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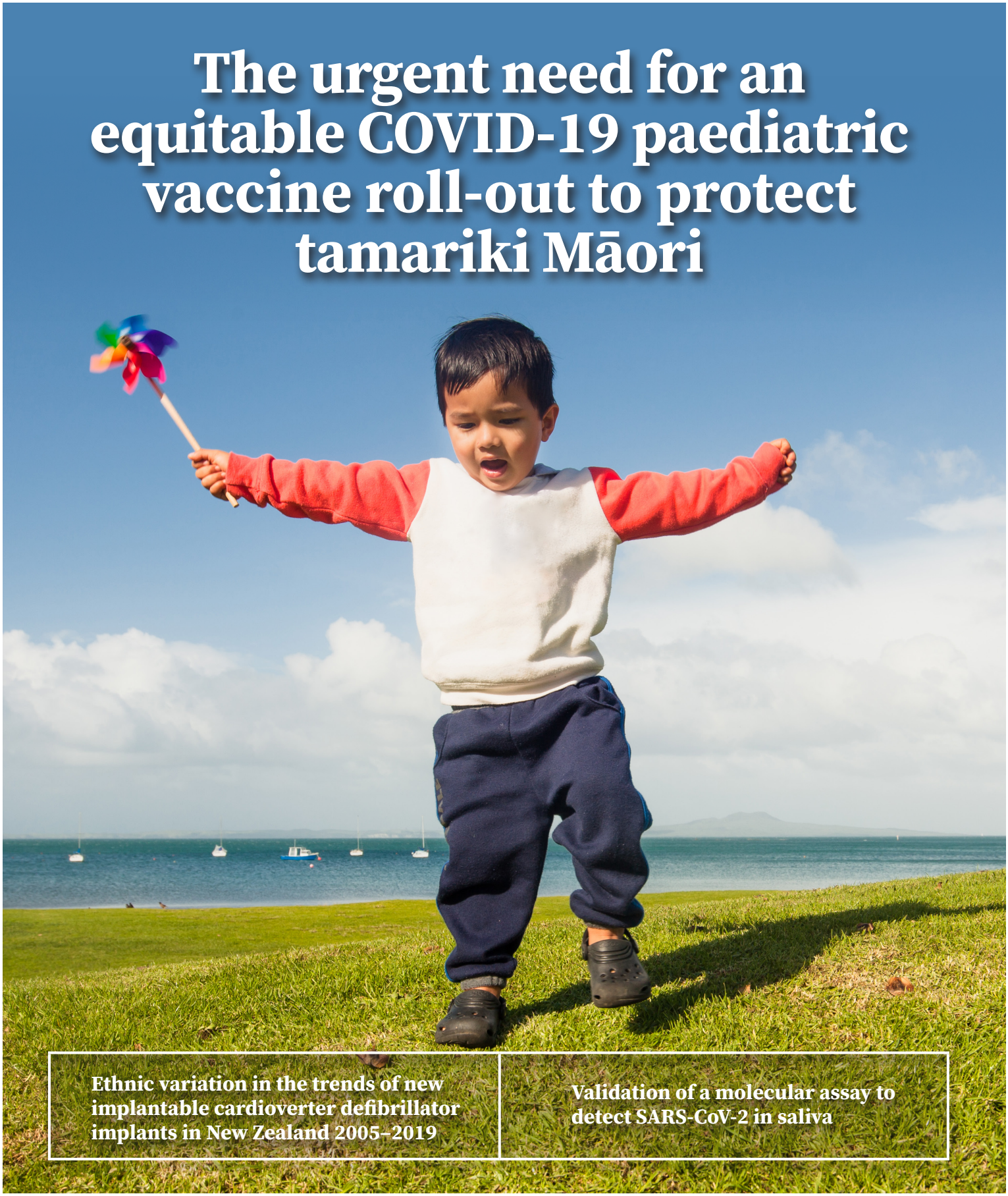
# The urgent need for an equitable COVID-19 paediatric vaccine roll-out to protect tamariki Māori



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## Ethnic variation in the trends of new implantable cardioverter defibrillator implants in New Zealand 2005–2019 (ANZACS-QI 63)

Fang Shawn Foo, Mildred Lee, Katrina K Poppe, Corina Grey, Geoffrey C Clare, Martin K Stiles, David Heaven, Matthew Webber, Matire Harwood, Rod Jackson, Andrew J Kerr

There is marked ethnic variation in implantable cardioverter defibrillator (ICD) implant rates in New Zealand. The highest implant rates were among Māori, followed by Pacific, European/Other and Asian ethnicities. Implant rates have increased significantly among Pacific, Māori and Asian ethnic groups but have plateaued in European patients in the past seven years. The more rapid increase in implant rates in these groups may be due to a greater clinical need or more equitable treatment over time. However, further research at an individual patient level is needed to determine whether implant rates are high enough to represent equity in patient selection for ICD implant.

## The Choosing Wisely campaign and shared decision-making with Māori

David Tipene-Leach, Anna Adcock, Sally Abel, Derek Sherwood

This work identified some structural issues in Choosing Wisely New Zealand that have limited the campaign's ability to mitigate health inequities for Māori and helped to define a potentially transformative way forward. There was wide agreement among our participants that shared decision-making is not just a quality practice, but that it also has the potential to address health inequity among Māori by facilitating participation in healthcare that better meets self-identified need. "Practitioner dependent" factors like consumer trust, autonomy, good relationships and rapport with health providers and culturally appropriate resources are important and are as demanding of attention as systemic causes of health inequity, such as inadequate access to services, the social determinants of health and the structural determinants of health, including racism.

## Validation of a molecular assay to detect SARS-CoV-2 in saliva

Janet L Pitman, Arthur J Morris, Stephen Grice, Jay T Walsh, Leyi Wang, Martin D Burke, Amanda Dixon-McIver

This paper presents the validation results of a qPCR test that was developed at University of Illinois Urbana-Champaign (UIUC) for non-invasively detecting the SARS-CoV-2 virus in saliva and tested in Aotearoa New Zealand laboratory. We used saliva samples that were collected from individuals that had also had nasal swabs taken at the same time. The nasal swabs for just over a third of these people were positive for SARS-CoV-2. Our results showed that the UIUC qPCR test is highly accurate (99.1%) for detecting SARS-CoV-2 in saliva and can detect very low copy numbers of SARS-CoV-2 in saliva. This UIUC qPCR for SARS-CoV-2 is as accurate as the qPCR tests used for detecting SARS-CoV-2 in nasopharyngeal samples in New Zealand. These results confirmed that this reliable option for SARS-CoV-2 testing, including for diagnostic testing for asymptomatic people requiring regular screening.

## Patient perspectives on the use of health information

Rosie Dobson, Robyn Whittaker, Helen Wihongi, Penny Andrew, Delwyn Armstrong, Karen Bartholomew, Andrew Sporle, Susan Wells

This study explored patients views and level of comfort with the use of their personal health information by the district health board. The study found that most people surveyed were comfortable with the health service using their health information beyond their personal care but only if (1) it was de-identified (their personal details were removed first), (2) its use would benefit others, (3) it was done with the correct approvals, (4) the data are stored securely and (5) it remained within the health system.

## An audit of nurses using standing order directives to administer medications to children at risk of contracting rheumatic fever

Karen Hoare, Tracy McKee, Laura Broome, Rhys Vaughan-Jones, Rawiri Jansen, Nicolette Sheridan

Nurses working in 61 schools in South Auckland have been trained to treat Māori and Pasifika children with sore throats and skin infections. They provide the appropriate medicines direct to the families of the children. This initiative has improved access to medicines for children and potentially prevented them from becoming sick with acute rhematic fever.

## Clinical outcomes of campylobacteriosis: a case series analysis of hospitalisations associated with the Havelock North Campylobacter outbreak

Bridget Wilson, Nicholas Jones, Tim Wood, Anita Jagroop-Dearing, Jan Kubovy, Michael G Baker

This paper is an updated analysis of hospitalisations associated with the 2016 Havelock North Campylobacter outbreak (HNCO). It highlights the serious health impacts that occurred from this outbreak, including an estimated 67 hospital admissions among 58 individuals that were at least partially attributable to the HNCO.

## Repeated laparoscopies for pelvic pain: doing the same thing over and expecting a different outcome?

Karen Joseph

Many women in New Zealand suffer from pelvic pain, which adversely impacts their quality of life and that of their loved ones. One common treatment is laparoscopic (keyhole) surgery. Sadly, this does not help some women and brings only brief improvement for many others. As a result, many undergo further surgery. While international and New Zealand guidelines recommend against having repeated surgeries, this seems to still be a common practice, particularly in Canterbury, which puts women through the risks of surgery as they continue to suffer pain. There are a number of possible reasons why so many women are having multiple operations, but there needs to be more investigation to explore these and thus guide improvements in care.

## A broken neck: outcomes from conservative management of C2 fractures in older adults

Krystina V Common, H Carl Hanger

C2 fractures in older people cause substantial morbidity and loss of function in older patients. Despite the majority needing inpatient rehabilitation and complications related to the collar or immobility being common, three-quarters of patients were still able to return home. Walking ability declined and most needed some walking aid post fracture.

## Is not fasting before cardiac catheterisation better than fasting? A systematic integrative literature review

Tristin L Kimpton, Kim Ward

Historically, patients undergoing cardiac catheterisation have not been allowed to eat or drink for at least six hours prior to their procedure. Fasting in this context has recently been questioned by scholars around the world. This literature review has shown that being able to eat and drink in the lead up to this procedure is considered safe and beneficial for the patient. However, guidelines and practices are inconsistent and further research needs to be done to encourage hospitals around New Zealand and across the world to change their practice.


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# The urgent need for an equitable COVID-19 paediatric vaccine roll-out to protect tamariki Māori

Owen Sinclair (Te Rarawa), Jin Russell, Danny de Lore (Ngāti Tuwharetoa), Erik Andersen (Ngāti Raukawa), Teuila Percival, Siouxsie Wiles

The design of COVID-19 vaccination programmes for children is currently being debated locally and overseas[1] where studies have shown that ethnic minority and Indigenous children are disproportionately experiencing severe illness and hospitalisation due to COVID-19 and so have more to benefit from a vaccine. In this editorial, we argue for a vaccination programme for all New Zealand children to be rolled-out as soon as possible after regulatory approval, and that the design of the paediatric vaccine roll-out should be underpinned by equity to uphold the Crown's obligations to Māori under Te Tiriti o Waitangi.

Current vaccination strategies have failed to achieve equitable levels of vaccination against COVID-19, with Māori currently the least vaccinated of all major ethnic groups. According to the Ministry of Health, 71.4% of eligible Māori have been administered two vaccine doses, compared to 84.2% of Pacific Peoples, >99% of Asian and 87.9% of European and other ethnicities.[2] The lower immunisation rates have already resulted in tamariki Māori and their whānau having the highest burden of COVID-19 infections. Māori represent 45% of COVID-19 cases and 36% of all hospitalised cases in the current delta outbreak despite comprising only about 16.5% of the total population.[3] As of the 28 November 2021, seven (41.2%) of the 17 deaths from the delta variant have been Māori, the highest total for any ethnic group.[4]

The COVID-19 pandemic is unfolding before a background of Māori having the worst overall health statistics of any ethnic group in Aotearoa and therefore being the most vulnerable to COVID-19 disease.[5] The long-term effects of colonisation, dispossession, systemic racism and intergenerational poverty have entrenched poor socioeconomic outcomes for Māori.[6] The failure of successive New Zealand governments to sufficiently address the drivers of inequitable health outcomes has resulted in policy that continually disadvantages Māori.[6]

The COVID-19 response will be seen to have disadvantaged Māori. Despite 250 years of differential Māori suffering in every epidemic to have arrived in Aotearoa,[7] multiple mistakes were made during the pandemic response. The government failed to design a plan specifically for Māori or to properly allow Māori to protect themselves from COVID-19, as guaranteed under Te Tiriti o Waitangi. Māori leaders' opposition to government decisions throughout the pandemic reflects inadequate consultation and a failure to reach agreement with Māori. Māori stakeholders have also been critical and opposed to the shift to the COVID-19 Protection Framework.[8] They observed that allowing individuals to cross the border from Tāmaki Makaurau and loosening the international border before Māori achieve vaccination coverage equal to the broader population would negatively and disproportionately affect the health of tamariki Māori and their whānau.[9]

It is vital that health equity for Māori is kept in mind when making decisions regarding the paediatric vaccine roll-out in Aotearoa. We must not repeat the failures that led to the existing vaccination inequities for Māori, inequities that are not a matter of chance but the result of structural racism


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and inequity by design.[10] The decision to phase the vaccination roll-out according to age and diagnosed pre-existing conditions failed to account for (i) the younger age structure of the Māori population, (ii) the greater burden of Māori disease, both diagnosed and undiagnosed, at younger ages,[11] (iii) the significant barriers for Māori accessing healthcare and (iv) their justified distrust of the health system.[12]

These same factors will be present for tamariki Māori in any future paediatric vaccine roll-out. The paediatric roll-out is an opportunity to learn from previous errors and protect Māori.

## The case for a vaccine roll-out for children under 12 years

Although early reports suggested that COVID-19 was a benign illness for children, subsequent studies have shown that children are at risk of harm from both the direct and indirect impacts of COVID-19 infection and the pandemic. Because evidence suggests that Māori children are at a higher risk of all harms, we argue that Māori children should be prioritised in any paediatric vaccination programme.

## Direct harms to children of COVID-19 infection

COVID-19 is generally a milder illness among children in comparison with older age groups.[13] Less than 2% of symptomatic children require hospital admission,[1] and admissions in children can be brief, precautionary, for social reasons or due to parental or caregiver COVID-19 illness. An estimated 2–13% of hospitalised children require intensive care.[1] O'Driscoll et al estimated that the age-specific fatality ratio for children aged 5–9 years is approximately one death per 100,000 infections (IFR 0.001%; 95% credible interval, 0–0.001).[14] Globally, paediatric case fatality ratios differ according to context, with low- and middle-income countries reporting over 90% of the global tally of paediatric COVID-19 deaths.[15]

Deaths among healthy children due to COVID-19 are rare. However, when interpreting COVID-19 mortality statistics, the generally low mortality rate among children should be considered. Between 10 March 2020 to 10 February 2021, there were 66 COVID-19-associated deaths in 5–11-year-old children in the United States.[16] While lower than the number of deaths due to influenza and pneumonia among the same age group (n=84) over a similar period in 2019, this still placed COVID-19 among the top-ten leading causes of deaths for 5–11-year-old children.[16] Comparing COVID-19 mortality statistics with the average pre-vaccination deaths per year for other vaccine-preventable childhood viruses, including rotavirus and varicella, supports rolling-out the COVID-19 vaccine to all children.[17]

International evidence shows higher COVID-19 infection rates in Indigenous and ethnic minority children (Black, Hispanic and American Indian and Native Alaskan).[18,19] Children of racial minority groups are also more likely to be hospitalised with more-severe COVID-19.[19] Similarly, certain pre-existing conditions increase the risk of serious illness and hospitalisation due to COVID-19.[13] These are conditions that disproportionately burden tamariki Māori,[20] who are therefore expected to suffer more hospitalisations and more-severe illness as COVID-19 spreads.[21] Specific conditions associated with negative outcomes from COVID-19 infection that have higher rates in tamariki Māori include obesity, diabetes and asthma and chronic respiratory conditions.[20, 22] In a large systematic meta-analysis, one in 20 children with comorbidities experienced severe illness due to COVID-19 infection, compared to one in 500 children with no pre-existing comorbidities.[23] The risk of mortality from COVID-19 infection for children with comorbidities was almost three-times that of children with no comorbidities.[23]

Multisystem inflammatory syndrome (MIS-C), which causes fever and inflammation in multiple organ systems, is a rare and severe complication of COVID-19 infection in tamariki.[24] The incidence of MIS-C is approximately one in 3,000 infections, and the median age of incidence is 8 years.[25] Overseas, MIS-C occurs more frequently among marginalised Black, non-Black Hispanic, Pacific and Indigenous children.[25, 26]

Evidence is also emerging of persistent symptoms, such as cough, headache, fatigue, chest and abdominal pain and concentration difficulties, in children following COVID-19

infection—that is, "long-COVID."[27] However, further research is required, as the small number of studies published to date all contain major methodological limitations. In the majority of studies reviewed, symptoms did not persist longer than 12 weeks.[27] It is unclear what proportion of infected children experience long-COVID. Nonetheless, even a small proportion would be concerning since large numbers of children will continue being infected.[27] A recent preprint study of almost 12,000 children and adolescents in Germany, found that fatigue, cough and throat/chest pain were more common in children and adolescents at least three-months post COVID-19 infection compared to the control group, but persisting symptoms were less frequent among children and adolescents compared to adults. [28]

These international data raise the real concern that the direct impacts of COVID-19 infection will disproportionately affect tamariki Māori.

