administration (FDA) with 15 of these for the treatment of cancer.[3] There are now over 100 drugs approved for use in oncology with many of these recommended for multiple indications. These treatments are given with the aim of allowing patients to live longer and better, but they also have the potential to contribute to patient morbidity.[4] The risk of harm is amplified when prognosis is poor and time is short.

There is a paucity of relevant information on the clinical benefit/harms of treatments as the patient reaches end-of-life, and the decision to continue chemotherapy in this setting is a complex one, involving patient, physician and societal beliefs. With recognition of the importance of high quality end-of-life care, the spotlight has now turned to chemotherapy to evaluate what value it provides during this time. In patients with advanced non-small cell lung cancer, early palliative care has been

associated with improved quality of life, less aggressive medical care and importantly an improved median overall survival.[5]

With the mandate of ensuring the safe delivery of health care to its constituents and growing concerns that end-of-life chemotherapy was leading to a "bad death", the National Confidential Enquiry into Peri-Operative Deaths (NCEPOD) in the UK undertook a nationwide audit to review all cases of death within 30 days of chemotherapy administration.[6] During a two-month period, 47,050 chemotherapy doses were given with 1,044 deaths observed. The case notes and follow-up questionnaires of a subset (478 of 1,044) of the patients were reviewed by a panel of oncologists, nurses, pharmacists and patient advocates.[6] In the advisors' opinion there was room for improvement for care in 49% of the patients, with care reported to be well below an acceptable standard in 8%.[6]

The 30-day mortality rate provides a technically feasible approach to rapidly identify a cohort of patients that oncologists can look back on and learn from.[7] This has been investigated at many institutions since then, with mortality rates varying from 3.1–12.3%.[8–12] With the increasing importance of clinical governance and the rising cost of chemotherapeutic-based health care, we looked to investigate the 30-day post-systemic therapy mortality in a large tertiary centre in New Zealand as a key performance indicator (KPI) for our oncology practice.[13]

Methods

This study was conducted at Auckland City Hospital. This is a regional cancer site offering medical oncology and haematology care in a centralised manner to three neighbouring district health boards, servicing a population of approximately 1.4 million people.

Local approval was achieved. Chemotherapy prescriptions and clinical notes are stored electronically at Auckland City Hospital. Cases were identified through the pharmacy records and clinic appointment records. This list was cross-referenced against New Zealand Health Information Services Mortality collection (MORT) to generate a list for case finding. This was also compared to hospital clinical records and mortality documentation.

The study included all adult patients who had at least one cycle of chemotherapy from 1 October 2014 until 30 September 2015 under medical oncology at Auckland City Hospital. Patients receiving concurrent chemoradiation were included. Patients receiving treatment under haematology or treated in private practice were excluded. The definition of chemotherapy included all cytotoxic drugs and oral targeted therapies were excluded. Oral targeted therapies were excluded due to the challenges in defining the patient populations with our current databases. Cases included were those where patients died within 30 days of their last chemotherapy dose administered from 1 October 2014 until 30 September 2015.

This was compared to data collected in a similar project from 1 October 2008 until 30 September 2009 (NTX/10/05/EXP). An identical protocol was used to define eligible patient populations and determine 30-day mortality. Any patient who died within 30 days of their last dose of systemic therapy was included. This was calculated per course.

The information captured for the audit included: age, ethnicity, sex, cancer diagnosis, stage of disease, ECOG performance status,[14] chemotherapy regimen, line of chemotherapy, cycle of treatment and the intent of treatment (curative vs palliative). If the performance status was not documented in the clinical notes, then this was documented retrospectively. Both prospective and retrospective documentation of performance status was performed. Performance status was a key concern as is an important prognostic tool. A score of 0 represented asymptomatic patients (fully active); 1 represented symptomatic but completely ambulatory; 2 represented symptomatic with less than 50% of the day in bed; 3 represented symptomatic with more than 50% of the day in bed; and 4 represented bedbound. A score of 5 represents death.

Curative treatment included adjuvant and neoadjuvant treatment and chemotherapy given with curative intent. Palliative chemotherapy referred to therapy given to improve symptoms and to prolong life. The cause and location of death was recorded where available. Both inpatient and outpatient notes were recorded. Data was extracted by two independent investigators to minimise bias. Cause of death,

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however, was documented by one investigator. In cases where this was not clear, this was reviewed in conjunction with another investigator.

Results

1,965 patients received 2,145 courses of chemotherapy at Auckland Hospital from 1 October 2014 until 30 September 2015. Of these, 47 patients (2.2%) died within 30 days of SACT. Of these 47 patients, treatment was given with palliative intent in 42 patients (89.4%) and curative intent in five (10.6%). From October 2008 to September 2009, 43 patients (2.8%) died within 30 days of SACT. 30-day mortality data was similar across the two time periods (2.2%—2009 vs 2.8%—2015).

Across both time periods examined, the majority of patients who died were being treated with palliative intent, 51 patients (87%) in 2009 and 42 patients (89.4%) in 2015. The median age was similar at 59 years and 61 years respectively (Table 1). Of the 47 patients who died during the period of interest in 2015, 28 (59.6%) died as an inpatient in hospital, with 19 dying outside of hospital (40.4%).

The results presented below relate to the cohort of patients who died within 30 days of systemic therapy.

Performance status

The percentage of patients with performance status documented increased from 30.5% in 2009 to 78.7% in 2015. In 2015, performance status at the time of the last

Table 1: Demographics of patients dying within 30 days of therapy over the two time periods.

	2009 n=43 (%)	2015 n=47 (%)
Median age (range)	59 years (31–81 years)	61 years (25–83 years)
Gender		
Male	17 (39.5)	19 (40.4)
Female	26 (60.5)	28 (59.6)
Treatment intent		
Curative	2 (4.7)	5 (10.6)
Palliative	41 (95.3)	42 (89.4)
ECOG		
0	2 (4.7)	3 (6.4)
1	2 (4.7)	16 (34.0)
2	3 (7.0)	9 (19.1)
3 or 4	4 (9.3)	9 (19.1)
Not recorded	32 (74.4)	10 (21.3)
Type of cancer		
Gastrointestinal	12 (27.9)	16 (34.0)
Breast	12 (27.9)	13 (27.7)
Lung	4 (9.3)	9 (19.1)
Gynaecological	3 (7.0)	2 (4.3)
Skin	5 (11.6)	2 (4.3)
Head and neck	0 (0.0)	2 (4.3)
Genitourinary	2 (4.7)	1 (2.1)
Other	5 (11.6)	2 (4.3)
Median time from treatment to death (range)	14 days (0–30 days)	16 days (0–29 days)

Table 2: Comparison with reported international 30-day mortality rates post-chemotherapy.

	Auckland New Zealand	Ballarat Australia (Yoong et al)[12]	Royal Marsden UK (O'Brien et al)[9]	Christie UK (Khoja et al)[8]
30-day mortality rate	2.2%	3.4%	8.1%	4.0%
Treatment-related mortality	0.23%	0.79%	0.61%	0.44%

cycle of chemotherapy was zero in three patients (6.4%), one in 16 patients (34.0%), two in nine patients (19.1%) and three or four in nine patients (19.1%). Performance status was not documented in 10 patients. Of those patients with a performance status of 3/4, 55.6% (five of nine patients) were treated as an inpatient. All patients treated with curative intent had a performance status of 0 or 1.

Line of therapy and cycle of treatment

Approximately half the patients during both periods were receiving first-line of therapy (62.8%—2009; 44.7%—2015) (Figure 1). In 2009, 14% had had at least three prior lines of therapy. In 2015 this was 17%. This indicates that the cohorts of patients were not heavily pre-treated. Of interest, approximately half the deaths occurred during the first cycle of treatment (53.5%—2009; 48.9%—2015) (Figure 1).