## Indirect harms to children of COVID-19 infection and the pandemic

Because COVID-19 is generally milder in children, some say the purpose of a paediatric vaccination would be to protect adults. We argue that vaccinating children has direct benefits for children, as well as reducing risk to adults which indirectly benefits our tamariki. There is evidence that infected tamariki are less likely than adults to transmit the virus in educational settings.[29] But infected children can still transmit the virus to members of their households,[30] and if Māori children are not vaccinated to the same extent as other groups, Māori households can be expected to experience a greater number of COVID-19 infections.

This will place tamariki Māori at great risk of indirect harms, including illness, disability, hospitalisation and/or loss of a parent, caregiver, whānau member. These outcomes would result in life-long psychological, socio-emotional and socioeconomic harms. Between 1 March 2020 and 30 April 2021, an estimated 1.1 million tamariki worldwide lost a primary parent or grandparent caregiver to COVID-19,[31] and this loss is up to 4.5-times more likely to be suffered by Indigenous and ethnic minority children.[31] A study published in *Pediatrics* estimated that, between 1 April 2020 and 30 June 2021, 140,000 children in the United States lost a parent or grandparent caregiver. This study estimated one in every 753 white children lost a parent or grandparent caregiver, compared to one in 412 Hispanic children, one in 310 Black children and one in 168 Indigenous children (American Indian/Alaskan native).[31]

The wider psychosocial impacts of COVID-19, especially prolonged lockdowns, have been damaging to children. Lockdowns and periods of isolation and quarantine deprive children of enjoyment from school, friends and activities and challenge their mental health.[32] The stress of lockdowns and repeated bouts of isolation and quarantine will have life-long negative effects through the educational inequities of remote learning and family violence,[1,33,34] and if their vaccination coverage is lower, then tamariki Māori and their whānau will continue to be disproportionately affected by these burdens.

We believe that if children were asked whether they want to receive the same immunisation as their parents, protect their whānau and communities, stop the spread of COVID-19 and reduce the chance of isolation, quarantine and lockdown, their response would be an overwhelmingly positive "Yes!"

## Māori sociodemographic factors favour higher transmission of COVID-19

According to the 2018 census, 32% of Māori are under 15 years of age, versus only 19.6% of the total population. Because of this younger age structure, fewer Māori are currently eligible for vaccination. According to the 2013 census, 50% of all tamariki Māori also live in the lowest three deciles on the New Zealand Index of Deprivation.[35] This places tamariki Māori at greater risk of negative health outcomes due to social, political and environmental factors, including inequities in access to healthcare,[36] inequities in access to well-resourced schooling,[37] poor-quality housing and/or housing security[38] and overcrowding and multi-generational homes.[37]

The SARS-CoV-2 delta variant is highly transmissible. In the current outbreak, the

majority of transmission is occurring within households, with the secondary attack rate estimated to be 45.6%.[39] Importantly, 20% of Māori households are classified as crowded, compared to 4% of European households.[37] Several studies have shown that vaccination reduces household transmission,[40–42] We expect the converse to be true; as the number of unvaccinated children within a household increases, the risk of household transmission of COVID-19 will increase. These factors, together with many Māori living in multi-generational homes, put tamariki Māori and their whānau at higher risk of COVID-19 from household transmission.

## The emergence of new SARS-CoV-2 variants poses an ongoing risk to Māori

Globally, transmission rates for COVID-19 remain high. This increases the likelihood of the virus evolving further and of new, more-transmissible and more-severe variants emerging. For example, the SARS-CoV-2 delta variant evolved to become 97% more infectious.[39] In late November, a new "variant of concern" designated "omicron" was identified.[43,44] It will be weeks or months before we understand omicron's transmissibility and disease severity, but preliminary data from South Africa suggest that the risk of reinfection with omicron could be approximately three-times higher than for the beta and delta variants.[45] Furthermore, health officials in South Africa have reported a rapid increase in hospitalisations, including in children under the age of four.[46] The emergence of omicron and newer variants poses an ongoing risk to the health of Māori communities, especially if their vaccination coverage remains inequitable.

## Inequities in healthcare predispose tamariki Māori to worse COVID-19 outcomes

International studies have shown a large decrease in healthcare utilisation for non-COVID illness in countries with large COVID-19 outbreaks. Any disruption to healthcare provision in Aotearoa would disproportionately affect tamariki Māori, given their higher burden of disease and because of multiple other systemic issues, including that Māori receive lower-quality care from the health system compared to non-Māori.[38,47]

The health system has long failed to achieve equitable outcomes from childhood immunisations for Māori, and tamariki Māori remain at significantly greater risk of immunisation-preventable diseases, including pertussis[48] and measles.[49] Although there were improvements between 2009 and 2017, those gains have since been lost. The two-year immunisation levels are 70.2% for Māori compared to 86% for New Zealand European.[50] The reasons for this lower uptake are systemic.[51] This lower immunisation rate leaves tamariki Māori vulnerable to predictable resurgences of these diseases when restrictions are lifted. Worse health outcomes for tamariki Māori from COVID-19 infection concurrent with other vaccine-preventable or seasonal respiratory illnesses are predictable.

## The urgent need for an equitable paediatric COVID-19 vaccine roll-out

Paediatric vaccine decisions have been described as "more complex" given the relatively lower risk COVID-19 poses to children.[1] We argue that paediatric vaccine decisions should be made on the basis of a collective risk–benefit analysis rather than an individual framework alone. Principles of justice and equity are also compelling reasons to prioritise tamariki Māori in any paediatric vaccine roll-out. Tamariki Māori have the right to protect themselves and participate in the protection of their whānau, hapū and iwi. The principle of tino rangatiratanga derived from Te Tiriti o Waitangi supports the right of Māori to express their mana motuhake and make autonomous decisions regarding health systems for Māori. Decisions based on the needs of the general population exacerbate risks for Māori and do not comply with the principles of equity and active protection afforded to Māori by Te Tiriti.

Equity for Māori and upholding Te Tiriti o Waitangi should be central to decisions regarding vaccine approval for children under 12. Decisions regarding vaccine approval should go beyond an individual risk–benefit approach and include the wider benefits of vaccination for children, whānau and their communities. The benefits

of vaccination to all children include protection from infection, severe illness, hospitalisation and health complications. Paediatric vaccination will also protect household members from hospitalisation and death, reduce overall community transmission and avoid isolation, quarantine, school closures and other indirect harms.[1]

Planning for an equitable paediatric vaccine roll-out for all New Zealand children is an urgent priority. Colonisation left Māori in a society that has failed to protect their health historically.[52] They are less equipped to deal with disease, and their tamariki already experience a disproportionate amount of disease in New Zealand. The impacts to tamariki Māori from COVID-19 infection will not be the same as for children from affluent families living in stable housing.

Given their increased risk of hospitalisation and severe illness, tamariki Māori vaccination rates should be the prime health target for New Zealand's paediatric vaccine roll-out. It would be both inadequate and ineffective if total child population targets are used without regard to differential access for Māori. One key lesson from the adult Pfizer COVID-19 vaccine roll-out is that, to obtain high vaccination rates, we must focus on the most vulnerable and start with the hard to reach. Iwi and Māori provider partnership and resourcing should occur early to enable Māori leadership to design, develop and implement an effective vaccination programme for tamariki Māori.

## What could an equitable vaccine roll out look like?

Planning for an equitable paediatric vaccine roll-out is a matter of urgency. A school-based vaccination programme would have significant benefits, such as reduced barriers to access. Because the majority of tamariki Māori are clustered in low-decile schools, a simple and obvious solution is to begin the roll-out at schools below, say, decile 4. This approach was used successfully to provide school lunches to underfed children. If Medsafe approves vaccination for 5–11-year-olds before the February 2022 school semester, a rapid school-based roll-out in partnership with iwi and Māori providers should be pursued to protect as many children as possible. Consultation with Māori as an afterthought is unacceptable.

The paediatric vaccine roll-out should also include primary healthcare vaccine sites in partnership with Māori authorities.[53] Providing paediatric vaccines at school sites, and then at primary healthcare sites, would ensure the most equitable access.[53] Substantial increases in funding and resources should be urgently allocated to Māori health providers and providers in low-decile communities well in advance to allow for recruitment of new staff and efficient planning.

This proportionate approach based on equity would prioritise Māori and provide more to those who need it most. It would not deprive anyone of healthcare and is more likely to result in an equal outcome than an approach that does not acknowledge the greater risks and barriers for Māori. Due to the existing health and socioeconomic inequities, tamariki Māori and their whānau deserve a greater share of resources to attain the same level of health enjoyed by non-Māori.

We write this editorial knowing that there has never been a national roll-out of any health intervention designed and targeted to benefit Māori. The adult COVID-19 vaccination programme, which resulted in stark inequities for Māori, is an example of the norm for health programmes in Aotearoa. Programmes that disregard the structural racism and disadvantages faced by Māori result in differential outcomes and harm. We ask those in charge of designing the paediatric vaccine roll-out to consider the principles of equity, Te Tiriti o Waitangi and social justice and to take this historic opportunity to change the direction of the last 250 years. Our tamariki deserve this.

**Competing interests:**
Nil.

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# Ethnic variation in the trends of new implantable cardioverter defibrillator implants in New Zealand 2005–2019 (ANZACS-QI 63)

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## ABSTRACT:

**AIMS:** Ethnic variation in implantable cardioverter defibrillator (ICD) implant rates have been reported internationally but have not previously been examined in New Zealand. This study examined trends in new ICD implants by ethnicity over an extended period.

**METHODS:** All patients who received a new ICD implant between 2005 and 2019 were identified using the National Minimum Dataset, which collects information on all public hospital admissions in New Zealand. Ethnicity was classified using the following standard prioritisation: Māori, Pacific, Asian and European/Other. New ICD implant rates were analysed by ethnicity and age groups.

**RESULTS:** A total of 5,514 new ICDs were implanted. New ICD implant rates increased from 41.4/million in 2005 to 98.2/million in 2019, an average increase of 5.4%/year ($p<0.01$). The highest age-standardised implant rates were among Māori, followed by Pacific, European/Other and Asian ethnicities. The largest increase was seen in Pacific people at 8.9%/year ($p<0.01$), followed by Māori and Asian people at 4.7%/year and 4.3%/year respectively (both $p<0.01$). In European/Other patients, ICD implant rates increased by 10.3%/year ($p<0.01$) between 2005 to 2012, then plateaued at -0.4%/year ($p=0.71$) between 2012 to 2019. By 2019, the age-standardised implant rates in Māori and Pacific people were two-fold higher than European/Others.

**CONCLUSION:** There is marked ethnic variation in ICD implant rates in New Zealand. The higher implant rates in Māori and Pacific parallel known ethnic differences in rates of underlying cardiac disease. The more rapid increase in implant rates in these ethnic groups may represent more equitable treatment over time.

Variation in implantable cardioverter defibrillator (ICD) implant rates by ethnic groups have been identified in the United States and the United Kingdom, with African American and South Asian patients being less likely to receive an ICD compared to White patients.[1–4] However, there is limited information on ethnic disparity in ICD implant rates elsewhere. In New Zealand, there is variation in cardiovascular and non-cardiovascular risk factors, investigation, management and outcomes by ethnicity.[5–19] ICD implant rates for Māori, Pacific, Asian and New Zealand Europeans have been reported for a single year,[20] but whether the reported trend has persisted over a longer time-period is unclear. The main ethnic groups in New Zealand also have differing age structures,[21] but the age-specific ICD implant rates by ethnicity are unknown.

The rate of ICD implants has increased globally in recent years.[22] In patients with heart failure with reduced ejection fraction ICDs have an important role in the prevention of sudden cardiac death,[23–26] in addition to risk factor modification and pharmacological treatment. In New Zealand,

ICDs are indicated for primary prevention of sudden cardiac death in patients <75 years old with symptomatic heart failure with reduced ejection fraction, and for the secondary prevention of sudden cardiac death in patients who have survived a cardiac arrest.[26] ICD implant rates in New Zealand have increased significantly over the past decade,[27] with substantial regional variation.[28] This paper aims to provide an analysis of trends in new ICD implants in New Zealand by ethnicity over the past 15 years.

# Methodology

All patients who received a new ICD implant, including cardiac resynchronisation therapy defibrillators, between 1 January 2005 to 31 December 2019 were identified using the National Minimum Dataset, which collects information on all public hospital admissions in New Zealand. The Dataset does not include procedures from private hospitals, but ICD implants were rarely performed in the private sector over the study period, as device costs were not covered by health insurance providers in New Zealand. ICD implants were identified using specific codes from the Australian Classification of Health Interventions (ACHI), which were issued as part of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD10-AM) procedure coding[29] (Supplementary Table 1). Specific prioritisation and categorisation rules were applied using a previously validated methodology, which had an excellent ability to capture all permanent pacemaker (PPM) and ICD implants nationally, differentiate between PPM and ICD implants and distinguish between new and replacement procedures.[30] Replacement ICD procedures were excluded from this analysis.

Self-identified ethnicity is routinely recorded in all national health databases in New Zealand following a standardised protocol. For patients with multiple ethnic groups recorded, a modified prioritisation of the Ministry of Health's Ethnicity Data Protocols was used to assign each individual to one ethnic group.[31] Prioritisation was performed in the following order: Māori, Pacific (Tokelauan, Fijian, Niuean, Tongan, Cook Island Māori, Samoan, Other Pacific), Asian (Indian, Southeast Asian, Chinese, Other Asian) and European/Other (Middle Eastern, Latin American, African, Other Ethnicity, Other European and New Zealand European). The sole exception were Fijian Indian patients, who were categorised as Indian (in the Asian group) rather than Pacific, as a previous local study demonstrated that these patients have cardiovascular risk profiles that are more similar to Indians than other Pacific groups.[32] As Europeans represent >90% of the European/Other group, this group is referred to as "European" in the rest of this paper. Over the study period, the proportion of the population the main ethnic groups were as follows: Māori: 15.7%, Pacific: 6.4%, Asian: 11.8%, European: 66.1%.[21]

## Statistical analysis

Implant rates per million population by ethnicity were calculated using the number of new ICD implants as the numerator and the estimated population of New Zealand for each year as the denominator.[21] The estimated population of New Zealand by ethnicity (the denominator) is prioritised in the same method as described above. These data are available in the 2018 New Zealand Population Projections from Stats NZ.[21] Age-specific rates for the age groups <40, 40–69, 70–79 and ≥80 years by ethnicity were calculated. Due to low implant volumes in some age groups, age-specific rates were also combined for the three years at the beginning and the end of the study period (2005–2007 and 2017–2019) to facilitate comparisons. Implant rates per million population were age-standardised using the direct method with the European Standard Population.[33] Trend analysis of age-standardised implant rates was performed using a "joinpoint" regression model, to accommodate non-linear trends over time.[34] The process fits the simplest model that the data allow and tests whether one or more joinpoints, which indicate a change in slope of the trend, are statistically significant. Annual percentage changes in trend were calculated. Version 4.7.0.0 of the Joinpoint Regression Program was used.[35] Other analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

### Ethics

This is a sub-study of ANZACS-QI, which is part of the wider Vascular Informatics using Epidemiology and the Web (VIEW) programme. The VIEW programme was approved by the Northern Region Ethics Committee Y in 2003 (AKY/03/12/314), with subsequent amendments to include the ANZACS-QI registries, and with annual approvals by the National Multi-region Ethics Committee since 2007 (MEC07/19/EXP).

## Results

A total of 5,514 new ICDs were implanted between 2005 and 2019. New ICD implant rates increased by 137% over the 15-year period, from 41.4 per million in 2005 to 98.2 per million in 2019, an average increase of 5.4% per year (95% confidence interval (CI): 4.7–6.1%, p<0.01).

### Age-specific trends by ethnicity

In all age groups <80 years, Māori and Pacific people had higher implant rates through most of the study period. Asians consistently had the lowest new ICD implant rates across all age groups, with the lowest rate in patients <40 years. Māori and Pacific people in the 40–59 years and 60–69 years age groups had substantially higher age-specific implant rates compared to Europeans and Asians (Figure 1, Supplementary Figure 1). Of note, at the beginning of the study there were no implants in Pacific people over 70 or Māori and Asians over 80. However, new ICD implants in octogenarians across all ethnicities represented only 2.4% of all new ICD implants over the study period (Supplementary Tables 2 and 3).

### Trends in age-standardised new ICD implant rates by ethnicity

Between 2005 to 2019, the highest age-standardised new ICD implant rates were among Māori, followed by Pacific, Europeans and Asians. In 2005, age-standardised new ICD implant rates were higher in Māori and Pacific people than Europeans. Since 2005, the largest increase in new ICD implant rates was seen in Pacific patients at 8.9% per year (95% CI: 6.1–11.7%, p<0.01). New ICD implant rates increased by 4.7% per year (95% CI: 2.2–7.2%, p<0.01) in Māori and increased by 4.3% per year (95% CI: 1.3–7.4%, p<0.01) in Asians. In Europeans, new ICD implant rates initially increased by 10.3% per year (95% CI: 17.1–13.6%, p <0.01) between 2005 to 2012, but then plateaued at -0.4% per year (95% CI: -2.6–1.9%, p=0.71) between 2012 to 2019. By 2019, the age-standardised new ICD implant rate in Māori and Pacific people were approximately double that of Europeans and three- to four-fold higher than Asians (Figure 2).

## Discussion

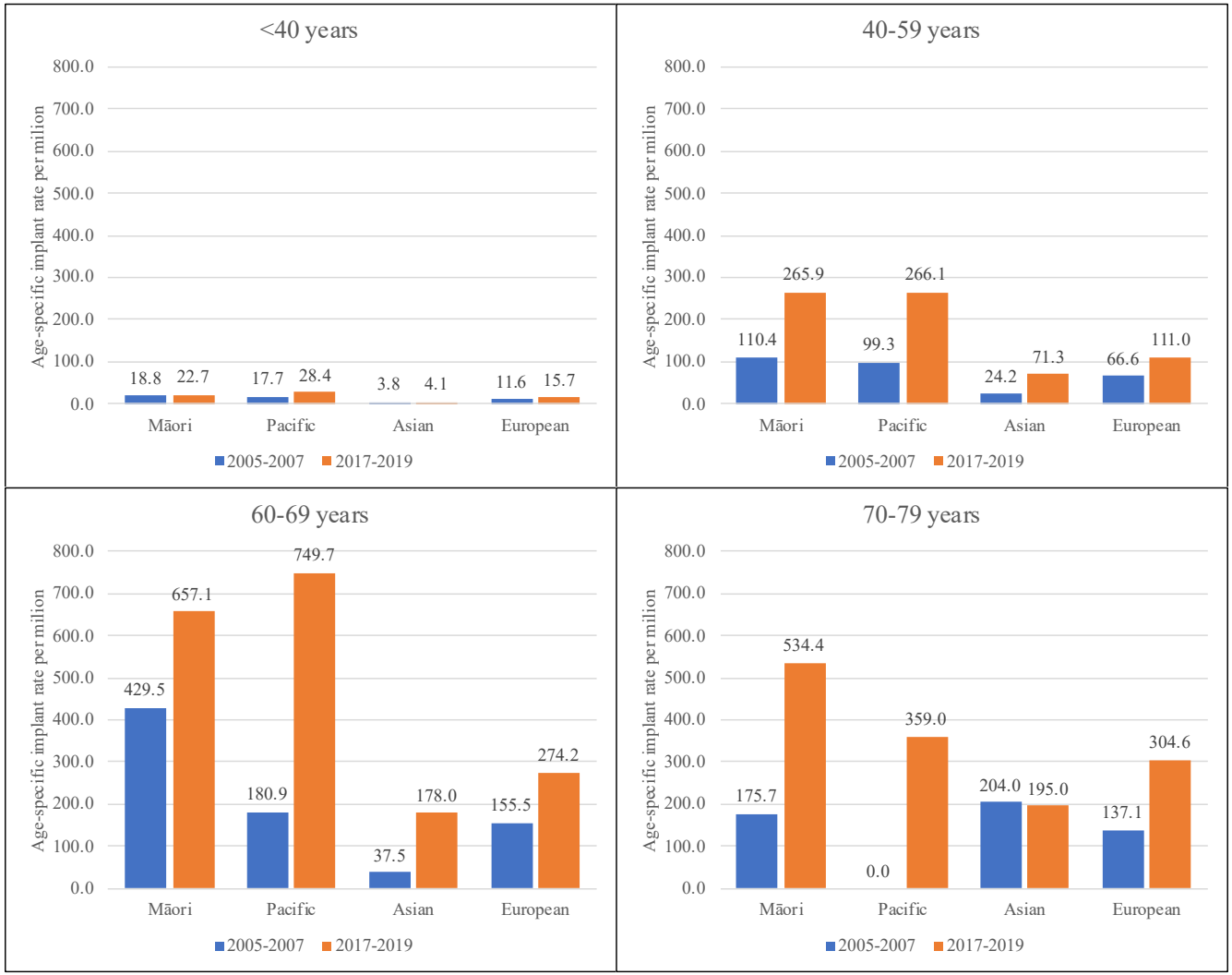
This is the first nationwide description of ICD implant trends by ethnicity in New Zealand over an extended time-period. In 2005 the age-standardised implant rates for Māori were higher than for Europeans, but implant rates among Pacific people were similar to those for Europeans. By 2019, implant rates in Europeans had plateaued, but implant rates for both Māori and Pacific people continued to increase and diverge from Europeans, resulting in Māori and Pacific people having more than twice the implant rates of Europeans.

Wilson et al have previously shown that Māori patients had a higher crude ICD implant rate compared to Europeans in 2010, but the crude implant rates in Pacific patients lagged behind Europeans despite their known higher incidence of ischaemic heart disease.[20] We have shown that, although the age-standardised ICD implant rates plateaued in European patients in recent years, rates have continued to increase for both Māori and Pacific people.

### Are ICD implant rates in New Zealand equitable?

In New Zealand, there is evidence of inequitable distribution of risk factors, investigation, management and outcomes for both cardiac and non-cardiac disease.[5–19] Although we have reported higher and increasing rates of ICD implantation in Māori and Pacific people relative to Europeans, a key question arising from this work is what the ideal rate of ICD implants should be if clinical guidelines for implantation were strictly adhered to.[23–26] Any gap between the ideal rate and observed rates may be attributable to unwarranted variation and therefore evidence of inequitable treatment. In this study we cannot

**Figure 1:** Age-specific new ICD implant rate per million population by ethnicity and age groups from 2005–2007 to 2017–2019. Age group ≥80 years not included as they accounted for only 2.4% of all new ICD implants.



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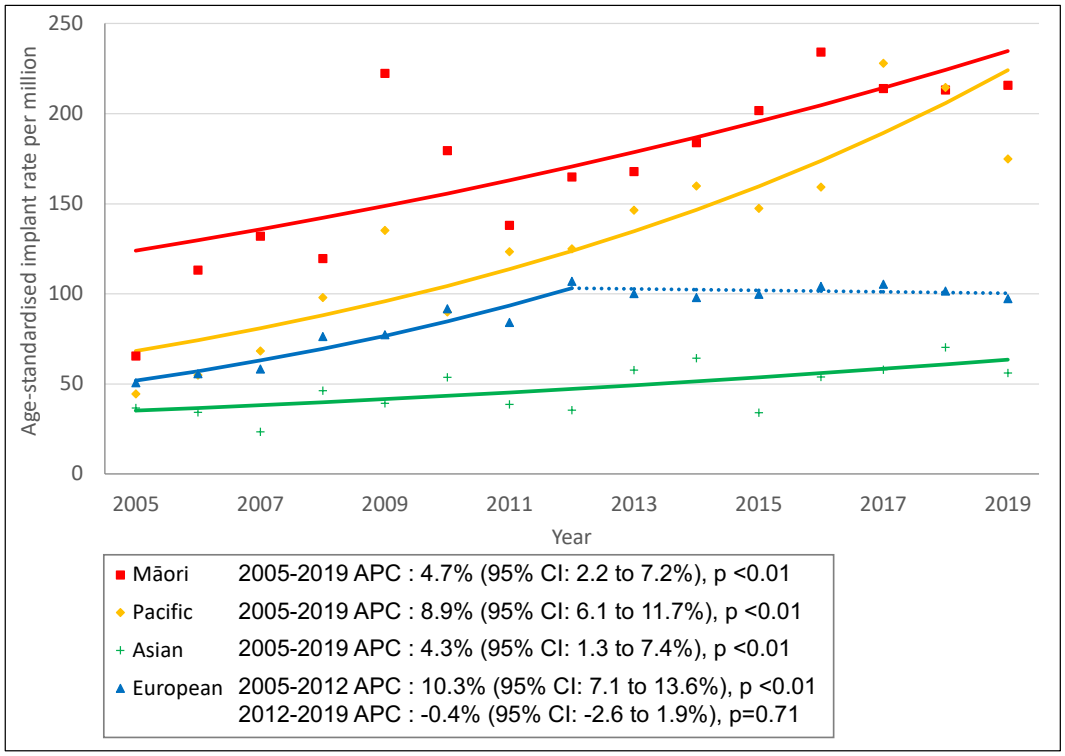
give a definitive answer to this question as a full clinical description of the populations eligible to receive an ICD is not available.

We recently performed an analysis using national administrative datasets, which found that the rates of incident heart failure are two-fold higher in Māori and Pacific patients compared with Europeans (Chan et al, submitted for publication). This confirms other data demonstrating that Māori and Pacific had higher rates of prior heart failure and heart failure hospitalisation compared to Europeans.[5,11,36] We also know that, compared with Europeans, the age-standardised burdens of hospitalisation or death due to ischaemic heart disease for Māori and Pacific people were two-fold greater in 2014–2015, and that the case fatality for acute coronary syndromes in 2014–2017 was two- to three-fold higher.[11,12] The at least two-fold incidence and mortality of both heart failure and ischaemic heart disease for Māori and Pacific people relative to Europeans is consistent with the higher ICD implant rates observed in this study. However, further work is required to determine whether implant rates are high enough.

In recent years, the age-standardised ICD implant rates in European patients in New Zealand have plateaued. At the same time, there has been a decline in hospitalisations and deaths due to ischaemic heart disease and heart failure [12] (Chan et al, submitted for publication). However, this does not take into consideration changes in clinical guidelines for ICD implantation in recent years, level of adherence to clinical guidelines, changes in rates of investigation and risk factor management. Further work is therefore needed to determine whether the appropriate implant rates have been achieved.

Interestingly, our study showed that Asians (including Indians) had substantially lower ICD implant rates compared to other ethnicities, even though Indians have among the highest rates of cardiovascular disease and diabetes in New Zealand.[5,11] Due to the small number of ICD implants in Asians,

**Figure 2:** Trends in age-standardised new implantable cardioverter defibrillator implant rates per million population by ethnicity. Solid trend lines indicate statistically significant changes and dotted trend lines indicate non-statistically significant changes. APC, annual percentage change; CI, confidence interval.





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we did not separate Indian and non-Indian Asians in this analysis. Previous research has shown that both Indian and non-Indian Asians had higher overall coronary revascularisation rates in addition to the lowest all-cause mortality after a myocardial infarction compared to other ethnicities.[9,11,12] Thus, the favourable cardiovascular outcomes and likely lower incidence of ischaemic cardiomyopathy in Asians may partially explain the lower rates of ICD implants in this ethnic group.

## Ethnic variation in ischaemic heart disease and implantable cardioverter defibrillator implants internationally

Ethnic variation in ICD implants has been reported internationally, but data are predominantly limited to the United Kingdom and the United States and only a small number of ethnicities were compared. In the United States, studies from the late 1990s and early 2000s showed that African American patients were less likely to receive ICD implants compared to White patients, irrespective of primary prevention or secondary prevention indications.[37,38] However, this disparity may have narrowed in recent years.[39] Previous studies have also reported that African American patients were less likely to receive coronary angiography and coronary revascularisation than White patients.[40] Mistry et al reported lower ICD implant rates in South Asian patients compared to White patients, despite a higher burden of coronary artery disease.[4] In these international studies, poor communication, system-wide failures to address health literacy, a lack of acknowledgement of cultural beliefs and language barriers were hypothesised as reasons for disparity in ICD implant rates.[2,4] However, in the United States' Get With The Guidelines – Heart Failure Program, there was still disparity in the rate of ICD use by ethnicity, even among patients who received counselling for ICD therapy.[41]

To ensure equitable treatment and to improve cardiovascular outcomes for Māori and Pacific patients, it is imperative that unwarranted ethnic differences at every stage of the management of cardiovascular disease, particularly for ischaemic heart disease and heart failure, is addressed: from risk-factor modification to treatment with pharmacologic therapy and coronary procedures, and finally with fair and appropriate patient selection for ICD implants. To achieve this, health services must, among other things, recognise the importance of effective communication, continuity of care and integrated models of care that respect and are aligned with the values of diverse communities.

## Limitations

This study is a descriptive analysis of ICD implant rates by ethnicity in New Zealand. It has been reported in the context of inequities of underlying disease burden at a population level. However, a detailed patient-level investigation of clinical, geographical or socioeconomic factors that may have impacted on implant rates is beyond the scope of this study.

Self-identified ethnicity may differ between national health databases and the national census. This study uses data from Stats NZ only, but trends in self-identified ethnicity over time is unknown.

Although there have been significant changes in population within each age band as well as age structure by ethnicity over the study period, the calculation of age-specific and age-standardised rates take these changes into account and minimise errors in comparison of implant rates between ethnicities.

Additionally, ICD implants for primary vs secondary prevention indications could not be reliably differentiated in the national level data.

## Conclusion

There is marked ethnic variation in ICD implant rates in New Zealand. Implant rates have increased in non-European ethnic groups but have plateaued in European patients in the past seven years. The higher implant rates among Māori and Pacific people parallel known differences between ethnic groups in rates of underlying cardiac disease. The more rapid increase in implant rates in these groups may be due to a greater clinical need or more equitable treatment over time. However, further research at an individual patient level is needed to determine whether implant rates are high enough to represent equity in patient selection for ICD implant.

# Supplementary Material

- View Supplementary Table 1: ICD10-AM codes for permanent pacemaker (PPM) and implantable cardioverter defibrillator (ICD) implants. If codes for ICD and PPM were both present in a single episode of care (EoC), this was categorised as an ICD implant. When codes for a new and replacement procedure were both present in a single EoC, it was categorised as a replacement procedure if replacement codes were present on the same day or earlier than the dates of the new procedure codes. Conversely, if replacement codes were one day or more after the date of new procedure codes, the procedure was categorised as a new implant.
- View Supplementary Table 2: Number of implantable cardioverter defibrillator implants by ethnicity and age-groups.
- View Supplementary Table 3: Age-specific new ICD implant rate per million population by ethnicity and age groups from 2005-2007 to 2017-2019. *European ethnicity includes European/other after ethnic group prioritisation for Māori, Pacific and Asian ethnicities. CI, confidence interval; ICD, implantable cardioverter defibrillator.
- View Supplementary Figure 1: Trends in new ICD implant rates by ethnicity and age groups. Excludes replacement procedures. ICD, implantable cardioverter defibrillator.

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# The Choosing Wisely campaign and shared decision-making with Māori

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## ABSTRACT

**AIMS:** Choosing Wisely seeks to prevent harm by reducing the number of unnecessary tests, treatments and procedures, and by promoting shared decision-making. This article scopes perspectives of Māori patients/consumers and Māori health practitioners around Choosing Wisely and explores shared decision-making between Māori and their medical practitioners.

**METHODS:** Eight Māori consumers and seven Māori health practitioners participated in a qualitative, semi-structured, in-depth interview study with an inductive thematic analysis.

**RESULTS:** Participant feedback spanned issues from lack of Māori participation in programme governance through to practical issues like meaningful and literacy-appropriate health messaging, traversing consumer, practitioner, organisational and health-system aspects. Feedback further focused on the patient having trust in the practitioner, a sense of autonomy and the availability of advocacy and support in the consultation.

**CONCLUSIONS:** Despite a late campaign collaboration with Māori, Choosing Wisely New Zealand is the first of the international programmes to acknowledge the possibility that their initiative might increase inequity for Indigenous populations. This enquiry highlights the need to consult Māori early and to infuse Treaty principles and Māori knowledge and custom at every stage of the programme.


Choosing Wisely is an international health quality improvement campaign that originated in 2012 in the United States. Its aims are to improve clinical outcomes by reducing low-value and inappropriate clinical interventions and to promote well-informed conversations about treatment options between patients and health professionals to improve decision-making.[1] Choosing Wisely was launched in New Zealand by the Council of Medical Colleges (CMC) in 2016. Initially, colleges and specialty societies reviewed a raft of standard medical practices and, by the end of the year, had issued a list of 50 recommendations around low-value tests, treatments or procedures.[2] The other strategy, promoting shared decision-making, is central to reducing unnecessary interventions and is a significant marker of quality practice in its own right.[3]

In 2019, determined not to exacerbate inequity across the range of health outcomes[4,5,6] for an already-underserved Māori population,[7] the CMC sought a collaborative relationship with the Māori Medical Practitioners Association (Te ORA). Choosing Wisely New Zealand primarily intended to contribute to shared decision-making between healthcare practitioners and Māori health consumers. The US-initiated Choosing Wisely campaign had never deployed an Indigenous lens to look at its programme.

Consequently, a Te ORA research team was commissioned to scope the perspectives of Māori health consumers and Māori health practitioners around the Choosing Wisely NZ campaign and its messages. Te ORA also wanted to examine the experience of (shared) decision-making between Māori and their medical practitioners and make recommendations to better inform an equity-focused Choosing Wisely campaign in Aotearoa New Zealand. This research produced the report[8] from which this paper is derived.

## Methods

This qualitative research seeks to be transformative in the identification of

structural issues within Choosing Wisely NZ that are inconsistent with the promotion of equity for Māori. We deployed a Kaupapa Māori Research methodology—that is, one conducted by, with and for Māori that centres the values and aspirations of Māori whānau, hapū and iwi.[9] The study was initiated and led by Māori researchers (DTL and AA) and guided by a small reference group of two Māori health practitioners and three Māori consumers, who provided advice and feedback throughout the study's design, implementation and analysis. Ethics approval was obtained from the New Zealand Ethics Committee, Te Rōpu Rapu i te Tika, on 15 October 2019 (ref 2019_46).