Cause and location of death of patients treated October 2014–September 2015

Of the five patients who died within 30 days of therapy who were being treated with curative intent, four were receiving first-line therapy and one second-line. Four of the patients died in cycle 1 of therapy. The remaining patient died in cycle 3. Cause of death was documented in three of the cases. In patients treated with curative intent, the majority of deaths were treatment-related
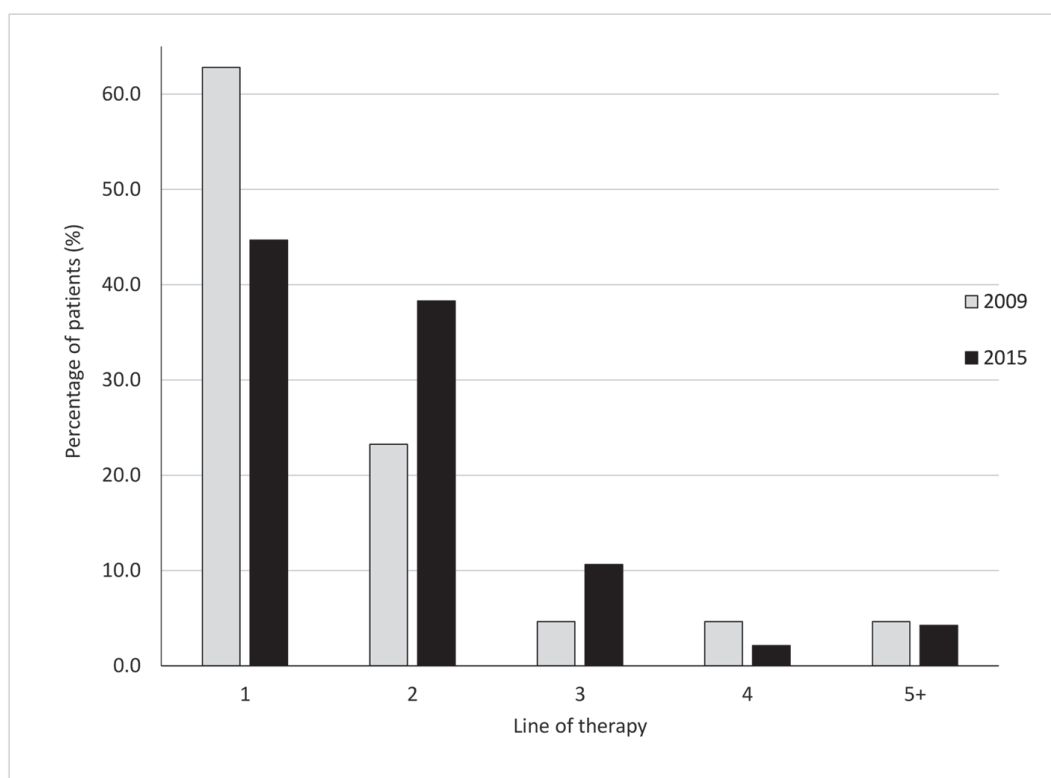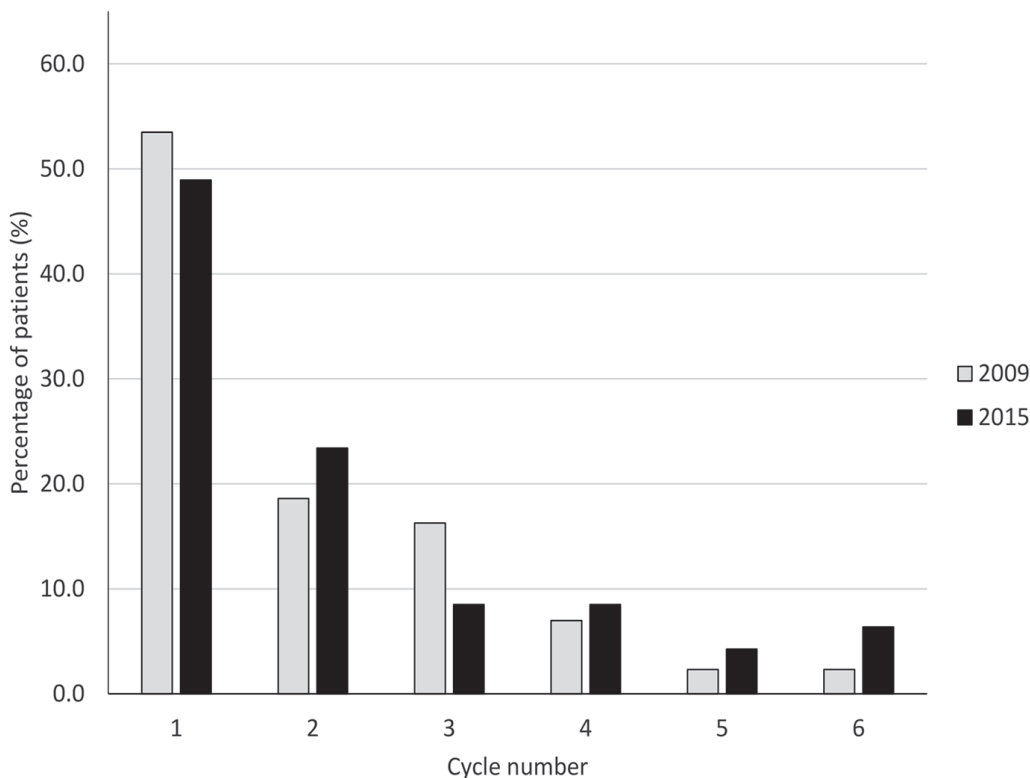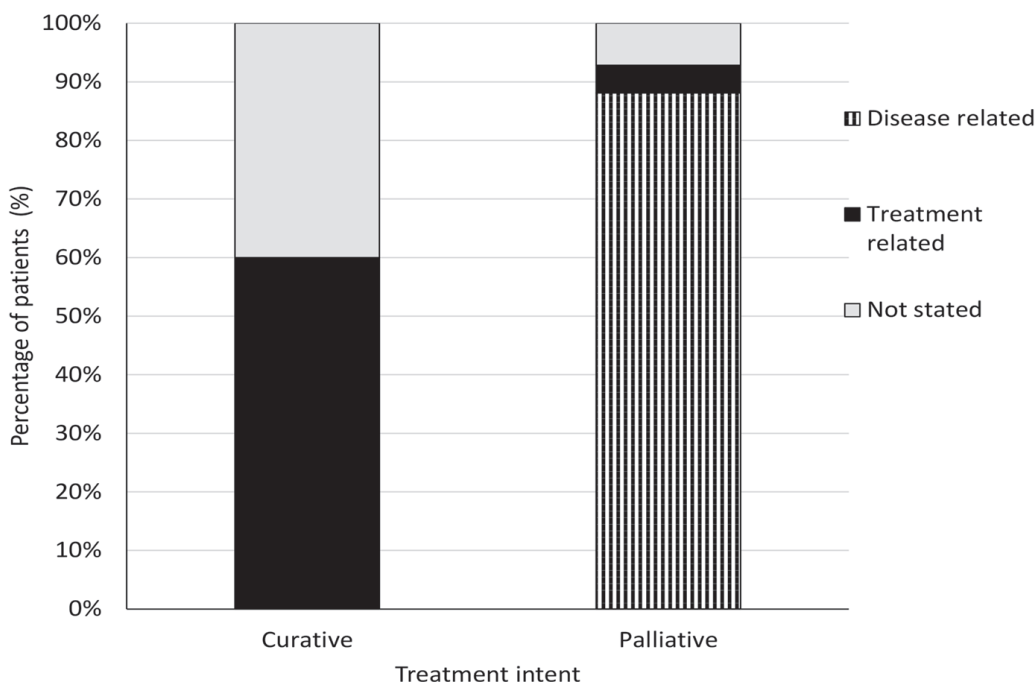
Figure 1:

Figure 2:

(three of five; 60.0%) in contrast to those treated with palliative intent where disease was the most common cause of death (37 of 42; 88.1%) (Figure 2). In the five documented treatment-related deaths, sepsis was the cause in four of these cases, with one case of drug-induced (docetaxel) pneumonitis. The percentage of all deaths within 30 days that were related to treatment was 10.6% in 2015. The overall treatment-related mortality was only 0.23%.

Discussion

This study demonstrated a post-systemic therapy 30-day mortality rate of 2.2% in our patient population. The results of this study are remarkably similar to the national survey conducted by NCEPOD in 2008. In this study they observed a mortality rate of 2.2% per patient treated. In their survey the percentage of patients who were being treated with curative intent was 14%

Figure 3:

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(compared with 14% in this study), the number of patients who died following cycle 1 was 52% (compared with 58%) and the number of patients who were on second-line or greater chemotherapy was 45% (compared with 41%).[6]

This study reinforces that the 30-day mortality rate is a feasible measure to assess patient outcome and represents a viable key performance indicator in this field. Limitations of this audit include its relatively small size and retrospective nature. This is confounded by insufficient and missing data, particularly relating to causality of death. In particular, it was not possible to determine the relationship between treatment and death in two patients treated with curative intent. An expanding area this series fails to address is the mortality of patients receiving targeted therapy. These represent a significant cost to the health sector, and the appropriateness of their use at this stage in a patient's clinical course also warrants careful consideration. The results of this study, however, emphasise the need to ensure ongoing accountability in the delivery of care at our centre.

The intent of treatment is key when implementing the 30-day mortality rate as a key performance indicator. A death of a patient receiving an adjuvant/curative treatment represents a devastating loss of life. In this group the observed chemotherapy mortality rate itself should be the measuring stick. In our series, five patients receiving adjuvant therapy died within 30 days of chemotherapy, of which three deaths (60%) were documented to be related to therapy. With respect to treatment-related deaths, our rate per total deaths (10.6%) was in keeping with other series (7.5% Royal Marsden, UK,[9] 23% Ballarat, Australia,[12] 11% Christie, UK[8] and 3.9% East Kent, UK[15]), but our absolute number was low at only five. Overall, our treatment-related mortality rate was only 0.23%. These cases are now reviewed and discussed at our local mortality and morbidity meetings.

In patients receiving palliative chemotherapy, death is the outcome of an untreated progressive tumour and there is a reflex desire to "do something" to delay this. Chemotherapy, in this context, is given with the goal of palliating symptoms and prolonging life. Modern chemotherapy

regimens may achieve these goals, but their inherent cytotoxic nature means that in a proportion of patients it can hasten or directly lead to death. Symptom relief is a strong motivator for undertaking treatment in patients.[16,17] As evidence linking aggressive end-of-life care to worse patient outcomes continues to emerge, the use of a 30-day post-chemotherapy mortality rate should gain traction as important quality indicator.[18] This is of relevance not only for the treating doctors and patients themselves, but also for health care providers to ensure the efficient allocation of increasingly scarce resources. It is important that we do not allow inappropriate treatment to delay good palliative care as ultimately this will result in poor-quality care. Recognising the challenges in prescribing in this setting, we recommend discussion of these cases in our mortality meetings.

There is little clinical guidance on what the expected minimum clinical benefit for which ongoing chemotherapy is indicated, as such societal expectations and health care structure dictate to what degree and how long chemotherapy is prescribed. The paradox of maintaining hope for positive outcomes despite the diagnosis of a terminal illness results in over-optimistic physicians[19] and patients who are willing to consider chemotherapy for small benefits.[16,20,21] When faced with similar hypothetical scenarios, oncologists would more readily opt out of treatment.[21] These differences may reflect the difficulty of making life-value judgements in hypothetical scenarios, but may also represent the difficulty in accurately communicating realistic outcomes of treatment.[22]

Large geographic variation in the percentage of patients receiving palliative chemotherapy in the last month of life exists, ranging from 8% in the UK,[9] 19% in Korea,[23] 16–23% in Italy[24,25] and 13–37% in Portugal.[26,27] Reasons for the use of chemotherapy in the last month of life have been investigated and include patient-driven and family-driven factors, quality of life improvement and symptom palliation, as well as uncertainty regarding prognosis and response.[28] The NCEPOD review emphasised the dilemmas facing clinicians' treatment decisions, with 20% of clinicians reporting the decision to treat as difficult in

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Table 3: Clinical practice interventions proposed.

Clinical practice interventions proposed
1. Three-monthly review of 30-day mortality with cases reviewed at the local mortality and morbidity meeting
2. Consideration of palliative chemotherapy in borderline performance status patients (>2) needs to be discussed within the specialist oncology team
3. Performance status should be documented at the time of assessment
4. The role of the specialist nurse as a patient contact is critical.

cases where patients had advanced disease and poor performance status.[6] In all, 6% reported they would have acted differently retrospectively and 13% felt the treatment decision may have been inappropriate.[6] We encourage the opportunity for these cases to be discussed within the smaller tumour-specific medical oncology teams as part of our peer review process.

Understanding the decision to prescribe chemotherapy particularly if the patient has a poor performance status is important. Factors such as the tumour sensitivity, predicted survival outcomes, side effects and underlying co-morbidities are relevant and need careful consideration.[12] A recent large national series from the UK looked at rates by age, income and body mass index.[11] We did not look into this degree of detail but their findings raise a number of key issues, particularly the impact of age on what a patient is willing to accept and a clinician willing to offer. There are substantial variations in patient attitudes when making decisions around chemotherapy.[16,17] In some circumstances, the principles of chemotherapy prescribing can be overridden by patient wishes and this has the potential to be to the detriment of the patient. Cessation of chemotherapy within the last two weeks of life has been set as a benchmark for improving clinical practice in the Quality Oncology Practice Initiative (QOPI) of the American Society of Clinical Oncology. It has been estimated that the appropriate use of chemotherapy in the last two weeks of life is less than 10%.[29]

However, studies have shown that oncologists are poor at predicting survival of patients with advanced cancer.[30–33] Palliative prognostic scoring tables have been advocated for guiding decisions but are complex.[34] Accurate assessment of a patient's performance status has been advocated as a useful alternative in daily practice. Reflecting this, advanced age and poor performance status have been identified as high-risk factors for mortality in solid tumours and lymphoma.[11,35–37] Documentation of the performance status is therefore of key importance in oncology practice. Despite this, this is poorly done.[24,38,39] In our initial patient cohort, performance status was only documented in 30% of patients but this improved to 70% in our latest cohort. A challenge with this is recognising the potential subjectivity with this score. The NCEPOD found that 21% of patients had a performance status of greater than 2.[6] Similar results were seen in our cohort (19%). Of these nine patients, six (66%) were receiving first-line therapy.

Oncologists need to be cognisant that the estimated treatment benefits may not be accurate when the patient would have not met the inclusion criteria for the study of interest. Additionally, the American Society of Clinical Oncology (ASCO) guidelines specifically recommend against the use of chemotherapy in solid tumour patients who have not benefited from prior therapy and who have a performance status score of 3 or more.[40] Poor performance status is recognised to be associated with poor survival, reduced response and increased toxicity from treatment.[41,42] Chemotherapy use in patients with a poor PS has not been shown to improve quality of life near death.[43]

This audit provides a platform to review local practices and outcomes outside a clinical trial. It raises clinicians' awareness and accountability when making treatment decisions and reinforces that careful patient selection is critical. While this key performance is specific to oncology, it highlights the importance of regular integration of

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KPIs in clinical practice to ensure quality care and accountability for our patients. Based on the results of this study, four interventions have been proposed (Table 3).