Māori healthcare consumers and Māori health practitioners were purposively recruited for this small qualitative study through community and professional networks. All 17 consumers and practitioners who were approached agreed to participate, although two pulled out. Fifteen participants (eight consumers and seven practitioners) were subsequently interviewed between November 2019 and February 2020. Participants were predominantly based in the North Island and urban areas. The consumers were from across the age range (20s–70s), and the health practitioners were doctors, nurses, midwives, pharmacists or Māori health provider managers. Interviews were conducted according to participants' preferences: one by telephone, one by Zoom and the majority in person at locations chosen by the participants. Participants gave written consent to participate and were assured of anonymity in any written or oral reporting.

The interview schedule was semi-structured. The Choosing Wisely campaign was explained using the Choosing Wisely resource *Communicating with your health professional: patients and consumers* (available from https://choosingwisely.org.nz/patients-consumers/), which illustrates how health consumers might better participate in decision-making by asking questions of the practitioner around the need for, and the risks of, a test, treatment or procedure and whether other options, including doing nothing, are viable. On this basis, and after and further discussion, participants were asked to share perspectives on Choosing Wisely, such as its principles, aims and potential value for Māori, and to critique the usefulness of the *Communicating with your health professional* resource for use with Māori consumers. Participants were then asked about their own experiences of shared decision-making in healthcare settings and for recommendations to improve what they had experienced.

Each interview took between 25 and 90 minutes and, with the participant's consent, was audio-recorded and transcribed. The data were analysed thematically, which entailed reading the transcripts closely, coding the data inductively and then creating, refining and finalising themes of participant talk.[10,11] All the coding and most of the thematic analysis was undertaken by AA. DTL and DS reviewed early themes and provided input into reorganisation and development of the final themes.

As well as being reviewed by the reference group, a summary of research findings and draft report was produced and sent to participants, who were encouraged to provide feedback (either in person, by telephone or by email) before the a formal report[8] was finalised. Input on the preparation of findings and the discussion for this paper was sought from SA, an experienced qualitative researcher.

# Results

The results are presented in two sections. The first, "Feedback on the Choosing Wisely campaign," includes three themes: the importance of Māori governance; the need to be careful with messaging; resources should be engaging for Māori. The second section, "Shared decision-making between Māori and their medical practitioner," is presented in four domains[12]: consumer, practitioner, organisation and health system. Each domain has 2–3 themes (Table 1).

## Feedback on Choosing Wisely

### The importance of Māori governance

All practitioner participants and one consumer raised concerns that Choosing Wisely had originated in the United States and that it had not been adapted well for local circumstances. Participants said that, due to a lack of engagement with Māori communities or Māori health professional groups until three years after its launch, the

campaign lacked any reflection of Māori knowledge systems, practices and customs.

The recommendations that emerged included that the campaign should move to involve Māori in key governance and decision-making positions and incorporate a "Māori lens" across all activities. The conversation needed to empower shared decision-making could then include a practitioner-led focus on holistic models of health and wellbeing and incorporate rongoā (Māori medicines) and karakia (prayers/incantations) as reasonable treatment options.

### The need to be careful with messaging

Both practitioners and consumers were critical of the campaign and its subsequent messaging that focused on the reduction of tests, treatments and costs associated to the health system when Māori were already under-served by that health system. Better messaging would be around the deployment of evidence-based medicine to provide equitable care, rather than any "cutting back" of care.

> *"I think that the explicit focus on over-treatment and over-utilisation of resources can overshadow the other important aspects that make up good quality care for any person... So how about shifting it towards being about the right thing, at the right time, and the right way, for the right person?" – Health practitioner 5*

After reading *Communicating with your health professional*, some participants felt that the campaign placed the onus for change on consumers rather than health professionals and that, although a focus on consumer autonomy in decision-making was important, there needed to be more emphasis on the practitioner creating welcoming environments and taking responsibility for facilitating shared decision-making and providing appropriate care.

> *"I hate going to the doctors. I would never ask any of those other things because I would just assume that the doctor is right... I don't think the onus should be on the patient to ask all these things, I think the doctor should definitely be telling you all these things." – Consumer 1*

### Resources should be engaging for Māori

Feedback on *Communicating with your health professional* was mixed. Both groups considered some of the language in the resource to be too complex, confusing or wordy.

> *"If I were to pick this up it would just be hard for me to be interested in reading it... You gotta make sure you can relate to it, be informative." – Consumer 7*

The resource advises consumers "to be honest" about their health issues, which some felt was insinuating they might be dishonest. In addition, asking consumers to make a longer appointment if their health issues are complex assumed that people understood whether their health issues are in fact complex. In addition, participants thought longer appointments would be unfeasible for most because of cost.

Both groups recommended that resources needed to be simple and realistic, to cater to different levels of health literacy, and both socially and culturally engaging for Māori (ie, incorporating the target audience into the design of the resource).

## Shared decision-making between Māori and their medical practitioner

### Health consumer

#### *Trust and autonomy*

Trust and autonomy were identified as key to shared decision-making, and this included knowing one's rights to question, to not feel coerced, to be informed, to have clear explanations and to be treated as an equal. On the other hand, it was noted that a lack of trust in health services creates anxiety, which in turn discourages participation and communication. Participants emphasised that health practitioners are responsible for ensuring whānau are supported to make positive health decisions and for promoting health literacy in strengths-based ways. A consumer participant talked about the sense of whakamā (shyness/reticence) that some Māori feel in health settings, for fear of coming across as unknowledgeable. Likewise, a health practitioner emphasised the need for whānau to be guided to engage in shared decision-making.

> *"From the patient's perspective, from the whānau perspective, they've always been taught that they're passive. And then they're encouraged to be another way, which is great, to take control. But you have to give them some tools so you don't set them up to fail." – Health practitioner 7*

#### *Appropriate shared decision-making resources*

Appropriate shared decision-making resources were described as culturally appropriate and friendly. They would include text and graphics or visuals that are relevant and engaging for Māori. Both practitioners and consumers frequently discussed the lack of access to resources for consumers as a barrier to shared decision-making. This is compounded by barriers to accessing healthcare in the first place because of cost, lack of transport and childcare, and the negative impact of trauma and life stresses on health-seeking behaviour.

> *"Because of the emotional overload in people's lives due to housing problems, stress, domestic violence, past history of trauma… prioritising health issues [is] very difficult." – Health practitioner 5*

#### *Importance of advocacy and support*

Good advocacy and support within healthcare settings, such as from whānau members, representatives, nurses and community support workers such as Whānau Ora navigators, were also considered important for shared decision-making. The benefits included having another person to contribute and interpret information and to ensure that rights and wishes were met. As one health provider stated, "even just an extra face in the room makes a difference" (Health practitioner 7). Similarly, a consumer reflected on the importance of whānau support.

> *"[To] have someone to advocate for you when you aren't necessarily in that right frame of mind to ask those questions, when you're just vulnerable… I had my Mum with me and so she was asking a lot of these questions." – Consumer 3*

### Health provider

#### *Competence and communication*

Clinical competence and efficacious communication were described by both groups as critical for shared decision-making. Consumer participants reported feeling able to make good decisions when health providers were thorough and informative. This included going through different scenarios to demonstrate their knowledge of health issues and treatment options. Health provider participants emphasised the importance of demonstrating competent judgement and providing opportunities for shared decision-making with all consumers regardless of whether their conditions were acute or chronic.

#### *Cultural responsiveness*

Cultural safety and cultural competency, which develop when trusting relationships are established and nurtured, were also identified as crucial. Being non-judgemental, genuine, supportive and understanding of context sat alongside acknowledging the validity of the Māori world and the importance of whanaungatanga (connecting/relationships) and holistic models of health. A consumer participant described this as creating a comfortable and safe environment. A health practitioner emphasised the importance of being a role model.

> *"As a health professional you're taught to not show too much of yourself. But what we're talking about is cultural safety, and realising how you can impact on people… For Māori it's really important—engaging and encouraging them to be part of the planning and decision-making… You have to establish and maintain trust for it to be effective… Health professionals sometimes don't realise how much they can be a role model by being a nice, caring person." – Health practitioner 7*

### Health organisation

#### *Model of primary care*

The pervasive model of primary care that results in short appointment times and workforce shortages that disrupt continuity of care were considered barriers to shared decision-making by both participant

groups. Consumers and health practitioners frequently discussed feeling rushed to get through consultations due to short appointment times, leaving needs unmet.

> *"There have been times I've gone to the doctor and they've just kind of skipped over a whole bunch of detail... but I felt out of line to question, I felt a bit rushed..." – Consumer 8*

#### *Detrimental impact of high practitioner turnover and burnout*

High rates of practitioner turnover and burnout, and the subsequent reliance on casual or temporary staff, were frequently discussed by both groups. Consumer participants talked about the importance of seeing the same health provider and developing a relationship over time, and the disruption that change can cause. Similarly, the health practitioners reflected on nationwide general practitioner shortages and the detrimental impact on continuity of care for whānau.

> *"There's GP shortages all over the country so whānau are struggling to get in, and the other thing is about the consistency of the GP you're seeing. [If you're] seeing locums there's no consistency in what the messages will be." – Health practitioner 2*

### Health system

#### *Tiriti o Waitangi obligations*

Both groups of participants identified that health practitioners and the wider providers failed to fulfil Te Tiriti o Waitangi obligations. In particular, they highlighted health inequities for Māori and the lack of Māori input into issues that affect them. Participants advocated for a tino rangatiratanga (self-determination/autonomy) approach, whereby communities and whānau are able to determine their own healthcare needs and control services.

#### *Increasing and supporting Māori health workforce*

There was concern about the lack of Māori in the health workforce. The implication was that addressing systemic inequities in health and improving Māori access to appropriate care and shared decision-making required placing Māori and Te Tiriti o Waitangi in the centre of the health system.

## Discussion

Choosing Wisely's intention of approaching Te ORA was to mitigate the increase in inequity for Māori, given that new initiatives are more readily taken up by the privileged.[13] Te ORA identified that the promotion of shared decision-making between healthcare practitioners and Māori health consumers were vital components of an improved Choosing Wisely.[7] Our participants rightly raised concerns about governance issues and decisions that saw Māori consultation begin only in year three and blamed the subsequent failure to deploy messages informed by Māori knowledge and cultural practice. Further, they critiqued the messaging focused on the reduction of tests, treatments and costs to the health system when Māori were already underserved, noting that a better messaging focus would have been around the deployment of evidence-based medicine to provide equitable care. At a more detailed level, they found Choosing Wisely to use "deficit" language overly focused on consumer behaviour change. Their comments indicated that Choosing Wisely resources needed to be health-literacy appropriate and engaging for Māori.[14] It has been shown,[15] and the Waitangi Tribunal WAI2575 enquiry has more recently argued,[16] that the principles of the Tiriti o Waitangi—that is, partnership, participation, protection, equity and options—are the basic building blocks for health promotion. Choosing Wisely had not lived up to those principles.

However, participants did recognise the value of the aim to promote better communication between the Māori consumers and their health practitioners, as well as clearly articulating the changes required. At the consumer level, trust, appropriate resources and advocacy and support were identified as significant. At the three provider levels, these required changes were identified: at the individual health practitioner level, cultural competence and safety; at an organisational level, a model of primary care that was Māori inclusive with adequate staffing; and at the health system level, appropriate levels of Māori in the workforce and Tiriti o Waitangi compliance.

Systematic reviews on shared decision-making among Indigenous peoples

demonstrate that there is limited literature in this field.[17] Some decision-making tools have been developed in other jurisdictions, with First Nations, Inuit and Metis peoples,[18] particularly for cancer care.[19] But tools and messages that focus narrowly on reducing tests and treatments, or on Indigenous patients posing the questions around medical advice, are problematic. These strategies also fail to acknowledge that individuals from under-served populations are the lesser partner in the power relationship of a medical consultation.[20] Other work with under-served consumers has found that the systematic training of health providers to work in ways that are culturally, linguistically and health-literacy appropriate, and that empower consumers, is required.[21]

This research highlights several broad strategies considered optimal for shared decision-making with Māori that can be applied across nearly all Māori health contexts. Firstly, Māori health equity must be prioritised, which includes a commitment by health programmes and health practitioners to privilege the knowledge, practices and customs of Māori in these contexts. Secondly, both individual and systems levels must recognise that developing connections and relationships is of central importance to the development of the trusting environment in which shared decision-making can occur. Supporting consumer trust and autonomy is appropriate in the consultation and at the systems level. Any national health campaign, including Choosing Wisely, would benefit from centring on Te Tiriti o Waitangi commitments and prioritising equity and the needs and aspirations of Māori from the outset.

Our participant recommendations cover systems issues, such as participation in programme governance, and practical and everyday issues that hamper quality improvement, such as literacy-appropriate health messaging. These findings are significant and an important contribution to the literature.

Although consumer participants covered a range of age groups and health providers were from a range of disciplines, the main limitation of this work was that the majority of participants were urban based. Further research exploring the views of more diverse Māori consumers and health practitioners would be beneficial.

In conclusion, this work has identified some structural issues in Choosing Wisely NZ that have limited the campaign's ability to mitigate health inequities for Māori and helped to define a potentially transformative way forward. There was wide agreement among our participants that shared decision-making is not just a quality practice, but that it also has the potential to address health inequity among Māori by facilitating participation in healthcare that better meets self-identified need. Others have thought similarly for other Indigenous populations.[22] Many of the ingredients for improved shared decision-making identified by our participants are supported by the literature: consumer trust,[23] autonomy,[24] good relationships and rapport with health providers,[25] culturally appropriate resources,[26] provider clinical competence and efficacious communication[27] and health provider cultural safety.[28] These "practitioner dependent" factors are important and are as demanding of attention as systemic causes of health inequity such as inadequate access to services, the social determinants of health[29] and the structural determinants of health, including racism.[30]

**Competing interests:**
Professor Tipene-Leach is Chair of Te ORA. Dr Sherwood was Chair of Council of Medical Colleges in New Zealand during the conduct of the study and received personal fees from them. Anna Adcock and Sally Abel were paid by Choosing Wisely Aotearoa New Zealand as contract researchers.

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# Validation of a molecular assay to detect SARS-CoV-2 in saliva

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## ABSTRACT

**AIM:** To validate a reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) assay to detect SARS-CoV-2 in saliva in two independent Aotearoa New Zealand laboratories.

**METHODS:** An RT-qPCR assay developed at University of Illinois Urbana-Champaign, USA, was validated in two New Zealand laboratories. Analytical measures, such as limit of detection (LOD) and cross-reactivity, were performed. One hundred and forty-seven saliva samples, each paired with a contemporaneously collected nasal swab, mainly of nasopharyngeal origin, were received. Positive (N=33) and negative (N=114) samples were tested blindly in each laboratory. Diagnostic sensitivity and specificity were then calculated.

**RESULTS:** The LOD was <0.75 copy per µL and no cross-reactivity with MERS-CoV was detected. There was complete concordance between laboratories for all saliva samples with the quantification cycle values for all three genes in close agreement. Saliva had 98.7% concordance with paired nasal samples: and a sensitivity, specificity and accuracy of 97.0%, 99.1% and 99.1%, respectively.

**CONCLUSION:** This saliva RT-qPCR assay produces reproducible results with a low LOD. High sensitivity and specificity make it a reliable option for SARS-CoV-2 testing, including for asymptomatic people requiring regular screening.


Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the current coronavirus disease 2019 (COVID-19) pandemic. Nucleic acid amplification testing using reverse transcription quantitative polymerase chain reaction (RT-qPCR) for SARS-CoV-2 genes is the diagnostic test of choice because it detects extremely low levels of virus within biological fluids. However, the sensitivity and accuracy of such tests are dependent upon the type of specimen, its method of collection and the RT-qPCR test itself.

In the haste to develop a detection test during the onset of the COVID-19 pandemic, specimens from the nasopharyngeal (NP) site were used. Although this specimen has become regarded as the gold standard test to which all others are compared, it has its own limitations. The NP site can be difficult to reach, impacting on NP specimen quality,[1] which in turn accounts for significant differences in NP assay sensitivity and increases the risk of false negatives.[2] Moreover, the invasiveness of sample collection often causes discomfort and is unpopular with those requiring frequent testing.