Conclusion

This study demonstrates our mortality rates are in keeping with international standards. This quality assurance initiative has allowed us to introduce recommendations to continue to raise the quality of patient care at our centre. There are no national benchmarks for what is an acceptable post-chemotherapy 30-day mortality rate, but we propose our results represent an initial step for us to build upon in practice. This highlights the value of collecting data beyond clinical trials to better understand the patients managed in our daily practice.

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Predictors of medical student remediation and their underlying causes: early lessons from a curriculum change in the University of Auckland Medical Programme

Brian Grainger, Jill Yielder, Papaarangi Reid, Warwick Bagg

ABSTRACT

AIMS: The purpose of this study was to identify predictors of remediation in a medical programme and assess the underlying causes and the quality of remediation provided within the context of a recent curriculum change.

METHODS: A mixed methods study incorporating a retrospective cohort analysis of demographic predictors of remediation during 2013 and 2014, combined with thematic qualitative analysis of educator perspectives derived by interview on factors underlying remediation and the quality of that currently provided by the faculty.

RESULTS: 17.7% of all students required some form of remedial assistance and 93% of all students offered remediation passed their year of study. Multivariate analysis showed international students (OR 4.59 95% CI 2.62–7.98) and students admitted via the Māori and Pacific Admission Scheme (OR 3.43 2.29–5.15) were significantly more likely to require remediation. Male students were also slightly more likely than their female classmates to require assistance. No effect was observed for rural origin students, completion of a prior degree or completion of clinical placement in a peripheral hospital. Knowledge application and information synthesis were the most frequently identified underlying problems. Most faculty believed remediation was successful, however, flexibility in the programme structure, improved diagnostics and improved access to dedicated teaching staff were cited as areas for improvement.

CONCLUSIONS: Remediation is required by nearly a fifth of University of Auckland medical students, with MAPAS and international students being particularly vulnerable groups. Remediation is largely successful, however, interventions addressing reasoning and knowledge application may improve its effectiveness.

Selection to medical programmes is based largely on academic merit. Nevertheless, some medical students require academic remediation, which is described in our context as formal, planned opportunities for a student to either repeat an identified aspect of the curriculum or be offered formal assistance to demonstrate clear achievement of the required standard. The outcome of successful remediation for a student is progression towards graduation and ultimately the ability to work as a doctor. In our experience, academic staff are delighted when remediation is successful, but the process of remediation is a significant resource commitment.[1]

Between seven and 28% of doctors will require remedial assistance at some point in their career.[1] Previous experience at the University of Auckland demonstrated

that from 2009 to 2013, between two and 13% of students required remediation in their initial year of the medical programme and by the final year between 11 and 36% were still requiring some form of remedial attention or monitoring.

Academic performance early in medical school has been shown to correlate both with performance later in the programme[2] and postgraduate ratings of clinical competence.[3] Moreover, the decision to provide students with remediation within the medical programme both affirms the multi-faceted admission process developed through consultation with a number of stakeholders, and recognises the investment made by student, families and the New Zealand Government. This includes the Māori and Pacific Admission Scheme (MAPAS)—an equity-targeted admissions process established in 1971,[4] which aims to develop a health workforce more reflective of the New Zealand society it aims to serve in accordance with the Treaty of Waitangi and the Australian Medical Council (AMC) standards on prioritising student diversity.[5]

Performance during medical school is strongly predicted by admission grade point average (GPA) on admission.[6,7] However, explicit predictors of risk have not previously been examined, nor whether this effect is sustained at all levels. Little is known about the effectiveness of remediation, with a recent systematic review identifying that many interventional studies have been uncontrolled with small sample sizes and few long-term outcome measures.[8]

The attitudes and perspectives of educators and supervisors are crucial to the successful conduct of remediation. Previous qualitative research in this area has identified uncertainty about the efficacy of remediation, with educators citing concerns about a lack of standardisation, a paucity of robust post-remediation outcome data and even scepticism about whether remediation actually occurred.[9] This uncertainty is important, as other work has demonstrated that clinical supervisors may be reluctant to fail underperforming students because of a concern over lack of remediation options[10] or a lack of available time to sufficiently deliver it.[8]

This study aims to investigate what factors increase the likelihood of requiring remediation during the University of Auckland medical programme, as well as examining the perspectives of academic staff about the quality and effectiveness of the remediation work they are involved with.

Methods

Study context

The University of Auckland medical programme is a six-year undergraduate degree in which students are selected into Year 2 either from an initial overlapping health sciences general university year, or after completing another undergraduate degree, usually in a health sciences field. There are specific admission pathways targeted at widening participation for applicants with verifiable Māori or Pacific Island ancestry (MAPAS) (25% of admissions) and those who have completed their primary or secondary education in a non-urban area (Regional and Rural Admission Scheme; RRAS) (17% of admissions). These admission pathways seek to ensure the health workforce reflects the community in which they will practice. The medical programme also admits approximately 20 international students annually, equating to just over 7% of total student intake. Years 2 and 3 (Phase 1) are based on the University campus and consist of learning applied basic sciences, while Years 4 and 5 (Phase 2) and Year 6 (Phase 3) involve clinical placements at hospitals and general practice settings throughout the greater Auckland region and in regional centres in the upper North Island.

Phase directors and seven teaching hospital site coordinators work in conjunction with academic departments to oversee the progress of students. Other key staff involved when students require remediation are: Directors of Medical Student Affairs, academic staff who provide support regarding pastoral issues impacting on progress, MAPAS academic and professional staff, Clinical Medical Education Fellows (CMEFs), who are early postgraduate doctors employed by the faculty to provide tuition to students.

Programmatic assessment includes written examinations, observed structured clinical examinations (OSCEs) and clinical supervisor reports at the conclusion of each attachment. Each year must be passed

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overall to allow the student to progress to the next, and remediation may be offered in a number of forms to those who fail to achieve this, as recommended by a board of examiners. This may take the form of a 'special' written examination, which is a supplementary repeat assessment offered when a student receives a failing grade in a single subject area and is offered additional academic support by departments and CMEFs. At a clinical level, a 'tag' for assistance during future attachments may be assigned by the board. This earmarks these students to their clinical preceptors as potentially requiring more academic support than their classmates, but the extent of support varies depending on the individual circumstances. More intensive remediation options include a directed selective in a particular area of medicine, or a specific period of intensive remediation at the end of their penultimate year (Year 5) before progressing onto Year 6. Alternatively, the board may recommend the student fail that year of study and repeat the following year. Subsequent failure of that repeated year results in exclusion from the medical programme.

The curriculum was reorganised recently to place more emphasis on longitudinal learning and programmatic assessment. This 'new' curriculum was introduced in a staged fashion to Years 2 and 4 in 2013, Years 3 and 5 in 2014 and finally Year 6 in 2015. Curriculum content is structured around five domains (Applied Science for Medicine, Clinical and Communication Skills, Personal and Professional Skills, Population Health and Hauora Māori) and this is delivered in a more longitudinal fashion across the programme than previously. Another key feature is thrice yearly summative progress testing, an assessment strategy developed independently in the 1970's at the University of Maastricht in the Netherlands[11] and the University of Missouri-Kansas City in the US.[12] It involves students at all levels sitting an identical comprehensive written examination requiring integrated knowledge of basic science and clinical practice across the entire curriculum. The test is set at the level of knowledge expected of a first-year postgraduate medical practitioner, and student progress relative to their own prior performance and that of their peers is tracked as they progress through the programme. A key philosophy of progress testing is early identification of academic issues and rapid remediation. Students in Phase 1 also have knowledge assessed by end-of-module examinations as well as written assignments and practical assessments at other stages throughout the programme. Clinical skills, communication and professional skills are assessed by a variety of methodologies, including workplace-based assessment, clinical examinations and a portfolio. As the introduction of this new curriculum represents a change in assessment structure, the quantitative analysis has been restricted to the time that has elapsed since its introduction.

Quantitative analysis

Anonymised data were obtained on all students who were offered formal remediation since the introduction of the new curriculum in 2013 and at each year level through until December 2014. Demographic data were obtained on student gender, year level, entry pathway (including possession of a prior degree), study location and type of remediation offered (special examination, tag, directed selective or repeating the year). Access to individual student files was not sought. To measure the effectiveness of this remediation, outcome data was also sought from each cohort in the following year—specifically whether the student successfully progressed in the programme, had to repeat a year level or was excluded. Results were analysed using Microsoft Excel and R statistical package (R Core Team, Vienna, Austria). Multivariate analysis was performed to determine which demographic factors best correlated with the need for remediation, with $p \leq 0.05$ deemed statistically significant.

Qualitative analysis

The lead faculty staff involved in medical student remediation were e-mailed an invitation to participate in a semi-structured interview. Twenty-two potential participants were identified. These included all three phase directors, all seven site coordinators, the two Directors of Medical Student Affairs, three academic staff responsible for the MAPAS programme and seven current and former CMEFs. Prospective participants were informed that involvement was voluntary and written consent was obtained prior to participation.

Between December 2015 and May 2016, the primary investigator (BG) conducted individual semi-structured interviews with each participant. These interviews were based on an interview guide comprised of open-ended questions relating to the role of each participant in providing remediation; problems faced by students and their underlying causes; the effectiveness of remediation; the amount of time spent providing remediation; knowledge of additional support services provided by the faculty and their effectiveness; and suggestions for improving the current remediation system. Additional questions were also asked on an *ad-lib* basis in keeping with a semi-structured design, allowing the interviewer to follow up on areas of interest that emerged. Interviews were recorded on a digital recorder and transcribed verbatim. Participants were given the opportunity to make amendments to their interview transcripts prior to them being analysed.

Data from the transcripts were coded and sorted into categories (BG), then arranged into themes using cross-sectional thematic analysis by the primary researcher as previously described by Mason.[13] The process of categorising the data and formation of themes was cross-checked by another member of the research team (JY), with the themes agreed on by both researchers.

Ethical approval

Approval was granted by the University of Auckland Human Participants Ethics Committee (UAHPEC) on December 11, 2015 (Ref: 016486).

Results

Quantitative analysis

As of December 2014, 165 students from Years 2–5 of the medical programme were identified as requiring some form of remediation since the staged introduction of the new curriculum. This represented 17.7% of all students who had been introduced to the curriculum by this time. The breakdown of students by phase is shown in Table 1.

Sixty-four students encountered their difficulties during Phase 1 of the programme (representing 12.9% of all students in this phase). For the majority of these (54 students) remediation was in the form of a special examination at the end of the year. These exams had an 87% pass rate. Fifteen students were required to repeat a year and all of these eventually passed, although for two this was not without a special examination at the end of the repeated year. Five students required remediation in both Year 2 and Year 3 during the observation period (these students were not counted twice)—for four this meant sitting consecutive special examinations in Years 2 and 3 and one sat a special in Year 2 and then went on to fail and repeat Year 3.

One hundred and one students encountered difficulties in Phase 2 (23.2% of students in this phase). Thirty-two of these students only required a brief period of intensive remediation before progressing on to the subsequent year without further intervention. Sixty-seven students were 'tagged' as requiring remedial assistance for

Table 1: Number of students requiring remediation during each phase.

Programme phase	Number of students	Progressed to subsequent year
Phase 1	**64** (5 remediated twice)	
Special written examination	**54**	47 (87%)
Repeat year	**15**	15 (100%)
Phase 2	**101** (14 remediated twice)	
End of year clinical examination	**32**	32 (100%)
Tagged	**67**	62 (93%)
Repeat year	**16**	16 (100%)

Table 2: Effect of student demographic variables on the need for remediation.

Variable	Programme overall			Phase 1			Phase 2		
	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI
Male gender	0.045	1.43	1.01–2.06	0.73			0.008	1.91	1.19–3.09
Entry pathway International MAPAS RRAS	<0.0001 <0.0001 0.93	4.59 3.43	2.62–7.98 2.29–5.15	<0.0001 <0.0001 0.81	5.25 6.84	2.13–12.46 3.65–13.17	<0.0001 0.007 0.85	4.78 2.15	2.21–10.40 1.23–3.77
Prior degree	0.97			0.91			0.85		

MAPAS—Māori and Pacific Admission Scheme.
RRAS—Regional and Rural Admission Scheme.

their subsequent year—27 of these were also required to complete an additional clinical skills examination and 17 were assigned to a directed selective (10 of these were in general medicine, five in general surgery, one in orthopaedics and one in geriatrics). Ninety-three percent of tagged students successfully passed their tagged year (excluding those who deferred or chose to withdraw from the programme themselves). Sixteen students were required to repeat a year and all of these eventually passed, although four still required further intervention at the end of their repeated year. Fourteen students required remediation twice and for two of these this meant failing a year despite being offered remediation.

Table 2 demonstrates the effect of student demographics on the need for remediation. International students were the entry group most likely to require remediation at any stage during the programme. Of the 31 international students requiring remediation across the programme, 25 (81%) reported first learning a language other than English and 30 (97%) came from countries where English is not the predominant language. MAPAS students were the next most likely group to require remediation and this reflected a significant over-representation at Phase 1 level, with the effect being less pronounced in Phase 2. Male students were also slightly more likely to require remediation than their female classmates during Phase 2 but not Phase 1. No significant difference was observed for RRAS students, those with a prior degree or those cohorted outside of the Auckland urban teaching hospitals in either Years 4 or 5.

Qualitative analysis

Fourteen of the 22 potential participants consented to the study and were interviewed. These interviews had a median duration of 35 minutes (range 11 to 56 minutes). Categories identified during analysis were grouped into two major themes: those that describe potential underlying causes for needing remediation; and those that identify the strengths of the current system for remediation or suggest areas for improvement.

Reasons for remediation

An under-developed ability to synthesise and apply theoretical knowledge was the most commonly cited reason for students to need remediation. It was mentioned explicitly by nine of the 14 participants in regard to students in all phases of the programme, and many of the other reasons mentioned can be subsumed within this category.

They're trying to learn absolutely everything to the nth degree and reading Harrison's [Textbook of Internal Medicine] or whatever and trying to learn that information, which is not what you require for medical [school] finals. I think they're getting completely buried and struggling with the volume of information rather than actually reading about the basics and covering large areas in a shallow amount of detail. So getting overwhelmed in reading one chapter of Harrison's on one particular subject and not covering basic things like ophthalmology or ENT or something. [P12]

A range of underlying causes for this problem were suggested by participants,

ranging from poor study strategies and self-management skills on the part of the student, lack of opportunities for clinical practice, poor English language skills and even in some cases, learning disability.

There was one instance when another physician suggested "Well that's an interesting thing, this guy's really smart when we're together but when it comes to written exams, it's just a total disaster!" Then he suggested "does he have dyslexia?" and then different interventions were targeted towards this student. [P11]

The progress test was mentioned explicitly by seven participants as being particularly sensitive at identifying students with a range of these problems, for example:

We're talking about a timed, written multiple choice exam that's very heavy on reading of content that's very dense and requires concentration over a three-hour period. So you can appreciate there are a number of subgroups who may have a problem with that. If your English language isn't great, if your reading speed isn't great, if your reading comprehension isn't great, if you have a learning disability that is as of now undiagnosed, you will have problems... This particular assessment...requires people to be very adept at all of those things as well as content matter expert. [P1]

Wider pastoral issues were also identified, and included unrealistic parental or self-expectation, financial problems, family issues and anxiety, particularly regarding performance in examinations.

Every once in a while I do find someone who simply doesn't have the intellectual or academic capacity to be a doctor. They're usually in this position because of someone's unrealistic expectations of them and whether that's their own or family...or societal expectation...people who realise...that this was their father's dream and not their dream [and] that actually "I love kids and I don't want to be a paediatrician and stick needles in and deal with them when they're puking—I'd much rather be a children's librarian!". [P1]

We select people...because they have perfectionistic traits that are very useful for other things, we put them under high pressure. They're not necessarily used to failing things or not being the best at things. They're away

from home, often learning new skills. Sometimes it's a matter of helping someone adjust their self-expectations or expectations from elsewhere that they're always going to get an A+, and if you get them to let go of that sort of pressure they start realising that they're human and they're fallible and they're not always going to get everything right. [P7]

Some participants also identified that MAPAS students as a group faced unique challenges, including an average GPA at entry two points lower than applicants to other admission pathways, prejudice from some peers regarding widening participation interventions and external pressures such as being the first in their family to attend university. However, there was also anecdotal belief that their performance in the later phases of the programme was not significantly different from their peers.

Generally speaking, most people would say that MAPAS students tend to shine as they go through the programme because they get into the real life situations the people skills...you know, it becomes more real for them rather than those fundamental science subjects. [P5]

Strengths of remediation

The majority of participants (10 of the 14) indicated they felt remediation was effective. Reasons cited included the sharing of information between stakeholders, express awareness by faculty of a wide range of possible underlying causes for poor academic performance and the use of an aggregate score derived through the thrice-yearly progress test rather than a single high-stakes examination.

I remember we had a student who was having problems only when it comes to OSCEs. When it came to written exams, he was good but when it came to OSCEs he had problems. So we identified that this was not a knowledge issue—there's something else happening here, probably a performance issue or a degree of anxiety. [P11]

Weaknesses of remediation

Among those who expressed reservations, the main areas of concern were the level of support provided to remediators and the expectation that remedial students simply undertake "more of the same" rather than have a specific, targeted approach.

Frankly the [clinical] teams are the ones tasked with patient care and patient safety.

They don't have time...I would recommend additional staffing resources so that we can assign struggling students to someone who can provide additional teaching and support, rather than just one or two meetings with a CMEF and then work on this in your own time. [P1]

We currently consider 'remediation' as repeating the year—I don't see that as remediation, I see it as doing the same damn thing all over again! The real remediation is the little bits around the side where we say you have to meet with the CMEFs etcetera. [P1]

Suggestions for improvement to the remediation system included more flexibility in the programme structure, improved diagnostics and improved access to dedicated teaching staff, particularly in remote areas.

The problem I have is that you come to those students who have passed everything clinically, everything in terms of knowledge base etcetera and then they fall over on the progress test. Should there be a back-up system? If you fail a [clinical] attachment... we have the ability either through the remediation period or the directed selective... I'd like to see us say that before you fail the year [based on the progress test], you have to sit an oral exam...Tell me about cardiac ischaemia. What is the pathophysiology? Where does each drug affect in that pathway? If you can demonstrate that in a completely different setting to a multiple choice exam that you know what you're talking about then you should get some kind of diversion programme. [P1]

I think the resource that we miss is Clinical Medical Education Fellows [CMEFs] and students often comment on that—that they don't have the access which people do in Auckland. So I think that's one resource we could potentially use more of. We've thought about [setting up a similar role in our site]. It would be a reasonably minor role I think it would be good to have there. So it's that extra bit of expertise which would be useful. [P2]

However, some participants expressed concern that the level of remediation already offered by the faculty was in some cases inappropriate and that there should be clear restrictions on exactly how much support is provided, for example:

We actually do an enormous amount for the medical programme, far more than we do for any other programme that I teach in, and one of the issues that we have talked about... is whether we're actually over-doing it to the extent that students expect that that's what life's going to be like and they don't develop the adequate resilience they need in order to become effective clinicians. So are we wrapping them in cotton wool and spoon feeding them too much? There's a certain point to which remediation may be effective if it leads to long-term improvement, but if it leads to the need to continually do it then we're going to end up with students who get through Year 6 and end up as poor clinicians. [P3]

Discussion

Medical students often require remediation (17.7%), with most students achieving a successful outcome. This proportion was higher in Phase 2 of our programme (23.2%) than during Phase 1.

Ninety-three percent of students who were offered remedial assistance managed to successfully complete the year of study in which it was offered, including all of those who were repeating a year. However, there was an 11.5% rate of needing additional assistance the following year. Previous studies indicate that remediation targeted at a specific assessment is unlikely to be associated with sustained long-term success,[14] however, broader remediation programmes encompassing a more generalised approach to skills and knowledge acquisition accompanied by personal support, are more likely to lead to sustained progression.[8]

Our qualitative analysis revealed a common belief among lead academic staff involved with remediation that knowledge application and information synthesis is frequently an underlying area of difficulty among this group of students. This is consistent with previous studies identifying that at-risk students commonly struggle with knowledge organisation and integration.[15] Participants identified several possible underlying causes for this, encompassing both student and institutional factors. Student factors such as self-regulated learning, motivation and interpersonal skills have been identified elsewhere as contributory to remedial difficulties.[16,17] However, our study also raised the possible role of institutional factors in providing students with the opportunities they need to

attain competency, an issue which has been highlighted elsewhere regarding the experience in procedural skills of newly-qualified postgraduate doctors.[18] Improved clarity and specificity regarding competence-based outcomes, as well as standardising available opportunities to achieve these across different clinical sites, are potential methods by which these factors may be addressed.

International students were the most likely entry cohort to require remedial assistance across the programme as a whole. The majority of the remedial international students in this study reported English as their second language and prior research from North America indicates such students have a significantly reduced pass rate for written multiple-choice medical licensing examinations.[19] However, recent Australian research has highlighted that international medical students also experience a range of other challenges, including social isolation, financial pressures and poor engagement with group learning activities.[20]

This study found that MAPAS students were 3.4 times more likely to require remedial assistance during the programme, but 6.8 times more likely during Phase 1, where they were the single largest at-risk group. This corresponds with lower tertiary level enrolment and retention rates observed among Māori in other tertiary degree programmes in New Zealand.[21] MAPAS students entering the medical programme under widening participation initiatives have a lower average GPA on admission and unsurprisingly are more likely to require remediation. Interestingly, the magnitude of this effect was smaller for students in Phase 2. A 20-year retrospective cohort study in the US demonstrated a similar trend with applicants admitted via widening participation interventions having lower admission scores comparable to regular admissions.[22] The impact of racism and colonisation are recognised to have given rise to a range of disparities between Māori and non-Māori.[23] Specifically, the secondary education system has been observed to result in inequitable outcomes for both Māori and Pacific students compared to other New Zealanders, with only 31.0% of Year 13 Māori and 29.5% of Pacific students attaining university entrance in 2015, compared to 57.4% of

New Zealand European students.[24] This may explain the increased need for remediation of these students at a tertiary level as observed here. The faculty is committed to increased student diversity in the medical programme to reduce these ethnic disparities in the medical workforce. It is also committed to providing support programmes to ensure that MAPAS students succeed and historical disadvantage is mitigated, working towards graduating doctors who both reflect and can serve the New Zealand population.