The use of saliva as a specimen for detecting SARS-CoV-2 is increasing around the world. Saliva samples perform well compared to NP in detecting respiratory viruses including coronaviruses,[3–6] with both SARS-CoV[7] and SARS-CoV-2[1,5,8,9] being present in high titers in saliva. The advantage of saliva is that it bypasses the need for invasive sample collection. Although it is an attractive option for frequent testing, there has been a cautious approach to saliva testing in Aotearoa New Zealand. The New Zealand Microbiology Network (NZMN) has recommended that any saliva test would need to be validated locally using well characterised samples that were positive for SARS-CoV-2 and that testing be performed in a diagnostic laboratory accredited by International Accreditation New Zealand (IANZ) and aligned with the ISO 15189 quality framework.[10] NZMN noted that the accuracy

of saliva tests is reliant upon the methods used for saliva collection, the extraction steps employed for the viral RNA and the commercial kit utilised.[10]

In September 2020, we established an international collaboration with investigators at the University of Illinois Urbana-Champaign (UIUC), USA, who had developed a simple and rapid direct saliva-to RT-qPCR assay for the detection of SARS-CoV-2.[11] The assay omits the common RNA extraction step and utilises a modified method of a commercially available RT-qPCR kit, thus avoiding reagent competition and supply-chain issues. It includes an initial heat step that inactivates the saliva sample, reducing viral transmission risk, as well as enabling accessibility of the viral genome to the PCR reagents. Finally, the subsequent addition of a detergent-buffer mix overcomes the drawback of saliva viscosity. This test has been approved for surveillance testing in a US FDA Emergency Use Authorization (EUA).[12]

The aim of the study was to validate the UIUC RT-qPCR protocol for detecting SARS-CoV-2 in saliva in two independent New Zealand laboratories by comparing our results to those measured at the UIUC laboratory (USA). This study used real-world saliva samples that were paired with nasal samples, of mainly NP origin, from participants that were positive and negative for SARS-CoV-2.

# Methods

## Test details

The validation was performed at Victoria University of Wellington (VUW) in Wellington and IGENZ Ltd in Auckland using both commercially available heat-inactivated SARS-CoV-2 (ATCC® VR-1986HK™) and saliva samples from consenting COVID-19 positive and negative participants located in Chicago and Wisconsin, USA. These samples, obtained by UIUC, were shipped to Aotearoa New Zealand for the studies described in this paper.

The RT-qPCR test used the ThermoFisher Scientific TaqPath™ COVID-19 Combo kit (Cat. No. A47814; ThermoFisher) and omits the RNA extraction step. The kit includes primers and probes specific to the SARS-CoV-2 nucleocapsid (*N*), spike (*S*) and replication (*ORF1ab*) genes and a spike-in bacteriophage (*MS2*) gene, with modifications to the manufacturer's instructions, as previously published.[11,13] Controls included a positive control (TaqPath™ COVID19 Control; ThermoFisher Scientific TaqPath™ COVID-19 Combo kit) at 25 copies per µL, negative control (UltraPure $dH_2O$) and no-template control (heat-inactivated saliva; collected in-house).

## Saliva collection

All but five participants had saliva and nasopharyngeal specimens collected contemporaneously. The five non-contemporaneously collected saliva samples were taken following a positive low viral load result obtained from a mid-turbinate swab. These later samples were included to deliberately include paired samples with low viral load as required for FDA EUA validation purposes, which were also included in this current study to ensure that it contained samples of low viral load.

Participants provided a saliva sample by following guidelines that instructed them to allow saliva to collect in the mouth before gently expelling saliva into the collection tube (passive drool method). They then capped their tube and handed it to the healthcare professional or collection-site staff, who placed it into a collection container. A healthcare professional collected the nasopharyngeal (N=142) or mid-turbinate (N=5) sample and transferred the swab into the collection media (per the comparator manufacturer's instructions). All nasal swabs (defined as both nasopharyngeal and mid-turbinate) were processed in the clinical pathology laboratory at the University of Illinois Chicago Hospital using an FDA EUA reference method for detection of SARS-CoV-2, the Abbott RealTime SARS-CoV-2 assay performed on the Abbott m2000 System with a limit of detection of 2,700 NDU per mL.[13]

Saliva samples that had been heat-inactivated at 95°C for 30 min in UIUC were divided into aliquots. Sample aliquots were stored for up to four months at -80°C before transportation from UIUC on dry ice to the two New Zealand laboratories. Even though the status of each aliquot was unknown upon arrival, samples were immediately placed in a random sequence and re-coded. Before testing, the heat-inactivated saliva

aliquot was diluted 1:1 (v/v) in a Tris-Borate-EDTA/Tween 20 mix.

A total of 147 paired saliva samples were received. Of these, 33 saliva samples were from people that tested positive for SARS-CoV-2 based on a nasal sample test result (N=28 NP specimens and N=5 mid-turbinate specimens). The remaining 114 saliva samples were from people that tested negative with SARS-CoV-2 based on a nasal sample test result (N=73 NP specimens and N=41 mid-turbinate specimens). One of these NP samples that tested negative for SARS-CoV-2 did test positive for SARS-CoV-2 in its accompanying saliva sample. The 34 paired samples that tested as positive either in both the nasal (NP or mid-turbinate) and saliva specimen (N=32), or in the nasal (N=1) or saliva (N=1) specimen only, are listed in detail in the results. Of the participants that tested positive (in either test), 26 were symptomatic and eight were asymptomatic.

## Analytical validation

The limit of detection (LOD) was determined by performing three separate experiments in triplicate, whereby the ATCC® SARS-CoV-2 control was serially diluted in heat-inactivated saliva from 192 to 0.75 viral copies per µL. The LOD was defined as the lowest concentration (and highest quantification cycle (Cq) value) at which at least two out of the three genes (*ORF1ab*, *N* and *S*) in all replicates were detected. The repeatability of the LOD was tested with 60 replicates at the LOD concentration to determine whether all 60 replicates would test positive. As a final measure of LOD, 20 heat-inactivated saliva samples spiked with 1x, 2x, 5x and 10x LOD concentrations of ATCC® SARS-CoV-2 control, and 20 heat-inactivated saliva samples negative for SARS-CoV-2 were tested blindly.

The stability of ATCC® SARS-CoV-2 control in heat-inactivated saliva was determined by preparing 12 replicates of saliva spiked with 1x, 2x, 4x, 8x and 16x LOD concentrations. Each of the replicates were divided into four groups and used either fresh or after one, two or three freeze-thaw cycles.

The cross-reactivity of Middle East respiratory syndrome coronavirus (MERS-CoV; ATCC® VR-3248SD™) was tested by preparing five replicates at 100 and 1,000 viral copies per µL of heat-inactivated saliva. These results were compared to heat-inactivated saliva spiked with ATCC® SARS-CoV-2 control at 10 viral copies per µL.

## Diagnostic validation

A positive result was defined as any sample with a Cq value of <39 for two or more of the SARS-CoV-2 gene targets and the spike-in control gene (*MS2*). An indeterminate test was defined as any sample with a Cq value of <39 for only one of the SARS-CoV-2 gene targets and the spike-in control gene (*MS2*). Samples that gave an indeterminate result were re-tested when sufficient sample allowed. A negative result was defined as a sample with a Cq value >39 for all three of the SARS-CoV-2 gene targets and a spike-in control gene (*MS2*) Cq value of <39. An invalid result was defined as any situation where either the spike-in control gene (*MS2*) had a Cq value of >39, the positive control had a Cq value of >39 or the negative control had a Cq value of <39.

The reproducibility of the assay was determined by processing, in three different laboratories (VUW, IGENZ and UIUC), 147 saliva samples in blinded experiments from individuals that were positive (N=33) and negative (N=119) for SARS-CoV-2. The Cq values for each gene in every sample were compared. The VUW results were used to compare with UIUC results for diagnostic validation.

The diagnostic sensitivity of the test was determined by comparing saliva assay results with those of contemporaneously collected nasal swabs. Thirty-three positive SARS-CoV-2 samples, each paired with either an NP (N=28, 85%) or mid-turbinate (N=5) sample, and 114 negative samples, each paired with an NP sample, were tested. Concordance of sample test results between all three laboratories was calculated. Statistical analysis for a qualitative test with calculated diagnostic sensitivity, specificity and accuracy with confidence intervals was performed. Test accuracy was calculated using a disease prevalence value (estimated for managed isolation and quarantine (MIQ) facilities) of 0.74% (1,201 confirmed cases out of 162,733 individuals through MIQ facilities).[14] Finally, hypothesis tests were carried out to determine whether there was a statistically significant difference between Cq values obtained in different laboratories.

## Ethics

Clinical trials comparing results from contemporaneously collected NP or mid-turbinate nasal swabs analysed by an FDA EUA reference method for detection of SARS-CoV-2, and saliva samples analysed by the UIUC assay (covidSHIELD), were approved by the Western Institutional Review Board, USA (WIRB 20202884). All participants gave written and informed consent both to the collection of all saliva samples and their use at external organisations for the purpose of test validation.

## In-use experience of the assay

The assay was accredited for surveillance use in December 2020. The ease of sample handling and rate of inhibited samples was assessed by failure of detection of the spike-in control, *MS2*.

# Results

## Analytical validation

The LOD of SARS-CoV-2-spiked heat-inactivated saliva samples in three replicate experiments was <0.75 viral copies per µL (or 1.875 viral copies per reaction) (Figure 1). A positive result was given to all replicates at 0.75 viral copies per µL using the diagnostic criteria of two or more genes being detectable.

The LOD of <0.75 viral copies per µL was confirmed by all 60 replicates being detected as positive of SARS-CoV-2 (data not shown) and by a blinded experiment whereby all SARS-CoV-2-spiked samples were detected as positive at concentrations ranging from 1 to 10x LOD, and all non-spiked samples were detected as negative (Figure 2). Freeze-thaw cycles did not change assay results, with only one replicate of the *ORF1ab* gene at 1x LOD concentration at Cq of >39 (data not shown).

The assay showed no cross-reactivity with a similar virus, MERS-CoV. All heat-inactivated saliva samples spiked with MERS-CoV had Cq values of >39, even at high concentrations of 1,000 viral copies per µL (Figure 3).

## Diagnostic validation

Positive and negative SARS-CoV-2 saliva samples assayed are displayed in Table 1. The Cq values for the 113 concordant negative samples were >39 (data not shown). Thirty-two of 33 saliva samples that were paired with a positive nasal sample (NP and mid-turbinate) were detected as positive in the saliva test, resulting in a sensitivity of 97.0% (95% CI 84.2–99.9%). One saliva sample paired with a negative NP sample tested as positive, resulting in a specificity of 99.1% (95% CI 95.2–100%). Thus, the overall test concordance between saliva and nasal specimens was 98.6%, and the saliva test accuracy was 99.1% (95% CI 95.9–100) (Table 2).

Of those paired with NP specimens only, 27 out of the 28 samples that were positive in the NP test were detected as positive in the saliva test, resulting in a sensitivity of 96.4% (95% CI 81.7–99.9). One saliva sample that was paired with a negative NP sample tested as positive, resulting in a specificity of 98.6% (95% CI 92.6–100%). Thus, the overall test concordance between saliva and nasal specimens was 98.0%, and the saliva test accuracy was 98.6% (95% CI 94.1–99.9) (data not shown).

The Cq values for all 33 positive SARS-CoV-2 samples are displayed in Table 3. The one saliva sample (#34) taken from a symptomatic participant that tested positive and was accompanied by a contemporaneously collected negative NP specimen is also included in Table 3. The variability of the 2^(-ΔCq) values between the two New Zealand laboratories was 0.24, 0.41 and 0.29 for the N, ORF1ab and S genes, respectively. A t-Test performed on the Cq values between the laboratories demonstrated no statistically significant differences. The low sample variability of 2^(-ΔCq) values (particularly those stored in different aliquots; data not shown) between the laboratories confirmed high reproducibility.

Two samples with very low viral load, #6 and #33, were received for testing in the New Zealand laboratories. The samples were tested immediately in the VUW laboratory but there was a delay of one week in sample processing at the IGENZ laboratory, which resulted in Cq values of >39. Given the positive results obtained from these specimens at VUW and the similarity in Cq values between the two New Zealand laboratories in all samples that were processed promptly, samples #6 and #33 were assumed to be degraded and IGENZ data were omitted from Table 3. Sample #33 had a very low viral load and was called as indeterminate by all three laboratories. Repeat testing

**Figure 1:** Three replicate experiments of SARS-CoV-2 spiked heat-inactivated saliva serially diluted from 192 to 0.75 viral copies per mL. The Cq values for the three SARS-CoV-2 specific genes (*N*, *ORF1ab* and *S*), as well as for the spike-in control gene (*MS2*), are shown. A Cq value of 40 was given to undetermined (absence of gene) results. This was the cycle number in which the reaction was stopped. Positive (PC), negative (NC) and no template (NTC) controls were included. Dashed line indicates the limit of detection (LOD) for each replicate experiment.

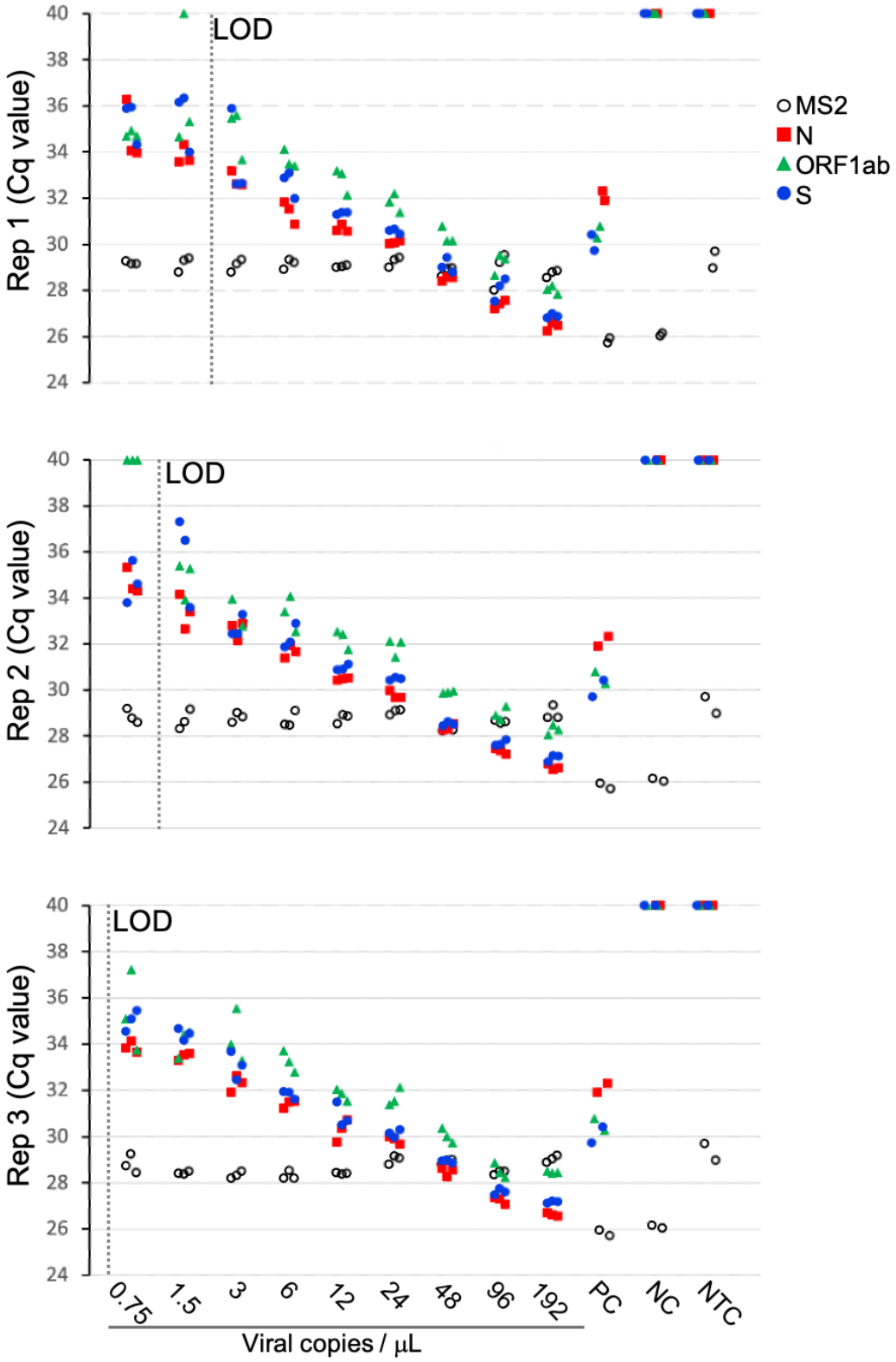



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**Figure 2:** A blinded experiment of heat-inactivated saliva samples that were either spiked with SARS-CoV-2 at 1 to 10x LOD concentrations (n=5 replicates per concentration; blinded positives) or not spiked (n=20 replicates; blinded negatives). The Cq values for the three SARS-CoV-2 specific genes (*N*, *ORF1ab* and *S*), as well as for the spike-in control gene (*MS2*), are shown. A Cq value of 40 was given to undetermined (absence of gene) results. This was the cycle number in which the reaction was stopped. Positive (PC), negative (NC) and no template (NTC) controls were included.

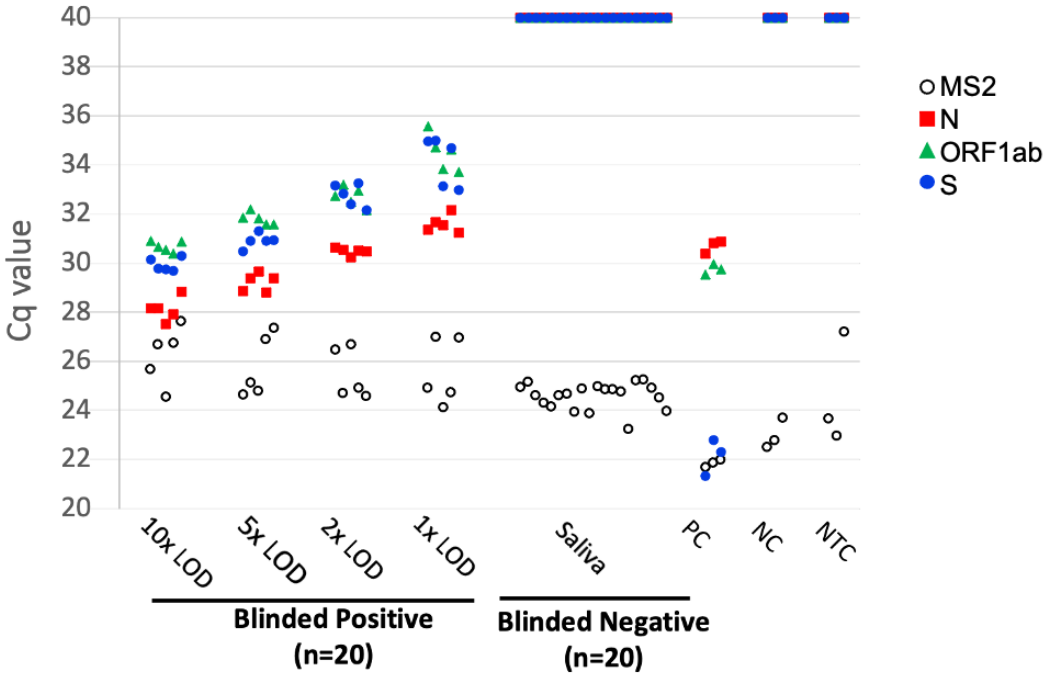
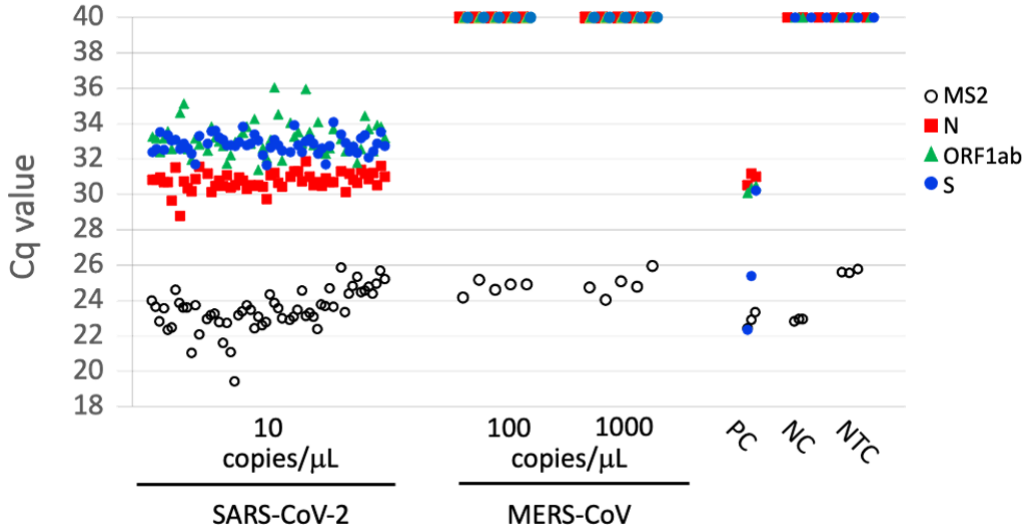



**Figure 3:** Cross-reactivity experiment where MERS-CoV spiked heat-inactivated saliva was not detected at high concentrations (n=5 replicates at 100 and 1,000 viral copies per µL), while SARS-CoV-2 spiked heat-inactivated saliva was detected in every sample (n=50 replicates at 10 viral copies per µL). The Cq values for the three SARS-CoV-2 specific genes (*N*, *ORF1ab* and *S*), as well as for the spike in control gene (*MS2*), are shown. A Cq value of 40 was given to undetermined (absence of gene) results. This was the cycle number in which the reaction was stopped. Positive (PC), negative (NC) and no template (NTC) controls were included.



(#33 re-test) by UIUC on the original sample showed all three genes as being detected and was subsequently recorded as a positive result. There was insufficient sample for repeat analyses at VUW. However, when the degraded sample was repeated by IGENZ, no genes were detected. Again, given the close concordance of all other results, the absence of detectable genes was attributed to deterioration of the sample over time of storage and during transportation (>4 months).

An additional 20 non-paired saliva samples (N=10 positive and N=10 negative) were also tested and exhibited 100% concordance between the three laboratories (Supplementary Figure 1).

### In-use experience

To 1 September 2021, we have tested 13,304 saliva samples. Saliva viscosity that required manual pipetting only affected two specimens, both from the same participant. No sample exhibited assay inhibition.

## Discussion

This study is the first to diagnostically validate a saliva test for SARS-CoV-2 in Aotearoa New Zealand. It used real-world paired saliva and NP samples from COVID-19 infected individuals, some of whom were exhibiting symptoms of COVID-19 infection (others were asymptomatic). Previous reports of sensitivities of SARS-CoV-2 detection in saliva are shown to be variable while specificity has been more consistent.[15] This emphasises the need for strict collection protocols and well-validated tests. The sensitivity (97.0%), specificity (99.1%) and accuracy (99.1%) of this UIUC saliva RT-qPCR test are very high, with the 98.6% concordance with NP and mid-turbinate specimens in all three laboratories. False-negative or false-positive results were not a test performance issue. The one positive saliva sample that was associated with a negative NP specimen suggests a difference in the timings of viral infection at the two anatomical sites during early or late disease. Overall, these results revealed the UIUC saliva RT-qPCR test to be a highly reproducible method for SARS-CoV-2 detection in both New Zealand laboratories. Moreover, the analytical validation using spiked saliva also exhibited a high sensitivity and specificity, as well as a lower LOD than that of another local NP qPCR assay reported recently (<2 versus ~10 copies per reaction, respectively).[16] The correlation of the Cq values for the three SARS-CoV-2 genes tested in each sample independently between the three laboratories was extremely high. This is particularly encouraging given the time between sample collection in the USA and processing in the New Zealand laboratories.

**Table 1:** Nasal Swab PCR as the reference test versus the saliva test.

| | **Reference nasal swab (nasopharyngeal and mid-turbinate)** | | |
|---|---|---|---|
| **UIUC saliva** | **Positive** | **Negative** | **Total** |
| Positive | 32 | 1 | 33 |
| Negative | 1 | 113 | 114 |
| Total | 33 | 114 | 147 |

**Table 2:** Diagnostic statistics for nasal swab PCR as the reference test versus the saliva test. The accuracy was calculated using a population prevalence of 0.74%, as estimated in MIQ.[14]

| **Statistic** | **Value (nasopharyngeal and mid-turbinate)** |
|---|---|
| Sensitivity | 97.0% (95% CI 84.2–99.9%) |
| Specificity | 99.1% (95% CI 95.2–100%) |
| Accuracy (prevalence 0.74%) | 99.1% (95% CI 95.9–100%) |
| Concordance | 98.6% |

**Table 3:** Concordance of Cq values of 34 positive SARS-CoV-2 saliva samples analysed independently in two New Zealand laboratories (Victoria University of Wellington (VUW) and IGENZ) and one US laboratory (UIUC) in blind experiments. Saliva samples were processed immediately after collection at UIUC but 4–6 months later in the New Zealand laboratories. A dash indicates data omission due to assumed sample degradation. A blank entry denotes that the sample was not re-tested in that laboratory due to lack of sample volume. All samples had paired nasal swabs (nasopharyngeal NP, or mid-turbinate MT) as listed, and all but one nasal sample were called positive. (Pos = Positive, Neg = Negative, Indet = Indeterminate). Asterisk indicates a discordant result between the nasal and saliva sample.

| Sample # | Nasal swab result NP/MT | Blinded saliva samples between three laboratories (Cq values) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *N* gene | | | *ORF1ab* gene | | | *S* gene | | | Final saliva result |
| | | VUW | IGENZ | UIUC | VUW | IGENZ | UIUC | VUW | IGENZ | UIUC | |
| 1 | Pos$^{NP}$ | 22.6 | 23.3 | 22.0 | 24.7 | 24.1 | 22.8 | 23.9 | 24.4 | 22.1 | Pos |
| 2 | Pos$^{NP}$ | 24.8 | 25.3 | 23.6 | 27.4 | 26.7 | 24.8 | 26.9 | 27.1 | 24.3 | Pos |
| 3 | Pos$^{NP}$ | 36.0 | - | 33.5 | 36.3 | - | 35.6 | 38.8 | - | 38.4 | Pos |
| 4 | Pos$^{NP}$ | 19.8 | 20.1 | 19.8 | 21.2 | 22.2 | 20.8 | 21.3 | 21.5 | 21.3 | Pos |
| 5 | Pos$^{NP}$ | 34.4 | 31.5 | 31.9 | 36.5 | 35.6 | 32.4 | 37.0 | 35.4 | 33.9 | Pos |
| 6 | Pos$^{NP}$ | 32.5 | - | 36.5 | >39 | - | 37.7 | 31.2 | - | 35.9 | Pos |
| 7 | Pos$^{NP}$ | 29.4 | 28.5 | 27.0 | 32.8 | 31.0 | 29.3 | 33.0 | 31.8 | 28.4 | Pos |
| 8 | Pos$^{NP}$ | 31.7 | 31.2 | 31.0 | 35.0 | 33.3 | 34.0 | >39 | 33.2 | 32.6 | Pos |
| 9 | Pos$^{NP}$ | 33.7 | 34.4 | 32.5 | >39 | 37.3 | 36.4 | 35.5 | >39 | 34.3 | Pos |
| 10 | Pos$^{NP}$ | 27.9 | 27.1 | 25.3 | 29.7 | 28.6 | 26.7 | 29.5 | 28.4 | 26.9 | Pos |
| 11 | Pos$^{NP}$ | 28.2 | 27.9 | 26.7 | 29.8 | 30.0 | 28.4 | 29.9 | 30.2 | 28.8 | Pos |
| 12 | Pos$^{NP}$ | 24.1 | 25.0 | 24.0 | 26.0 | 26.2 | 24.5 | 25.6 | 26.6 | 24.6 | Pos |
| 13 | Pos$^{NP}$ | 29.7 | 29.5 | 29.3 | 32.4 | 31.4 | 29.7 | 31.5 | 31.2 | 29.9 | Pos |
| 14 | Pos$^{NP}$ | 27.1 | 27.9 | 26.9 | 28.7 | 30.3 | 27.7 | 28.7 | 29.2 | 27.7 | Pos |
| 15 | Pos$^{NP}$ | 30.0 | 30.5 | 28.8 | 33.3 | 32.4 | 30.2 | 31.2 | 31.3 | 29.5 | Pos |
| 16 | Pos$^{NP}$ | 24.5 | 24.8 | 24.3 | 28.0 | 28.5 | 26.3 | 26.9 | 27.4 | 25.9 | Pos |
| 17 | Pos$^{NP}$ | 25.6 | 26.1 | 25.3 | 27.0 | 27.4 | 26.3 | 27.1 | 27.6 | 26.6 | Pos |
| 18 | Pos$^{NP}$ | 25.4 | 26.3 | 26.4 | 27.5 | 28.4 | 27.7 | 28.3 | 29.1 | 28.1 | Pos |
| 19 | Pos$^{NP}$ | 28.2 | 26.4 | 26.2 | 31.3 | 28.5 | 27.6 | 31.8 | 27.6 | 28.8 | Pos |
| 20 | Pos$^{NP}$ | 26.6 | 26.7 | 25.3 | 28.9 | 28.8 | 26.7 | 28.4 | 28.6 | 26.3 | Pos |
| 21 | Pos$^{NP}$ | 26.8 | 27.2 | 26.4 | 28.5 | 29.2 | 27.7 | 29.4 | 28.7 | 28.0 | Pos |
| 22 | Pos$^{NP}$ | 24.4 | 24.7 | 24.4 | 26.4 | 26.4 | 25.0 | 25.9 | 26.3 | 25.0 | Pos |
| 23 | Pos$^{NP}$ | 21.5 | 22.0 | 21.8 | 23.0 | 23.4 | 22.3 | 22.5 | 23.3 | 22.4 | Pos |
| 24 | Pos$^{NP}$ | 21.7 | 22.1 | 22.0 | 24.1 | 23.7 | 23.2 | 24.1 | 23.0 | 23.8 | Pos |
| 25 | Pos$^{NP}$ | 30.9 | 28.6 | 32.8 | 33.9 | 31.7 | 34.9 | 34.8 | 30.7 | 35.0 | Pos |

**Table 3:** Concordance of Cq values of 34 positive SARS-CoV-2 saliva samples analysed independently in two New Zealand laboratories (Victoria University of Wellington (VUW) and IGENZ) and one US laboratory (UIUC) in blind experiments. Saliva samples were processed immediately after collection at UIUC but 4–6 months later in the New Zealand laboratories. A dash indicates data omission due to assumed sample degradation. A blank entry denotes that the sample was not re-tested in that laboratory due to lack of sample volume. All samples had paired nasal swabs (nasopharyngeal NP, or mid-turbinate MT) as listed, and all but one nasal sample were called positive. (Pos = Positive, Neg = Negative, Indet = Indeterminate). Asterisk indicates a discordant result between the nasal and saliva sample (continued).

| Sample # | Nasal swab result NP/MT | Blinded saliva samples between three laboratories (Cq values) | | | | | | | | | Final saliva result |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *N* gene | | | *ORF1ab* gene | | | *S* gene | | | |
| | | VUW | IGENZ | UIUC | VUW | IGENZ | UIUC | VUW | IGENZ | UIUC | |
| 26 | Pos$^{NP}$ | 25.8 | 26.5 | 25.8 | 28.0 | 28.6 | 27.0 | 27.7 | 28.4 | 27.2 | Pos |
| 27 | Pos$^{MT}$ | 32.1 | 31.7 | 30.8 | 34.3 | 34.7 | 32.1 | 36.4 | 34.6 | 33.1 | Pos |
| 28 | Pos$^{MT}$ | 26.7 | 27.3 | 27.0 | 28.0 | 28.2 | 27.5 | 28.7 | 29.0 | 28.5 | Pos |
| 29 | Pos$^{MT}$ | 24.3 | 24.3 | 24.1 | 26.6 | 25.4 | 24.7 | 25.6 | 24.7 | 25.1 | Pos |
| 30 | Pos$^{MT}$ | 29.2 | 29.9 | 28.1 | 31.3 | 31.0 | 28.9 | 32.1 | 31.6 | 29.6 | Pos |
| 31 | Pos$^{MT}$ | 35.0 | 35.2 | 37.4 | 35.0 | >39 | >39 | >39 | 39.2 | 36.7 | Pos |
| 32 | Pos$^{NP}$ | >39 | >39 | >39 | >39 | >39 | >39 | >39 | >39 | >39 | Neg* |
| 33 | Pos$^{NP}$ | 35.2 | >39 | 35.6 | >39 | 37.3 | >39 | >39 | >39 | >39 | Indet |
| 33 (retest) | Pos$^{NP}$ | | >39 | 36.1 | | >39 | 35.9 | | >39 | 36.7 | Pos |
| 34 | Neg$^{NP}$ | >39 | 37.1 | 36.0 | >39 | >39 | 35.4 | >39 | >39 | 36.3 | Pos* |

The recent Simpson–Roche report on the country's COVID-19 testing strategy called for broadening the range of testing methods and recommended introducing saliva testing to increase the acceptability of testing across workforces in the community.[17] The availability of such an accurate saliva assay for selected testing situations, such as workplace testing, would significantly compliment the current NP testing used for New Zealand's public health response. The low LOD, as well as the inclusion of samples from asymptomatic individuals, confirms that this assay can detect infection in asymptomatic and symptomatic people. Early detection enables individuals to be isolated quickly, reducing the risk of transmission.

It should be emphasised that, in addition to the specific RT-qPCR test being used, appropriate saliva collection and preparation procedures are essential.[11] This is important due to varying sample viscosity, which if not mitigated can make aliquoting difficult, particularly when using robotic equipment. Moreover, those undertaking saliva testing need instructions on adequate hydration and the need to abstain from food or drink, other than water, for an hour before sample collection. Additionally, there have been concerns about exogenous substances causing assay inhibition. However, the testing of several candidate substances, including nasal spray, different mouth lozenges, nicotine and mouthwash, revealed that only toothpaste (and in only one of three samples) was associated with saliva assay inhibition.[12] This is supported by our experience, as after providing detailed collection instructions and compliance, we have yet to encounter saliva samples where the PCR reaction has been inhibited.