The most significant feature of the new curriculum was the introduction of the progress testing, which half of all participants mentioned as a sensitive measure of a range of remedial difficulties, although some also had concerns about the lack of specific expertise available for assisting students for whom it was an area of difficulty. More experienced institutions argue the detailed performance breakdown provided by progress testing is valuable in analysing problem areas and targeting remediation.[25] However, a recent qualitative study reported that students often did not find this useful.[26] More investigation is therefore needed in how to best use progress test results to accurately guide remediation.

Some participants identified learning disabilities as a specific underlying cause of difficulty with the progress test, particularly where performance in other forms of assessment was satisfactory. Prior research from the UK has indicated that up to 2% of medical students may suffer dyslexia and that this may manifest as poor performance with both literacy and non-literacy associated skills such as poor time management on clinical attachments.[27] While this study did not set out to identify students with learning disabilities, the University has formal processes for identifying and supporting students who have such disabilities. These assessment processes for learning disabilities are considered for MAPAS students requiring repeated remediation.

One limitation of this study was that the quantitative analysis was limited to the initial cohort who participated in the new curriculum, none of whom at the time of data collection had completed both Phase 1 and 2 under this new curriculum structure. As progress testing is designed to improve

longitudinal learning, further review of student outcomes in subsequent cohorts may yield different results. A further limitation is that students were not interviewed.

In conclusion, this cross sectional study has identified that a significant proportion of students require remediation, which is completed successfully. Long-term follow up of the students will assist in determining the impact of the new curriculum on the number of students requiring remediation in the final year of the medical programme. Targeted support for at-risk students continues to be a high priority for the faculty as we attempt to meet equity goals and successfully graduate doctors to serve all New Zealand populations.

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An in-country model of workforce support for trained mid-level eye care workers in Papua New Guinea and Pacific Islands

Julie Brûlé, Benoit Tousignant, Graeme Nicholls, Matthew G Pearce

ABSTRACT

To alleviate the significant burden of vision impairment and blindness in low-resource settings, addressing the shortage in human resources in eye care is one of the fundamental strategies. With its postgraduate training programmes, The Fred Hollows Foundation New Zealand (FHFNZ) aims to increase workforce capacity in the Pacific Island countries and territories and Papua New Guinea. This paper presents an in-country model to offer support to graduates, an essential element to retain them in the workforce and ensure they are able to perform the tasks they were trained to do. FHFNZ has designed a workforce support programme employing a standardised process, allowing comparable reporting and providing data for FHFNZ to evaluate its training programmes, outputs as well as professional recognition and integration in the workplace.

Blindness and visual impairment are significant public health concerns, impacting quality of life[1] and carrying economic consequences:[2] an estimated 285 million are visually impaired worldwide, of whom 39 million are blind.[3] Ninety percent of vision impairment is found in developing countries and approximately 80% of blindness is avoidable.[3]

The International Agency for the Prevention of Blindness and the World Health Organization's joint initiative, Vision 2020: the Right to Sight, aims to alleviate this burden.[4] One of the strategies within this framework addresses the shortage in human resources in eye care.[5–7]

The Fred Hollows Foundation New Zealand (FHFNZ) is a non-governmental organisation working to reduce the incidence and prevalence of avoidable blindness in developing countries throughout the Pacific Island countries and territories and Papua New Guinea (PNG).[8] FHFNZ has initiated regional postgraduate training programmes in Fiji and PNG for mid-level eye care workers (eye nurses and community health workers) and ophthalmologists through partnerships with local ministries of health and universities.[9–11] FHFNZ also supports students through tuition scholarships, accommodation allowances, as well as providing long-term ophthalmic equipment loans. There are now over 150 eye care nurses having graduated from the Postgraduate Diploma in Eyecare (PGDEC) working in Fiji, PNG, Solomon Islands, Samoa, Vanuatu, Tonga, Kiribati and Tokelau.

After the initial training of competent eye care workers, workforce support strategies are essential to maintain the effectiveness of eye care personnel[9] and introduce them to new skills and knowledge. Offering support to graduates once they've joined their country's workforce is considered paramount in retaining graduates within the workforce and ensuring they are enabled to perform the tasks they were trained to do.[9,10,12] With

a population of some nine million scattered across remote islands, the Pacific presents an inherent set of challenges: many graduates from FHFNZ eye care training programmes are working in isolated, under-resourced regions.

Although many training programmes aimed at developing human resources in eye care have been implemented worldwide, few reports exist on the impact of training and the integration of graduates into their professional role.[11,13–16]

To meet the workforce support needs of its graduates, FHFNZ designed a workforce support (WFS) programme, which aims for the provision of complete and consistent support to graduates. The programme also serves as a means to systematically gather data in order to track the professional integration of the trained eye care workers. The current WFS programme was designed to assess key factors of motivation, essential to workforce retention and maintenance (professional integration, financial compensation, working conditions, opportunities for education and career progression, self-confidence)[10,17,18] as well as some of the WHO's general building blocks of health systems: leadership/governance, health workforce and service delivery.[19] Between October 2013 and December 2015, 66 PGDEC graduates have undergone a WFS visit.

Workforce support (WFS) programme

In line with FHFNZ's commitment to long-term sustainability within its programmes, the WFS programme has been developed to be delivered by trained in-country senior eye care personnel. The programme aims to arrange a WFS visit to graduates within one year of graduation, and then again every 2–3 years following. A WFS visit lasts at least one full day and includes technical/skills support, as well as assistance with eye clinic management issues and advocacy with authorities, when required.

Whenever possible, a preliminary survey is completed by the graduate prior to the WFS visit. This survey gathers data such as background information on the workplace, equipment and supplies availability, confidence levels regarding clinical skills and diagnosing/treatment competencies. The survey also helps to plan complementary

training from the WFS visitor, in order to reinforce the graduate's confidence in areas where it may be lacking.

To ensure that the support provided to all graduates is both exhaustive and consistent, a standardised WFS package was developed to focus on four areas:

1. Evaluation of clinical competencies

An assessment of clinical skills is conducted with both written and clinical testing; observation of clinical skills in action is performed whenever possible.

This assessment of clinical knowledge is part of a process to establish the knowledge retention curve of graduates, with items repeated on each WFS visit. The test items were developed to allow both the evaluation of agreement with graduate self-reported knowledge at the time of the WFS visit, and comparison with a similar assessment, which had been performed upon completion of the training.

2. Evaluation of the systems and workplace

A review and audit of the eye care provider's data collection system is conducted and graduates are encouraged to use reporting templates to record clinical encounters. These reports help establish a portrait of eye care and disease burden in a given area. Moreover, these reports describe the workload faced by graduates, data that can be used to advocate for their roles as eye care providers.

A review of stock control systems, as well as an audit and review of recent patient record cards are also completed. The use of a patient satisfaction questionnaire is discussed and encouraged as a way to promote self-reflection and quality control.

3. Evaluation of professionalism and accountability to lifelong learning

Evidence of self-assessment and reflection are reviewed and discussed. The individual requirements and opportunities for further training are assessed, as is the graduate's awareness of available support programmes, including continuing education provided by FHFNZ. Print copies of relevant continuing education materials are provided at the visit.

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4.   Evaluation of the WFS visit

Feedback on the WFS visit experience is obtained from the graduate.

Following the visit, analysis of the WFS report information is performed and used to plan future curriculum development, plan future support and guide the selection of continuing education topics when hosting in-country workshops throughout the various Pacific countries. Data on indicators of the graduates' professional integration at a regional level are also secondarily extracted.

Conclusion

This comprehensive workforce support programme, based on WHO's building blocks for health systems, is designed to offer in-country, best-quality support to the graduates of eye care training programmes. It addresses key factors in workforce maintenance and retention and gathers data that can be used for advocacy to employers and authorities. Workforce support is tantamount to maintaining a vibrant, competent and engaged workforce in the home countries once the graduates have been trained; it is also an important step towards sustainability of any workforce development programme.

The WFS programme employs a standardised process, allowing comparable reporting, providing valuable information for FHFNZ to evaluate its training programmes, outputs, data pertaining to equipment and stocks availability, knowledge retention, clinical skills retention as well as professional recognition and integration in the workplace. It offers an opportunity to improve the delivery of eye care services as a result.

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Cricket, collision and coronary clot

Gary TE Lau, Ali Khan

Acute chest pain, even in the context of an evident cause such as musculoskeletal trauma, can disguise other significant underlying pathology. This case highlights how an index of clinical suspicion for an additional evolving condition can avert misdiagnosis.

Case report

A 30-year-old man encountered an elbow-to-chest collision with a co-player during a cricket match in an attempt to catch a ball, resulting in a fall and right wrist trauma. He returned home only to present to the emergency department (ED) two hours later with worsening right wrist swelling and mild chest pain. His right wrist was swollen and likely fractured. The chest pain was presumed related to the sports injury.

While waiting for his wrist trauma management in ED, his chest pain got worse; an electrocardiogram (ECG) taken at that point showed anterior ST-segment elevation with reciprocal ST-depression in the inferior leads (Figure 1). Initial troponin-I was normal (<15 ng/L).