This study does have limitations. At the time that this study was performed, there was no community transmission of SARS-CoV-2 in Aotearoa New Zealand. Therefore, it was impossible to obtain locally collected samples. Diagnostic validation using paired contemporaneously collected samples was essential to enable diagnostic validation of this test. This was required as part of IGENZ accreditation to ISO 15189 standards by International Accreditation New Zealand. Collaboration with UIUC enabled this validation study to take place. Although the number of positive pairs was limited, it was similar to many other studies.[15] We acknowledge that an increased number of positive pairs would enable greater understanding of variation between the two sample sites. The high analytical sensitivity and concordance, particularly with the NP samples, are specific to this assay and its sample preparation methods and cannot be taken as an indication of other assays' performance. Saliva samples were obtained after comprehensive advice on hydration and avoiding food and drink. Assay performance may not be the same if collection advice is not followed.

Saliva is likely to participate in SARS-CoV-2 transmission due to the virus replicating in oral epithelial and salivary gland cells.[18] As saliva contains large numbers of oral epithelial cells, the detection of SARS-CoV-2 in this specimen is indicative of local virus production and does not rely on the virus passing through the oropharynx from the nasopharynx. Different replication rates at either site may result in a sample from one being positive when the other site is negative.[1,19,20] Moreover, there is emerging evidence that breakthrough infections in some people vaccinated with the Janssen Ad26.COV2.S COVID-19 and Pfizer/BioNTech vaccines elicit tissue compartmentalisation, whereby SARS-CoV-2 is detectable only in saliva and not in the nasal passages.[21] Our results support this disparity in viral load between tissue sites, but prospective studies are required to understand how frequently this occurs and how it impacts on diagnostic test performance.

Supply-chain issues, in particular the reagents and consumables required for RNA extraction, have hampered the testing of NP samples during the pandemic. The UIUC protocol bypasses the RNA extraction step and, in doing so, removes the supply-chain issues associated with this step. Furthermore, self-collection of saliva samples reduces the need for health professionals at collection sites and the heat-inactivation step reduces the risk of exposure to medical laboratory workers.

The country has now completed more than three million NP tests,[22] which is similar to the number of saliva tests conducted at UIUC.[23] SARS-CoV-2 testing used for our public health response needs to be scalable overnight, from the baseline

testing of ~3,000–5,000 per day to more than 30,000 per day during possible community outbreaks.[22] This responsiveness has been achieved using the NP test. The NP swab remains the choice of the Ministry of Health for routine public health testing. However, a role for saliva testing in situations where high-frequency testing is required is now accepted.[24] This saliva test is also highly scalable and over 10,000 samples could be processed in one diagnostic laboratory in a single day.

# Conclusions

The UIUC RT-qPCR has been tested locally and has been found to be an assay with high analytical and diagnostic sensitivity. It showed 99.1% accuracy and 98.1% concordance to that of nasal swabs in all three independent laboratories. In-use experience to date has not encountered either aliquoting problems or inhibited reactions. As a non-invasive test, it has significant appeal where high-frequency testing is required.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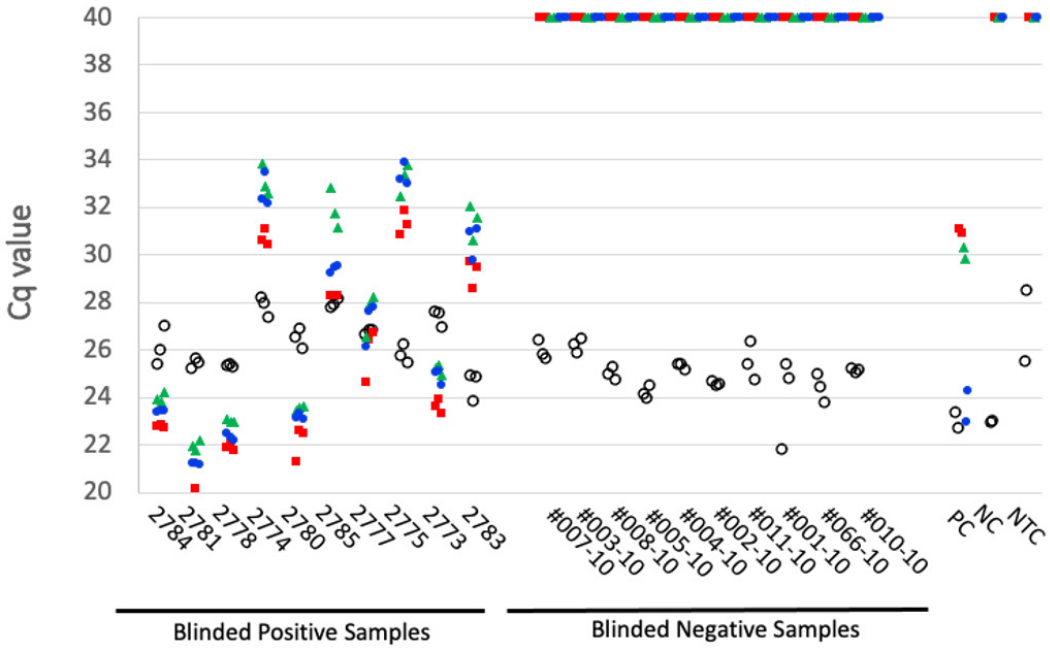
# Supplementary Material

**Supplementary Figure 1:** Twenty saliva samples (10 positive and 10 negative) processed blind in triplicate by both New Zealand laboratories (data for Victoria University of Wellington shown) demonstrated 100% concordance with UIUC saliva results. Positive (PC), negative (NC) and no template (NTC) controls were included.



**Competing interests:**
Dr Walsh reports grants from National Institutes for Health (NIBIB) and from the Rockefeller Foundation during the conduct of the study. He also reports that he is on the Board of Managers for SHIELD T3, an LLC whose mission is to provide SARS-CoV-2 tests based upon the technology described in this manuscript, and that he oversees SHIELD Illinois, a group within the University of Illinois that provides SARS-CoV-2 testing across the state of Illinois based upon the technology described in this manuscript. His remuneration is not supplemented by either the SHIELD T3 or SHIELD Illinois activities. Dr Pitman reports other from Rako Science during the conduct of the study. Dr Dixon-McIver reports other from Rako Science outside the submitted work. Dr Morris reports other from IGENZ outside the submitted work. Dr Grice reports personal fees from Rako Science outside the submitted work, and that Rako Science has licensed trade secrets related to the covidSHIELD protocol. Dr Wang reports they have a patent saliva-based molecular testing for SARS-CoV-2 pending to Diana Rose E Ranoa, Robin L Holland, Fadi G Alnaji, Kelsie J Green, Leyi Wang, Christopher B Brooke, Martin D Burke, Timothy M Fan, Paul J Hergenrother.

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# Patient perspectives on the use of health information

Rosie Dobson, Robyn Whittaker, Helen Wihongi, Penny Andrew, Delwyn Armstrong, Karen Bartholomew, Andrew Sporle, Susan Wells


## ABSTRACT

**BACKGROUND:** The digitalisation of health records generates significant individual-level data that hold great potential for research and practice. However, it remains unclear how healthcare consumers in Aotearoa New Zealand feel about the use of their health information beyond their own care. Understanding how patients want their own health information accessed/used by others is vital to ensure health services and researchers use data in a patient-informed manner.

**AIM:** This survey aimed to investigate patient perspectives, including preferences, needs and concerns, on the use of, and access to, individual healthcare information.

**METHOD:** A mixed-methods cross-sectional survey of adult patients (n=1,377) in Waitematā District Health Board inpatient and outpatient services during November–December 2020. The survey was online and on paper and available in 10 languages.

**RESULTS:** Over 80% of participants were comfortable with their health information being used across the scenarios presented (range: 81–89%). Māori were significantly more likely than non-Māori to be comfortable with their health information being combined with the health information of others to better understand population needs (p=0.006). The level of comfort with the use of individual health information was related to assurances that its use was for public good, data were stored securely, individual privacy was maintained, the information was accurate and there was communication on how it was used.

**DISCUSSION:** This study has shown that most healthcare consumers are comfortable with the health service using their de-identified health information beyond their care if it benefits others.


The digitalisation of health services around the world has made patient health information more accessible for secondary uses. There is significant potential for the use of this information to improve services and health outcomes, and therefore the demand for access to this information is growing. Internationally, studies have shown widespread public support for secondary uses of health information as long as it is for "the greater good" or public benefit.[1–3] Trustworthiness, privacy and data security are key themes in public surveys, and individual consent is acknowledged as not always being necessary.[1,4] Concerns have centred on misuse of data and the potential for harm as a result, alongside potential commercial gain.[4,5] In general, there is a call for more transparency,[6–9] accountability to protect against data misuse[6–7] and public engagement and communication with consumers.[1,4,10]

In Aotearoa New Zealand, many of these issues are considered in the National Ethical Standards for Health and Disability Research and Quality Improvement,[11] including Māori data sovereignty.[12] Moving towards more insights from accessible health and social data to support not just health service delivery, but also policy development, research and service planning, is included in the Ministry of Health's Digital Health Strategic Framework[13] and Hira, the national health information platform.[14]

Over the past six years Waitematā District Health Board (DHB) has been incrementally introducing new electronic health information systems across its two hospitals (Waitakere and North Shore). The Leapfrog Programme has intentionally been moving towards a more digital and mobile system that supports good clinical workflow and ensures that necessary information is available at the point of care to support good patient outcomes and experience.[15] One of the outcomes of these developments has been the large increase in the amount

of electronic health information available for uses such as service review and quality improvement, future service planning and potentially for research. These initiatives are more easily conducted, and much more granular and useful, when the information can be electronically linked (across different IT solutions) and presented to services and clinicians in usable formats (eg, interrogatable dashboards and graphs).

What is not clear is how New Zealanders feel about the use of their health information beyond their immediate healthcare, or whether people are aware that service and population-level activities may be using their health information to inform improvements in health services and future service planning. Although one early study in the New Zealand primary care setting highlighted hesitancy in the secondary use of personal health information beyond individual care,[16] that study was conducted prior to the widespread digitalisation of health services. More recent work exploring perspectives on the use of individual data in New Zealand has mainly focused on the general public's views outside the health service setting.[17–19]

Globally, machine-learning techniques and artificial-intelligence-derived algorithms are being developed based on large electronic health datasets that can predict health outcomes after treatment or procedures,[20–21] support clinical decision-making (eg, identify early signs of sepsis)[22–24] and identify abnormalities in images (eg, retinal screening).[25–28] There is growing interest to use patient health information for these purposes in New Zealand.[29–31] To determine whether such methods could be useful in New Zealand clinical practice, they must be tested on large electronic databases of New Zealanders' health information. Such uses need to be weighed against the potential risks and the concerns of our population, such as those around the security and confidentiality of the information and the risk of perpetuating biases in historical practices due to the quality and incompleteness of existing data.

Understanding how patients want their own health information accessed and used is vital to ensure health services use health information in an appropriate and patient-informed manner. This project aims to investigate perspectives on the use of, and access to, individual healthcare information in people currently engaged with the Waitematā DHB hospital services collecting this information. Specific objectives include to investigate:

- perceptions on how health information is currently used by health services
- preferences on the use of health information, including level of comfort with health information being used in different ways
- concerns around use of health information for different purposes.

# Method

A descriptive cross-sectional survey was conducted with current patients of Waitematā DHB health services. The description of the survey is described according to the CHERRIES checklist (Supplementary Material 1).[32]

## Survey design

A study advisory group was established to help decide on the study procedures and survey questions. This group included representation from health service consumers as well as experts from a range of settings, including Waitematā DHB (clinicians, funding and planning, Māori Health, innovation), primary care and the University of Auckland. Following the drafting of the questions by the advisory group, the questions were pre-tested in an interview format with a small number of members of the target population. The English-language survey was then refined based on the pre-testing and finalised. The survey was designed in paper format and uploaded into an electronic format on the DHB platform before being loaded onto tablets for administration.

The survey covered the following:

- introduction and definitions
- perceptions on how health information is currently used by health services
- level of comfort with health information being used in different ways
- situations where permission is needed before individual health information is combined with others

- concerns about how health information used
- demographics.

The survey incorporated both closed and open-ended questions to gain more in-depth information and allow participants to elaborate further. The survey was then further pre-tested by researchers, members of the study advisory group and young people. The final survey was further translated into nine other common languages in the DHB population: te reo Māori, Samoan, Tongan, Simplified Chinese, Traditional Chinese, Tagalog, Hindi, Japanese and Korean.

The survey was identical for all participants (no randomised items), and participants were able to go back and change their responses before submission. Adaptive questioning was used where appropriate to minimise response burden and reduce the complexity of questions. There was a total of 12 questions over four pages in the final online survey. Individual questions were not mandatory.

## Ethics approval

Ethical approval for this study was obtained from the New Zealand Health and Disability Ethics Committee (20/NTA/2). Research approval from Waitematā DHB was obtained.

## Inclusion criteria

The intention of the survey was to be broadly representative of adult patients of the DHB (both admitted to hospital and those attending clinics). By recruiting participants at the time of an encounter with the DHB, we considered that patients would have some understanding of the nature of the health information collected and the uses of such information in their current context. Inclusion criteria were: (1) current user of Waitematā DHB inpatient and outpatient services, (2) 16 years old or over and (3) able to provide consent to participate. Exclusion criteria included being too unwell (as deemed by the patients' healthcare professional), patients in the acute mental health unit and paediatric patients and their families.

## Procedures

All patients who fit the inclusion criteria were eligible to participate. Potential participants were recruited from hospital wards, outpatient clinics and DHB health clinics in the community. Patients were invited to participate by DHB staff (eg, ward nurses, clinic reception staff) or DHB interns or volunteers and provided with a tablet to complete the survey on. Paper copies of the survey were also available upon request. Those attending outpatient appointments, including telehealth, were emailed the link to the survey after their appointment, through the standard DHB processes, to complete at their own convenience. If a patient wanted assistance to complete the survey, a trained team member was made available to assist them with completing it either in person in the clinic/ward or over the phone. Surveys completed by phone or on paper were entered into the online version of the survey by a member of the research team. Participants could choose to complete the survey in any of the ten languages, and a sign-language interpreter was available to assist patients with hearing difficulties if needed. Trained team members were available to support visually impaired patients to complete the survey.

Before commencing the survey, participants were provided with information about the study and details of who to contact if they had questions. They were also asked to provide consent before being given access to complete the survey. Participation was entirely voluntary and there was no incentive provided for participation.

## Statistical analysis

Survey data were analysed and summarised using descriptive quantitative analyses. Chi-square tests were used to assess differences between groups. All statistical tests were two sided at a 5% significance level. Qualitative comments were analysed using a simple general inductive thematic approach to identify common themes and meanings from the data.[33] Only completed surveys, with correct unique IDs, were included in the analysis and no time limit was imposed. Cookies were not used to assign identifiers to each computer, and IP address information was not available. Therefore, checks for multiple entries from the same individual were performed manually by looking for identical survey responses in the qualitative data. Ethnically congruent researchers translated qualitative data from surveys completed in non-English languages before analysis. Ethnicity

was coded as per New Zealand Ministry of Health's protocol for the reporting of ethnicity data, with the "total response (overlapping)" output method used for reporting in this paper.[34]

# Results

A total of 1,379 people completed the survey between 18 November and 23 December 2020. Two surveys were identified as duplicates and excluded. Therefore, the final sample size was 1,377. Due to the survey being available in different formats across multiple settings, the view and completion rates are unknown. Only 150 (10.9%) participants chose to complete the survey in paper form, with the remainder completing it online. A total of 52 participants (3.7%) completed the survey in languages other than English (Chinese=14, Korean=11, Hindi=10, Samoan=7, Tagalog=5, Japanese=3, Tongan=2)

## Demographic information

The demographic breakdown of respondents can be seen in Table 1.

The proportion of participants identifying as Māori and Pacific in the current study (12% and 8% respectively) was higher than in the estimated total Waitematā DHB population (9% and 7% respectively). In contrast, the proportion identifying as Asian (14%) was lower than in the estimated total Waitematā DHB population (26%). Although the survey sample included adults from ages 16 to 95 years, comparatively fewer participants were aged 45 years or younger than might be expected given the estimated proportion of the total Waitematā DHB population (51.4%).

## Current use of health information

Participants were asked what they thought the health service was currently using their health information for in relation to their current (or most recent) visit. Many participants reported that they thought the DHB was using their health information in the ways presented (range: 67–92%) (Table 2). A total of 53% (n=728) participants responded "Yes" to all items. When referring to scenarios relating to combining health information with others (Scenarios E and F), over 20% of participants reported that they were unsure whether the health service was already doing this.

## Comfort with use of health information

Next, participants were asked to rate their level of comfort with the DHB using their health information across the different scenarios on a Likert scale from 1 (very uncomfortable) to 5 (very comfortable). Results can be seen in Table 3.

Over two-thirds (69%; n=953) of participants were comfortable across all items presented, and only 3% (n=43) were uncomfortable across all items.