An acute invasive coronary angiography was performed, which demonstrated thrombotic occlusion of proximal left anterior descending (LAD) artery (Figure 2). Percutaneous intervention with thrombus aspiration and deployment of a drug eluting stent was performed (Figure 3). ECG post-procedure showed resolution of ST segments. A transthoracic echocardiogram revealed severe hypokinesis of the LAD territory myocardium with mild LV systolic dysfunction (ejection fraction 40–45%). Subsequent assay showed a peak troponin-I level >40,000ng/L.
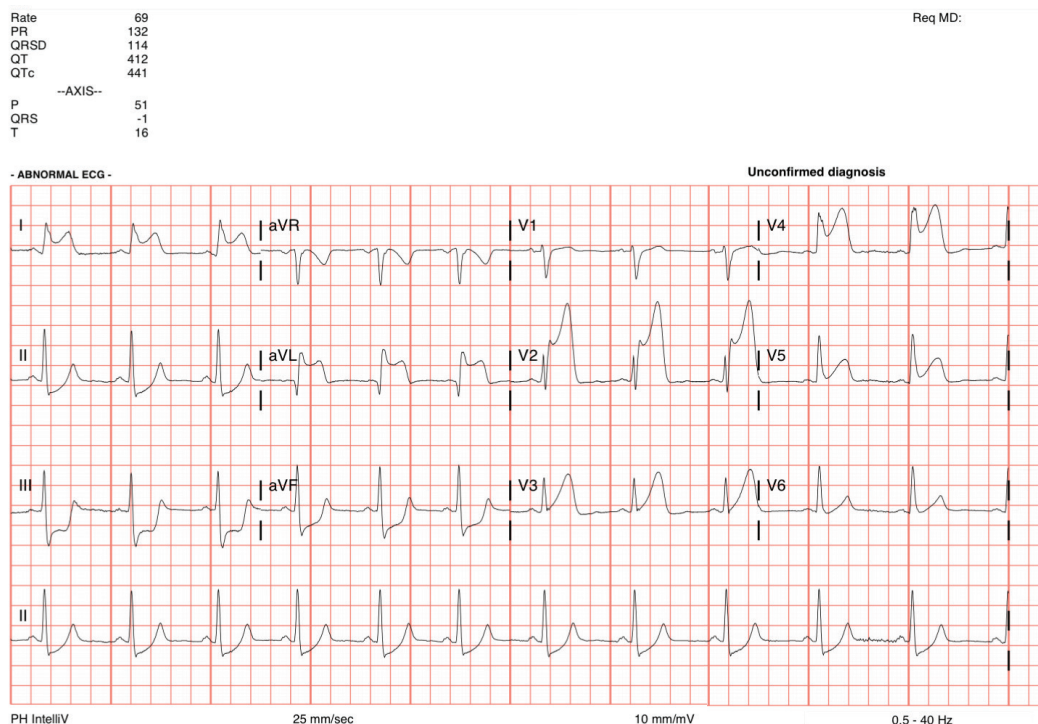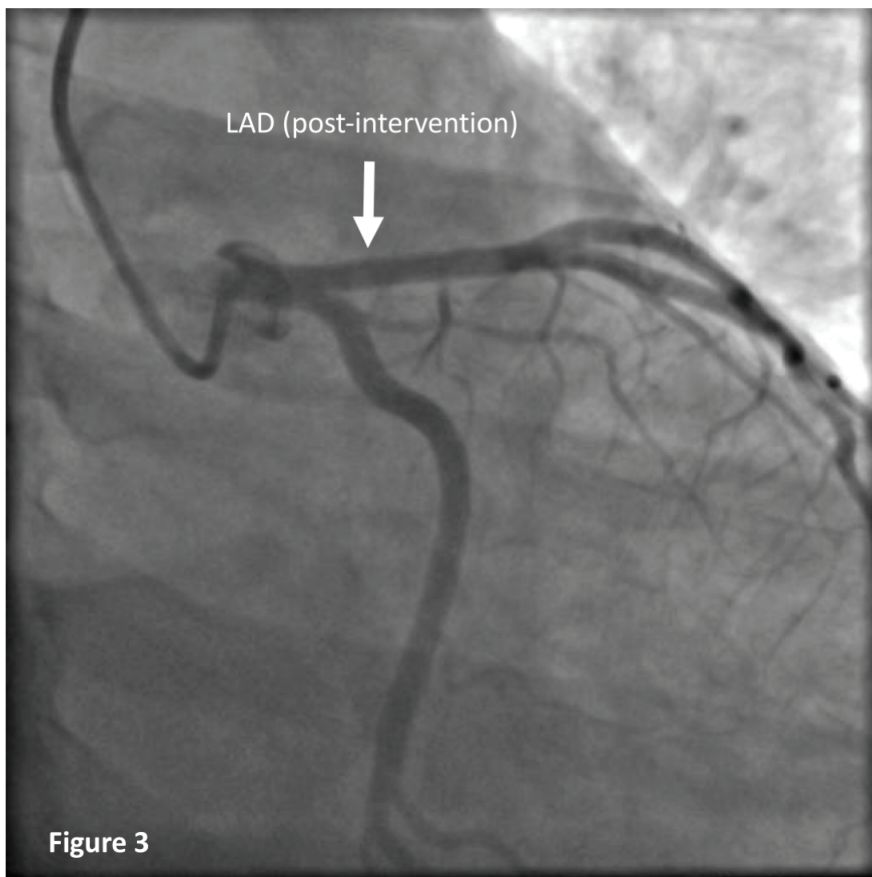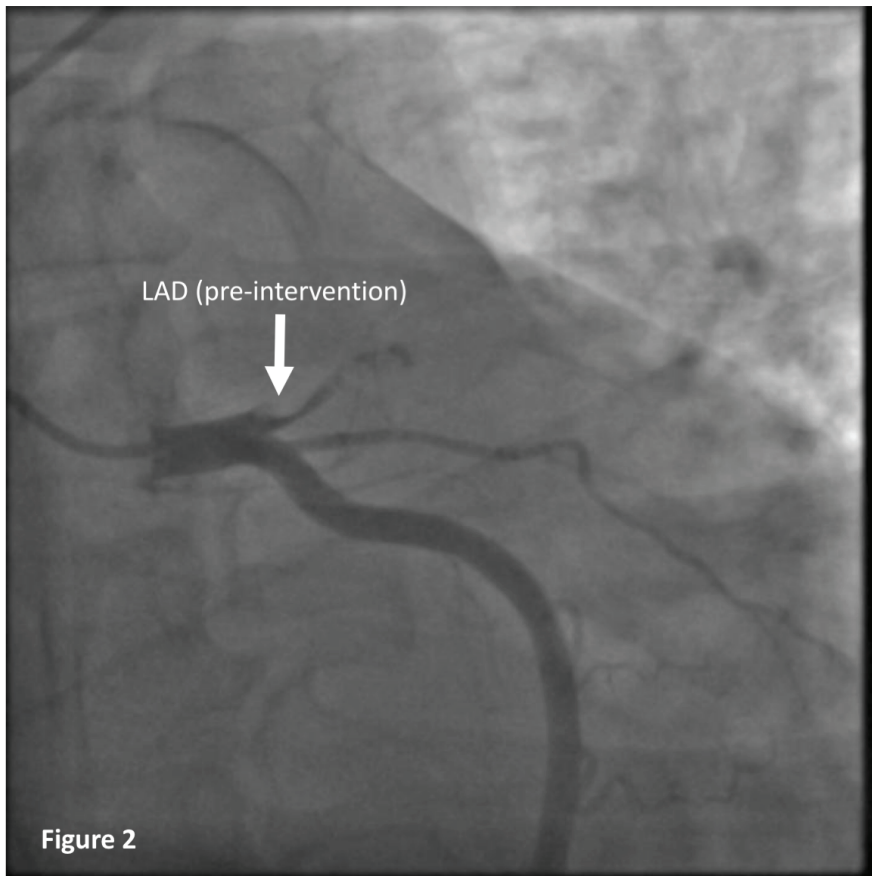

Figure 1

LAD (pre-intervention)

Figure 2

LAD (post-intervention)

Figure 3

He was discharged on medical therapy after conservative management of his wrist fracture.

Discussion

Cardiac complications from blunt chest trauma include myocardial contusion, wall or pericardial rupture, arrhythmias, valvular injury or haemopericardium with or without tamponade.[1] Acute myocardial infarction following blunt chest trauma is rare and coronary artery dissection is the most commonly reported cause. Other possible mechanisms include intimal tear or rupture of an existing plaque with thrombus formation or spasm.[2]

In acute myocardial infarction following blunt chest wall injury, the LAD is the most common vessel affected—likely due to its anatomic predisposition to direct trauma and deceleration injury.[3,4] Intravascular imaging, particularly optical coherence tomography (OCT) in this context would be valuable to evaluate the mechanism leading to the coronary event. A potential cause in this case could be coronary artery dissection or less likely a traumatic plaque rupture, in absence of traditional cardiovascular risk factors and absence of coronary disease elsewhere. Traumatic intra or extramural coronary haematoma could have been contributory.

Conclusion

Chest pain in the context of trauma, although most likely musculoskeletal, can potentially mask an evolving concomitant cardiac event. Exercising a sensible clinical suspicion for any progression or variation of the character of pain can sometimes alter direction of management from simple analgesia to life-saving cardiac interventions.

Competing interests:
Nil.
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Are young people eating their way to bowel cancer?

Jacqui Keenan, Alan Aitchison, Frank Frizelle

The rate per capita of colorectal cancer (CRC) in New Zealand is currently one of the highest in the world, and while there is encouraging evidence that the incidence of this disease is starting to decline in those aged 50 to 80 years, this is partially offset by a significant increase in the number of under 50 year olds.[1] Specifically, between 1995 and 2012, the incidence of distal colonic cancer in men increased by 14% per decade, the incidence of rectal cancer in men increased by 18% and that in women by 13% in patients aged under 50 years. This is in line with a rising incidence of early-onset CRC in young people worldwide,[2] the reason for which is currently unknown.

Studies to date suggest that most early onset CRC develop in the distal large bowel (including the rectum)[2] and again New Zealand is no exception.[1,3] In molecular terms, proximal and distal cancers are generally considered to present as distinct subtypes, with proximal cancers more likely to display a high degree of microsatellite instability (MSI-H) while retaining a wildtype *APC* tumour suppressor gene (*APC*-wt). In contrast, protein truncating mutations in the *APC* gene that characterise the classic adenoma-carcinoma pathway are more often present in microsatellite stabile (MSS) distal cancers.[4] However, this generalised proximal/distal model for CRC molecular subtypes is now being challenged with evidence that young people are presenting with *APC*-wt/MSS cancers.[5] It is possible that the presence of a wild-type APC gene in a young person presenting with a distal cancer may simply reflect insufficient time for an APC mutation to develop. However, evidence that APC-mutant /MSS cancers of the distal colon in young people have a better prognosis than APC-wt/MSS early onset CRCs in this location[5] suggests these cancers more likely comprise two distinct molecular subtypes, and that the patients presenting with APC-wt/MSS distal cancers may have a different genetic risk profile for CRC development.

Histological examination reveals that a disproportionate percentage of early onset cancers present with a mucinous phenotype and that a subset of these cancers are classified as signet ring based on more than 50% of cells showing evidence of intracellular mucin accumulation. This is exemplified by a recent study of early onset CRC in New Zealand, which identified eight of the 50 cases as mucinous (16%) and a further five cases (10%) as signet ring cell cancers in under 25 year olds presenting with CRC.[3] Signet ring cell cancers are typically characterised by markedly reduced or absent E-cadherin expression, which renders the cells unable to maintain cell-cell contact, and the presence of signet ring cells in carcinomas with mucinous differentiation is associated with poor prognosis.[6] Thus, reduced or absent expression of the E-cadherin tumour suppressor gene may prove to be an underappreciated risk factor in the genesis of early onset CRC. This may reflect a germline mutation in the *CDH1* (E–cadherin) gene, similar to that identified as the primary risk factor for patients presenting with familial gastric cancer.[7] However, the worldwide increase in early onset CRC coupled with the finding that a family history of CRC is not necessarily a risk factor for this disease[3] hints more at the involvement of environmental and/or lifestyle factors, and this is reinforced by studies which find that people who migrate from low- to high-risk areas of the world rapidly assume the CRC risk of the host country.

We are particularly interested in diet as a potentially modifiable factor associated with increased risk of early onset CRC in New Zealand. For example, the global obesity pandemic that is being driven by the increased supply of cheap, sweet, energy-

dense foods is one risk factor that stands out in this age group,[8] and a meta-analysis of glycaemic index and glycaemic load suggests there is an overall direct association between carbohydrate-rich diets and human CRC.[9] Moreover, evidence that obesity can drive epigenetic change in the mouse colon[10] hints at epigenetic modification of promoter regions of genes resulting in altered gene expression in the absence of altered DNA sequence. Thus, the reduced expression of E-cadherin in early onset CRC could potentially link back to diet. We also have preliminary evidence of a role for gut bacteria in the aetiology of this disease. Our research shows the presence of *Bacteroides*

fragilis, that are capable of expressing a toxin that targets and cleaves E-cadherin, more often in stool samples from CRC patients when compared to age-matched controls.[11] Moreover, these bacteria are associated with increased risk of colon carcinogenesis in a Canterbury cohort,[12] and we are currently determining whether the *B. fragilis* toxin is also capable of epigenetic modification of the E-cadherin gene.

Collectively, these studies demonstrate that the incidence of early onset CRC in New Zealand is increasing and that a better understanding of what drives carcinogenesis in these young individuals is needed if we want to reverse this trend in the future.

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Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding

Present guidelines are conflicting for patients at high risk of both cardiovascular and gastrointestinal events who continue to require non-steroidal anti-inflammatory drugs (NSAIDs).

These researchers hypothesised that a cyclooxygenase-2-selective NSAID plus proton-pump inhibitor is superior to a non-selective NSAID plus proton-pump inhibitor for prevention of recurrent ulcer bleeding in concomitant users of aspirin with previous ulcer bleeding. Five hundred and fourteen patients with arthritis, cardiothrombotic disease and recent upper gastro-intestinal bleeding were enrolled. After ulcer healing they received either celecoxib or naproxen treatment. Both groups also received treatment with a proton-pump inhibitor. Those in the celecoxib cohort were shown to have significantly less recurrent gastro-intestinal bleeding over the next 18 months.

The researchers concluded that in patients at high risk of both cardiovascular and gastrointestinal events who require concomitant aspirin and NSAID, celecoxib plus proton-pump inhibitor is the preferred treatment to reduce the risk of recurrent upper gastrointestinal bleeding. Naproxen should be avoided despite its perceived cardiovascular safety.

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Patient-reported outcomes in patients undergoing arthroscopic partial meniscectomy for traumatic or degenerative meniscal tears

The proposition reviewed in this study is whether patients undergoing arthroscopic partial meniscectomy for traumatic tears report better outcomes than those who undergo the surgery for degenerative tears?

Three hundred and ninety-seven patients (42% women) were included in the study. Participants with degenerative tears reported significantly larger improvement than those with traumatic tears. However, the researchers suggest that the difference was not clinically meaningful.

They conclude that there is no relevant difference in outcome after arthroscopic surgery, and our results question the current tenet that patients with traumatic meniscal tears have greater improvements in patient-reported outcomes after arthroscopic partial meniscectomy than those with degenerative tears.

BMJ **2017; 356:j356**

Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome

The Dravet syndrome is a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate. It has been suggested that cannabidiol might be an effective treatment for such patients but previous reports have shown mixed results.

In this randomised placebo-controlled trial, the researchers have assigned 120 patients to receive either cannabidiol or placebo, in addition to standard antiepileptic treatment. They report that the median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo.

These encouraging results were offset by the adverse effects noted in the cannabidiol group. These included sleepiness and elevated liver enzymes in some patients. Adverse events led to withdrawal of treatment in eight patients of the cannabidiol group and one in the placebo group.

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A case of regurgitant vomiting

By E.C. Barnett, M.R.C.S., Capt., N.Z.M.C.

Mr N. first seen February, 1916. Previous history: Some six months before, while resident in England, he had shown symptoms of duodenal ulcer, in consequence of which his appendix was removed. On his arrival in New Zealand all his old symptoms recurred, and a gastro-enterostomy was performed (by the late Dr. A.A. Martin). I saw the patient four days afterwards, when he felt very well. He remained so for six more days, when vomiting commenced, which, in spite of dieting and washing-out of the stomach, gradually increased in severity, and it was obvious that the patient's life could only be saved by another operation.

On the eighteenth day, under general anaesthesia, I opened the abdomen. Great difficulty was experienced in opening into the general peritoneal cavity owing to the dense adhesions between the great omentum and the parietal peritoneum. After these had been broken down, I examined the anastomosis; the no-loop operation had been performed and appeared to be functioning all right; no distension of the loop was present; but I found it impossible, on account of adhesions, to lift up the anastomosis and the posterior wall of the stomach. No kink could be found in the efferent part of the bowel. The pylorus was greatly enlarged, very inflamed, and held down by adhesions; in fact, I came to the conclusion that it was malignant. I found it very difficult to decide what was the best thing to do, but, realising that if nothing was done the patient must die, I decided to do an anterior gastro-enterostomy. This was done, selecting for the anastomosis a piece of small intestine about eighteen inches to two feet from the previous anastomosis.

The after history surprised us all. No vomiting occurred, and at the end of three weeks, when the patient left the hospital, he had put on weight. Three months afterwards his weight had increased by three stone. When last seen, early this month, he was very well—"never felt better"; the only thing he notices is that he finds it better to take four or five small meals a day instead of three large ones.

Abstracts for the 235th Scientific Meeting of the Otago Medical School Research Society

Wednesday 21st September, 2016

Interrogation of arcuate nucleus GABAergic NPY neural circuitry in prenatally androgenised female mice

Marshall CJ, Campbell RE

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Fertility is governed by gonadotropin-releasing hormone (GnRH) neurons that reside in the hypothalamus. GnRH neurons are ultimately regulated by circulating steroid hormones that act via an upstream neural network, essential for orchestrating reproductive function. A recently defined neural circuit between steroid hormone-sensitive GABAergic neurons in the arcuate nucleus (ARN) and GnRH neurons is enhanced in prenatally androgenised (PNA) mice that model polycystic ovarian syndrome (PCOS), implicating them in the steroid hormone mediated regulation of fertility. Recent evidence has revealed that a large subset of ARN GABA neurons co-express neuropeptide Y (NPY),[2] a signalling molecule that is known to regulate GnRH neurons. The aim of these experiments was therefore to assess whether this NPYergic subset of ARN GABA neurons is similarly impaired in PCOS.

AgRP-Cre;τgreen fluorescent protein (GFP)-reporter mice were treated with a sesame oil vehicle (VEH) alone or with dihydrotestosterone (250μg, PNA) in late pregnancy. GFP expression in ARN NPY/GABA somata and fibre processes was coupled with immunofluorescent detection of progesterone receptor (PR) to assess ARN NPY/GABA progesterone sensitivity, or GnRH to assess their innervation of GnRH neurons. Fewer PR-positive cells were detected in the ARN of PNA female mice (108.4±6.2 cells/section, n=10) compared with VEH females (137.2±5.8 cells/section; n=8, $P<0.01$). However, in ARN NPY neurons, there was a near complete lack of PR immunoreactivity overall (<0.5%). ARN NPY neurons appear to heavily innervate GnRH neuron somata and proximal dendrites, however, the density of innervation was not different between VEH (n=5) and PNA (n=8) mice. These data suggest that NPY/GABA composes a significant subpopulation of progesterone-insensitive ARN GABA neurons, which project heavily to GnRH neurons irrespective of PNA treatment. This subset of neurons is therefore likely not to be the same population of ARN GABA neurons previously shown to be perturbed in PCOS model mice.

Increased permeability is an inherent defect in the colonic epithelium of Crohn's disease patients

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It's unknown if the increase in intestinal permeability in Crohn's disease (CD) patients is a cause or consequence of inflammation. *In vivo,* interactions between the microbiota, epithelium and immune system prevent investigation of the intrinsic properties of each component. Therefore, we have used colonoids, which are 3D "miniguts" grown from adult colonic stem cells, to determine if the permeability of the intestinal epithelium is altered in CD patients independent of the effects of the immune system and luminal bacteria.

Colonoids were grown from crypts isolated from transverse colonic biopsies from healthy and CD patients. Localisation of tight junction (TJ) and polarity proteins, the major determinants of the epithelial permeability, were determined by immunofluorescent microscopy. Permeability of the epithelium was determined by FITC-dextran uptake into the colonoids over 24h. Statistical significance was determined by Student's *t* test.

There was an apparent loss of polarity of the epithelium in CD colonoids evident as a redistribution of the polarity markers, actin and E-cadherin, from the membrane into the cytoplasm of the epithelial cells. This was associated with a redistribution of the barrier-forming TJ proteins, occludin and ZO-1, from the junction to the basolateral membrane and into the cytoplasm. Additionally, the pore-forming junctional protein, claudin-2, was concentrated in the TJ of the CD colonoids, whereas in the control colonoids it was distributed throughout the basolateral membrane. Significantly, the epithelium of the CD colonoids ($132\pm44\times10^{-8}$ mgcm^{-2}) was ($P<0.005$) more permeable than the epithelium of control colonoids ($7.89\pm1.54\times10^{-8}$ mgcm^{-2}), as determined by FITC-dextran uptake over 24h.

These data indicate that the colonic epithelium of CD patients has an inherent permeability defect due to redistribution of the junctional proteins. This occurs independent of the bacteria and immune system, suggesting that the increased epithelial permeability is a cause, not a consequence, of inflammation in Crohn's disease.

Repression of mutant ataxin-1 gene during early postnatal development minimises the progression of mouse Spino-cerebellar ataxia type 1

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Spino-cerebellar ataxia type 1 (SCA1) is a human autosomal dominant, progressive neurodegenerative movement disorder, characterised by loss of motor coordination and degeneration of Purkinje neurons of cerebellum. SCA1 is caused by an unstable expanded CAG trinucleotide (Q) repeat (39-82Q) in the ataxin-1 gene. The aim of the study is to identify the impact of mutant ataxin-1 (82Q) overexpression in Purkinje neurons during early cerebellar development prior to the onset of ataxic symptoms.

We used a Purkinje neuron (PN) specific conditional Tet-OFF (doxycycline, dox, regulated) transgenic SCA1 mouse that overexpresses 82Q repeats in the ataxin-1 gene. To understand the impact of 82Q during development, we treated mice with dox 200mg/kg in their diet for the first six weeks of life to prevent 82Q overexpression and then removed dox to resume 82Q overexpression for six weeks (82Q 6OFF-6ON), 12 weeks (82Q 6OFF-12ON) and 18 weeks (6OFF-18ON). We assessed mouse motor performance using an accelerating rotarod and immunohistochemical detection of calbindin and vesicular glutamate transporter 2 to assess PN structure and climbing fibre (CF) synaptic inputs respectively.

Twelve week-old SCA1 82Q ON mice showed significant deficits in motor performance (two-way ANOVA, $P<0.01$, $F_{(1,23)}=10.45$) and shrunken PN dendrites with stunted CFs (unpaired T-test, $P<0.0001$). In contrast, 82Q 6OFF-6ON and 82Q 6OFF-12ON mice where 82Q expression was prevented early in life and then turned back on, performed normally (two-way ANOVA, $P>0.1$, $F_{(1,17)}=0.4166$ and two-way ANOVA, $P>0.1$, $F_{(1,35)}=1.946$). 82Q 6OFF-18ON mice showed mild motor impairment (two-way ANOVA, $P=0.07$, $F_{(1,29)}=3.506$) but remarkably, PNs and CFs were normal in all dox-repressed SCA1 mice compared to WT (one-way ANOVA, $P>0.2$, multiple comparisons).

Our results indicate that the developing cerebellum is highly vulnerable to 82Q overexpression and repressing 82Q overexpression minimises the progression of the disease. Further, our study also emphasises the importance of treating SCA1 disease early in life.

In vitro effect of cigarette smoke on DNA methylation in oral cells

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Despite tobacco use being a major risk factor for oral cancer, little is known about tobacco-related DNA methylation in oral carcinogenesis. Therefore, we examined the DNA methylation status of genes involved in TGF-β signalling, a key pathway in carcinogenesis, in oral epithelial cells (OEC) treated with cigarette smoke condensate (CSC).

The dose- and time-dependent effect of CSC on proliferation of three OEC (OKF-4, OKF-6 and OKP-7) cell lines was evaluated using CellTiter-Blue assay. DNA and RNA were purified from cells exposed to 25 and 50µg/mL CSC for 72 hours. To validate the cigarette smoke treatment, expression of CYP1B1 gene (known to be up-regulated in smokers) was assessed in CSC-treated and control samples using a duplex Taqman assay. DNA promoter methylation was evaluated using Methyl-Profiler PCR Array (SABioscience, Qiagen) in two independent analyses, and the subsequent expression of differentially methylated genes was assessed.

CSC concentrations ≥50µg/mL were toxic in OEC. CYP1B1 expression was found to be variably up-regulated with CSC treatment in all cell lines except OKP-7. For methylation analysis, among the 22 genes in the array, SMAD3 and BMP4 were hypermethylated by $3.9\pm0.6\%$ and $4.8\pm2.2\%$ in OKF-4 and OKF-6 respectively; while in OKP-7, SMAD3, BMP4 and LTBP2 were hypomethylated by 8.3%, 35% and 12.3% respectively in one experiment and unaltered in the other (data are expressed as %±SEM). Though not significant, SMAD3 gene expression was 1.7 ± 0.1 and 2.6 ± 0.3-fold up-regulated in OKF-4 and OKF-6 respectively, while 1.5 ± 0.1-fold down-regulated in OKP-7 with CSC treatment.

CYP1B1 gene expression is a measure of tobacco exposure in smokers, and was found up-regulated in our CSC-treated samples, thereby validating our *in vitro* cigarette smoke treatment model. Methylation changes led to altered expression SMAD3 gene, which plays a vital role in physiological cellular proliferation and differentiation, and has also been implicated in carcinogenesis.

COMMD10: A novel regulator of ENaC endocytosis

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The epithelial sodium channel (ENaC) is a heterotrimeric, amiloride-sensitive Na$^+$ channel located at the plasma membrane of various tissues, including kidneys and the vasculature. ENaC abundance and activity at the plasma membrane is crucial for the maintenance of total body Na$^+$, blood pressure and blood volume. Over-activity of ENaC causes hypertension (Liddle's syndrome) making it important to identify potential regulators of ENaC abundance at the plasma membrane. The COMMD (Copper Metabolism Murr1 Domain containing) family have been linked to the regulation of the trafficking (transport to and from the plasma membrane) of various membrane proteins and thus the control of their abundance within the plasma membrane. Therefore our hypothesis is that COMMD10 regulates the trafficking of ENaC.

Knockdown of COMMD10 (C10KD) in Fischer Rat Thyroid (FRT) epithelia in Ussing chamber experiments caused a reduction in amiloride-sensitive short-circuit current (I_{sc}-amil) (mean relative to control ± SD, 1.00 vs 0.49±0.0007μA, *P*<0.0001, one-sample t-test, n=17) suggesting a reduction of ENaC at the plasma membrane. Using transferrin-546 (Tf-546) as a marker of the endocytosis pathway C10KD cells exhibit an increased Tf-546 uptake after two minutes compared to control cells (% uptake ± SEM, 11.33±1.453 vs 28.67±2.603, *P*<0.01, unpaired t-test, n=3) suggesting an increase in endocytosis in C10KD cells. Western blot analysis showed that stable C10KD increased protein level of the ubiquitin ligase Nedd4-2 (mean ± SD, 1.00 vs 1.77±0.17, *P*<0.01, one-sample t-test, n=4) suggesting an upregulation of ENaC ubiquitination and thus endocytosis. Transient knockdown of Nedd4-2 rescued I_{sc}-amil (mean ± SD, 0.49±0.025 vs 1.644±0.07μA, *P*<0.01, ANOVA with multiple comparisons, n=3) suggesting that C10KD increases ENaC ubiquitination through Nedd4-2 and therefore its endocytosis.

These results suggest COMMD10 is a regulator of ENaC endocytosis and thus could influence blood pressure regulation.

Glycosylated asparagines are important constituents for the shear force dependent activation of the epithelial sodium channel

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The epithelial sodium channel (ENaC) is expressed in the kidney and vasculature and crucial for electrolyte/fluid-homeostasis and blood pressure regulation. Abnormalities in ENaC activity are associated with hypertension. ENaC's activity is regulated by shear force (SF) (eg, at the endothelium due to the blood flow) and we hypothesise that glycosylated asparagines are important for the regulation of ENaC by SF by providing a connection to the extracellular matrix. We aimed to determine whether the asparagines themselves or the attached N-glycans are required for SF sensation.

Site-directed mutagenesis combined with two-electrode voltage-clamp experiments were performed. α-ENaC subunits were stripped of their *N*-glycans by individually disrupting the glycosylation consensus sequence (NXS/T) N312NS to N312NA (Mutant: S314A) and N511YT to N511YA (Mutant: T513A). In both mutants an impaired SF activation was observed compared with wildtype α-ENaC (mean difference ± SEM SF-activation, wildtype 63±10%; S314A 37±13%, *P*<0.01; T513A 28±6%, *P*<0.01, one-way ANOVA with multiple comparisons, n=20). Furthermore, the role of glycosylated asparagines for SF sensation was confirmed in experiments with the δ-subunit. While functionally related to the α-subunit (35% sequence identity), δ-ENaC is less responsive to SF and lacks the glycosylated asparagines responsible for SF sensation of α-ENaC. Insertion of asparagines corresponding to α N312 and N511, including their glycosylation consensus sequence, at the corresponding positions in the δ-subunit, generated two δ-subunit mutants (291NNS292 and LPH487NYT) with an increased activation by SF (mean difference ± SEM SF-activation, wildtype 8±2%; 291NNS292 17±3%, *P*<0.05; LPH487NYT 22±5%, *P*<0.01, one-way ANOVA with multiple comparisons, n=18–22).

These experiments confirm that glycosylated asparagines and the attached *N*-glycans in particular are crucial for SF-dependent activation of ENaC.

Evaluation of the National Minimum Dataset for a diagnosis of dementia

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To identify health-related outcomes from large administrative datasets there must first be an evaluation of data concordance between the comprehensive clinical information and data collections. The International Resident

Assessment Instrument (interRAI) is a validated source for capturing large repositories of valuable patient-specific information particularly for individuals with neurological conditions.

Our study examined the degree of consensus between the National Minimum Dataset (NMDS) and the interRAI in capturing a diagnosis of Alzheimer's and other dementias. De-identified NMDS International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) coded data from 1 September 2012 to 30 June 2014 was matched with the interRAI Home Care (HC) assessment records. A diagnosis of Alzheimer's and other dementias was compared for each individual present in both the clinical and administrative records in the 90 days preceding and subsequent to the date of diagnosis in the interRAI–HC. Diagnostic cogency was measured through sensitivity, specificity, positive predictive value (PPV), weighted kappa analyses and McNemar's test.

In the two large study samples (NMDS: n=62,584 and interRAI: n=22,656) the NMDS demonstrated moderate and significant agreement in capturing a diagnosis of Alzheimer's and other dementias when compared to the interRAI within three months. InterRAI assessments captured more diagnosis compared to the NMDS. There was 64.45% (95% CI: 62.30–66.61) sensitivity, 97.58% (95% CI: 97.38–97.78) specificity and the PPV was 77.53%. Weighted kappa coefficient (κ=0.67, 95% CI: 0.65–0.69) and the McNemar's test was significant at $P<0.000$.

Routinely collected administrative datasets such as the NMDS can be a valuable source for research to impact evaluation and inform care planning, resource allocation decisions and in predicting adverse health outcomes.

Development of an excitatory kisspeptin projection to the oxytocin system in late pregnancy

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The neuropeptide, kisspeptin is well-established as a regulator of fertility. However, kisspeptin also regulates other neuroendocrine systems, including secretion of the hormone oxytocin. Oxytocin is secreted by hypothalamic supraoptic nucleus (SON) neurons during birth where it induces uterine contractions. We have shown that kisspeptin administration increases the activity of oxytocin neurons in late-pregnant rats, but not in non-pregnant rats, and that kisspeptin expression in fibres around the SON is increased in late-pregnant rats. Here, we used retrograde tracing and immunohistochemistry to determine the origin of these kisspeptin-positive fibres.

Under isofluorane anaesthesia, female non-pregnant (diestrus) and late-pregnant rats were stereotaxically injected with a retrograde tracer (green fluorescent microspheres) into the left SON. Following recovery, rats were transcardially perfused, and immunohistochemical labelling for kisspeptin was performed on 30μm coronal brain sections. For late-pregnant rats, perfusion was on the expected day of birth.

Kisspeptin is synthesised by neurons in the hypothalamic arcuate, periventricular and anteroventral periventricular nuclei. Kisspeptin neurons in the arcuate nucleus and anteroventral periventricular nuclei were not retrogradely-labelled. By contrast, retrogradely-labelled kisspeptin neurons were observed in the periventricular nucleus. The number of retrogradely-labelled neurons was similar between non-pregnant rats (mean ± SEM, 18.4±3.9 cells per section; n=6) and

late-pregnant rats (16.6±2.6; n=4; P=0.74, Student's t-test). However, there was a higher number of kisspeptin-positive neurons in late-pregnant rats (9.4±2.7) compared to non-pregnant rats (2.4±0.69; P=0.01) and the percentage of retrogradely-labelled neurons that co-expressed kisspeptin was higher in late-pregnant rats (8.73±1.34%) compared to non-pregnant rats (1.62±0.75%; P=0.0008).

The results of this study suggest that kisspeptin neurons of the periventricular nucleus project to the SON and increase kisspeptin expression during pregnancy and so might be important for stimulating oxytocin secretion during birth.

Sleep-disordered breathing influences learning progress in children

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Sleep-disordered breathing (SDB) occurs in approximately 10% of young New Zealand children, interrupting their sleep quantity and quality. The most common cause of SDB in young children is enlarged tonsils/adenoids; adenotonsillectomy, the most common treatment, is successful in 75–100% of children. Untreated SDB may have long-term consequences, with previously found links to adverse behavioural-emotional and cognitive performance. Less well established is the association between untreated SDB and academic performance. The purpose of this study is to examine the inter-relations between SDB, cognitive-linguistic and behavioural-emotional functioning, and numeracy performance in eight-year old children.

One-hundred and fifty-four Dunedin children, aged 7.9–8.3 years (recruited at age three

as part of a larger, longitudinal study) were assigned an SDB score (possible maximum of 86) from parent-reported history of symptoms and clinical examinations of SDB features. Children completed tasks assessing early numeracy skills. Parents and teachers completed ratings of cognitive-linguistic and behavioural-emotional functioning.

The SDB score (median=13, range=0–48) was negatively related to numeracy (mean=58%, SD=19%) (β=-0.46, p=0.017, linear regression). Given that cognitive-linguistic and behavioural-emotional ratings (eg, ADHD symptoms, functional communication problems, learning problems) were predicted by SDB symptoms (β=0.02–0.30, p=0.041–<0.001, linear regressions), and these ratings also predicted achievement in numeracy (β=-0.66–-0.80, p=0.001–0.006, linear regressions), we used the Sobel-Goodman mediation test to look for indirect relations from SDB through cognitive-linguistic and behavioural-emotional correlates and found that functional communication problems and learning problems mediated the links between SDB and numeracy performance.

These findings add to the evidence linking SDB to poorer cognitive functioning and academic performance in school-aged children. The results indicate a need to screen for sleep difficulties in children when exploring barriers to children's behavioural-emotional adjustment and their learning progress, with further recommendations for assessment and intervention as appropriate.

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Abstracts for the 235th Scientific Meeting of the Otago Medical School Research Society

In issue 1448 (13 Jan 2017) of the *New Zealand Medical Journal* we published an incorrect version of the 235th Scientific Meeting of the Otago Medical School Research Society. The correct version is published in this issue.