The proportion of Māori participants who were uncomfortable with their information being used to make decisions about their healthcare in the future was significantly lower than the proportion of non-Māori who were uncomfortable with this: $\chi^2$ (2, N=1,377) = 7.73, p=0.021. Similarly, the proportion of Māori participants who were comfortable with Scenario F (their information being used to investigate how better to understand our population and their needs) was significantly higher than the proportion of non-Māori who were comfortable with this: $\chi^2$ (2,N=1,377) = 10.33, p=0.006.

Five percent of participants (n=68) were uncomfortable (ratings = 1 or 2) across both items relating to the combining of their health information with the information of others. The proportion of Māori participants who were uncomfortable with the combining of their health information (1.8%) was significantly lower than the proportion of non-Māori who were uncomfortable (5.4%): $X^2$ (1, N=1,377) = 3.83, p=0.050. Furthermore, 3% of participants (n=45) were very uncomfortable (ratings = 1) with the combining of their health information. The proportion of Māori participants who were very uncomfortable with the combining of their health information (0.6%) was significantly lower than the proportion of non-Māori who were very uncomfortable (3.6%): $X^2$ (1, N=1,377) = 4.16, p=0.041.

A total of 285 participants provided comments on their level of comfort, with 129 (45%) of these responses primarily reiterating that they were comfortable and happy with data being shared in the ways outlined.

Seven key themes in the responses were identified. The most common theme was

**Table 1:** Demographics of respondents (n=1,377).

| | n | % |
|---|---|---|
| **Age group** | | |
| 16–24 | 51 | 4% |
| 25–34 | 118 | 9% |
| 35–44 | 144 | 11% |
| 45–54 | 211 | 15% |
| 55–64 | 242 | 18% |
| 65–74 | 339 | 25% |
| ≥75 | 255 | 19% |
| Did not answer | 16 | 1% |
| Response invalid | 1 | 0% |
| **Age (Mean (SD), range)** | 58.78 (17.64) | 16-95 |
| **Gender** | | |
| Male | 593 | 43% |
| Female | 759 | 55% |
| Another gender | 12 | 1% |
| Did not answer | 13 | 1% |
| **Ethnicity**[1] | | |
| NZ European | 878 | 64% |
| Māori | 164 | 12% |
| Pacific peoples | 106 | 8% |
| Asian | 186 | 14% |
| MELAA | 15 | 1% |
| Other European | 105 | 8% |
| Other ethnicity | 15 | 1% |
| Residual categories | 20 | 2% |
| **Māori descent** | | |
| Yes | 190 | 14% |
| No | 1,125 | 82% |
| Don’t know | 21 | 2% |
| Did not answer | 41 | 3% |

**Table 1:** Demographics of respondents (n=1,377) (continued).

| | n | % |
|---|---|---|
| **New migrant**[2] | 103 | 8% |
| **Locality** | | |
| Rural | 175 | 13% |
| Urban | 1,158 | 84% |
| Did not answer | 40 | 3% |
| Response invalid | 4 | 0% |
| **Reason for encounter** | | |
| Attending a clinic appointment | 967 | 70% |
| Staying in hospital | 226 | 16% |
| A patient in the ED | 107 | 8% |
| Other | 50 | 4% |
| Did not answer | 27 | 2% |

[1]Total response output method used, therefore total exceeds 100%.

[2]Moved to New Zealand less than 10 years ago.

SD: Standard deviation; NZ: New Zealand; MELAA: Middle Eastern, Latin American, and African; ED: Emergency department.

**Table 2:** Current use of health information (n=1,377).

| Scenario | | Yes | | No | | Don't know | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % |
| A | To make decisions about your healthcare now | 1,264 | 92% | 53 | 4% | 60 | 4% |
| B | To make decisions about your healthcare in the future | 1,211 | 88% | 60 | 4% | 106 | 8% |
| C | To share with other health professionals involved in your care in this organisation | 1,206 | 88% | 46 | 3% | 125 | 9% |
| D | To share with other health professionals involved in your care in other organisations (eg, your GP, a private hospital, a hospital in another city) | 1,252 | 91% | 46 | 3% | 79 | 6% |
| E | To make decisions about improving this health service (eg, combining health information from lots of people to inform and improve the care for other patients using this service in the future) | 989 | 72% | 87 | 6% | 301 | 22% |
| F | To investigate how better to understand our population and their needs by combining information on our whole population to look at trends (eg, how the COVID-19 numbers were presented for different regions across the country) and to see where the needs are greatest (eg, to identify rest homes that needed help with COVID-19) | 926 | 67% | 82 | 6% | 369 | 27% |

GP: General practitioner.

**Table 3:** Rating of comfort for use of health information (n=1,377).

| Scenario | | Uncomfortable (1 or 2) | | Neutral (3) | | Comfortable (4 or 5) | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % |
| A | To make decisions about your healthcare now | 70 | 5% | 89 | 7% | 1,218 | 89% |
| B | To make decisions about your healthcare in the future | 77 | 6% | 83 | 6% | 1,217 | 88% |
| B | To share with other health professionals involved in your care in this organisation | 72 | 5% | 79 | 6% | 1,226 | 89% |
| D | To share with other health professionals involved in your care in other organisations (eg, your GP, a private hospital, a hospital in another city) | 78 | 6% | 74 | 5% | 1,225 | 89% |
| E | To make decisions about improving this health service (eg, combining health information from lots of people to inform and improve the care for other patients using this service in the future) | 80 | 6% | 146 | 11% | 1,151 | 84% |
| F | To investigate how better to understand our population and their needs by combining information on our whole population to look at trends (eg, how the COVID-19 numbers were presented for different regions across the country) and to see where the needs are greatest (eg, to identify rest homes that needed help with COVID-19) | 104 | 8% | 165 | 12% | 1,109 | 81% |
| G | To continue to help others even once you have died or have moved out of our district where your information continues to be useful and contributes to the full picture for (e) and (f) above. This is because removing health information of people can give us an incorrect or incomplete picture of what happened. | 113 | 8% | 147 | 11% | 1,117 | 81% |

GP: General practitioner.

that participants were happy with their data being used in ways that would help other people.

> *"Totally comfortable with the ways health information is used if it is used to benefit myself or someone in a similar situation as myself." – Female, 55–64 years, Pacific*

The second theme was that participants' level of comfort was linked to assurances that their privacy was maintained, that data were shared confidentially and that data shared beyond individual care were de-identified.

> *"As long as personal information is kept private and not shared in any form so identity is given then sharing info is fine. It needs to be stored in a manner where it can't be hacked or accessed by external sources when shared." – Female, 35–44 years, Māori*

The next theme was that participants wanted their health information to be used for the purpose it was intended for and that it remained in the health system (eg, was not shared with commercial companies (including insurance companies) or sold for advertising).

> *"As long as personal info is used only by legitimate parties—no buying my data for advertising." – Female, 25–34 years, NZ European*

> *"I wouldn't like my information to go out to other corporate bodies. I wouldn't like my information getting out and being used in the wrong way." – Male, 65–74 years, NZ European*

Another theme was that health information needs to be up to date and correct and that patients should have access to it and the ability to correct it.

> *"As long as my confidentiality is protected and not shared to insurance or other marginal stakeholders without my permission I am fine. However, I should be able to access all my information and correct any misinformation." – Female, 45–54 years, NZ European*

> *"It would be nice to have access to the same information being shared with others." – Male, 55–64 years, NZ European*

The next theme was that there was a lack of knowledge of how health information was used and that there needed to be improved communication about how it is being used and shared.

> *"I have never been advised by any health professionals of how my information is being used or why!!" – Female, 65–74 years, Māori*

> *"It is not possible to 'feel comfortable' when I do not know now how my health information is used, nor where I can find out" – Female, 65–74 years, NZ European*

A small group of participants commented that, for them to be comfortable, they needed to be asked permission before their data were shared or used outside their immediate care.

> *"I'd like to know before my information is shared so that I can give consent. I'm happy for my information to be used once I've moved out of the district or died if the data didn't include identifiable details (name, DOB, address)." – Female, 35–44 years, NZ European*

Finally, a small group of participants reported feeling uncomfortable with the sharing of their health information due to negative experiences and/or a lack of trust in the DHB.

> *"Due to serious inaccuracies in all of my recent clinic letters this year after accessing the [service name] at [hospital name] I am not comfortable with this information to be used to make decisions on my care and/or being shared with say my GP due to these inaccuracies." – Female, 35–44 years, NZ European*

## Permission for the combining of health information

Participants were asked whether there were any situations where they would want the DHB to get their permission before combining their data with other people's to understand the health of the wider population better. A total of 978 (71%) answered this question. The majority (758; 78%) responded that permission was not needed before health information is combined with others if:

1. their privacy is maintained (data are anonymous and no personal/identifying information is shared)
2. it is done so with the correct approvals
3. privacy/security of the data is maintained
4. it is done for the right reason (eg, to benefit others)

A total of 130 (13%) participants stated that permission must be sought in some situations. The specific situations described included:

1. when health information was being sent outside the medical profession or made public (eg, police, insurance, commercial companies, big tech/pharma)
2. when the health information was of a sensitive nature (eg, drug use, sexual history, domestic violence, gynaecology and women's health, rape/sexual assault, hereditary conditions, terminal illness, mental health, genetic/DNA information).

There were only 31 responses that indicated that participants wanted to be asked permission every time their health information was combined with others. A remaining 26 responses indicated that they were unsure, and 33 were unidentifiable or non-specific.

Twenty-three responses highlighted the importance of people being informed about when their data will be (has been) used irrespective of whether permission was required/wanted. Responses also stated that results/findings from sharing health information should be communicated to patients or made public.

### Concerns with the use of health information

Finally, participants were asked whether they had any further concerns about how the DHB looks after or uses their health information. Of the 956 that answered this question, 699 (73%) reported they had no concerns. From the 257 remaining comments, there were five main areas of concern identified:

1. concerns about cybersecurity and how data is stored
2. concerns about privacy and confidentiality of health information and that this needs to be assured to patients if health information is to be shared
3. concerns about incorrect information and that health information needs to be up to date and that patients have a way to correct their information if there are inaccuracies
4. that they should have access to all of their health information, including the health information that is being shared
5. that there is a lack of information being provided to patients on how health information is used and that the DHB needs to inform people how their data are used and stored.

## Discussion

This study found that most participants (current users of hospital and clinic services in Waitematā DHB) are comfortable with their health information being used by the health service (without additional consent) if:

- correct approvals are obtained
- privacy and security of the individual data and dataset is maintained
- the intention of the use of the health information is to benefit others.

Participants specified that there would be a need to seek individual permission for combining individual health information with others when data are of a sensitive nature or to be used outside the health sector (eg, shared with commercial organisations). Otherwise, the majority of patients in this study did not think that they needed to provide consent before their health information was combined with others. This is significant for, say, the development of artificial intelligence algorithms, where the completeness of datasets is essential to minimise bias.[35]

However, it is also clear from the responses that there is a need for more communication on how information is used, when it is used and the outcomes of its use. This includes communication about existing pathways for the use of health data without consent (ie, secondary use under the specific exemptions in the Privacy Act 2020, the Health Information Privacy Code, Section 22 of the Health Act 1956 for offer of service and the Health and Disability Ethics

Committees' waiver approvals for research). Many participants were unsure about what their health information is being used for, and if it were to be used for other purposes, they would want this to be transparent and fed back if possible.

The findings from this survey highlight that assurances around the security and privacy of health information are paramount for patients comfort in the use of their health information, which mirrors international research in this area.[1,3,36] Patients articulated concerns about cybersecurity, data storage, privacy and confidentiality of health information. It is important to note that this study was undertaken before the data breach at Waikato DHB,[37] which has resulted in a greater commitment to cybersecurity by the New Zealand health sector. It has also potentially resulted in the public having a greater awareness of the personal implications of cybersecurity threats. The health system will need to ensure ongoing communication to the public around the protective mechanisms for ensuring individuals' data are safe and that risks are minimised.

Another important message is that people want access to their own health information and the ability to correct any inaccuracies in the information. The Privacy Act 2020 and Health Information Privacy Code stipulate the right for individuals to access and request corrections to their health information stored by a health service.[38] Similar to our sample, research in a primary care setting discovered a strong interest in having access to personal health information.[39] Unlike primary care, where patient-portal use is now widespread, in secondary care, where there is not one single electronic health record, personal access to health information is difficult. With information currently held in multiple systems, the ability to correct patients' data in all systems is also more challenging. Several countries have a longer history of providing patient-accessible electronic health records than New Zealand.[40] The benefits of patient access include the opportunity to empower patients, inform patients about their health and involve patients in their own care.[41,42] However, some concerns remain around access barriers, including digital health literacy and use by those most in need, and clinician concerns around negative impacts on the patient–clinician relationship. Although much has been made of the ability for patients to correct information in their records, there is little published on the actual use and impact of patient requested amendments.[43]

This is the first study of its kind in a New Zealand hospital setting. The findings align with previous research, most of which has focused on the general public's views and the use of health information for research purposes. International literature has documented widespread public support for using health data for research under similar conditions to those we found, including the importance of its use being for the greater good and that privacy must be prioritised.[2,3] In contrast to previous work that has shown greater concern by Māori over the use of their data,[17] this study showed Māori were more comfortable with their data being combined with the health information of others. This is a potentially important finding that could inform national developments around Māori data sovereignty and health-data governance but will need to be further explored in more in-depth investigations. The concern in our sample for health information being shared with commercial companies is also consistent with previous work,[5] and the complexities associated with this warrant further investigation.

The generalisability of the findings from this cohort to the entire country's population is a potential limitation of this study. Although there was diversity in the demographics of the sample, it is possible that those who have a strong viewpoint (either positive or negative) were more likely to participate, or that, despite our efforts with translations and approaches to particular groups (including Māori, Pacific and Asian facilitators), people with greater distrust of the system, English as a second language or low health or digital literacy may have chosen not to participate. Despite this, the advisory group's perspective is that this was a relatively large and diverse sample from which to start informing further discussion and research.

A further limitation of the current study is the lack of information about the health services patients received at the time of

participation. Therefore, we cannot assess whether there was a correlation between services and views on health information use. There is the potential that recruiting patients when they were receiving health services may have resulted in more favourable results—that is, them answering the questions in the way that they perceived their health providers would prefer. To encourage patients to be honest and open in their responses to the survey, the survey was anonymous and participants could complete it after their encounter with the health service.

This initial survey has led to several further planned initiatives for the DHB and research. Findings are being presented around the DHB to continue conversations about improving communication with patients on what is currently happening with their health information, and to provide assurances around security measures, confidentiality of health information, processes for auditing access and processes for correcting health information. The Northern Region (Waitematā, Auckland, Counties Manukau and Northland DHBs) is enhancing regional data governance, to include consumers and Māori data sovereignty principles, and exploring consumers' access to their hospital-held health information.

The next phase of this research is to further explore the issues raised through in-depth interviews. We will talk with patients about potential modalities and messages for communication. We will work through possible future scenarios for the use of health information to determine how and when further communication or consent may be required. This will include the development of machine learning and artificial intelligence algorithms for New Zealand, based on our population data, and some of the intrinsic issues, such as the use of health information after death.

Importantly, major structural changes are planned for the New Zealand health system over the coming months. This will provide an opportunity to raise the public discussion around ownership of our health information within one national health system, and what we all want this to look like in the future.

## Supplementary Material

- View Supplementary Material 1: Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

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Nil.
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# An audit of nurses using standing order directives to administer medications to children at risk of contracting rheumatic fever

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## ABSTRACT

**AIM:** The following article reports an audit, conducted between July 2014 and July 2017, of adherence to best practice in medication administration and documentation by nurses.

**METHOD:** A sample of 47 registered nurses' (RNs') documentation relating to the administration of 939 medications using standing order directives were examined and scored by seven senior nurses and a medical practitioner against an audit tool. The scores were divided into four quartiles with the top two quartiles demonstrating best practice in adherence to safety standards for the administration of medication.

**RESULTS:** Forty-three RNs (91.5%) scored in the top two quartiles. The remaining four RNs (8.5%), following supervision by a senior nurse, subsequently demonstrated improvement in their documentation to the quartile one range of the audit tool. This audit demonstrates that, following education in diagnosis and treatment of common childhood conditions, the majority of nurses who were audited could diagnose simple conditions of childhood and safely administer medications to them. Moreover, two years after the programme was introduced, the serious sequelae of acute rheumatic fever (ARF) reduced in children aged 5–12 years.

**CONCLUSION:** RNs who took part in the audit used standing order directives to safely administer medications to children. RN prescribing throughout New Zealand should be explored as an effective means to provide timely treatment and improve patient outcomes.

Using standing order directives could be considered as elementary nurse prescribing. This topic has been under the spotlight in New Zealand since 2016, when the country's nursing regulatory body announced changes that allow registered nurses (RN) to prescribe from a formulary of subsidised medications.[1,2] The lowest level of nurse prescribing, whereby nurses can administer and supply medications, is by utilising standing order directives. A standing order is "a written instruction issued by a medical practitioner, dentist, nurse practitioner or optometrist. It authorises a specified person or class of people (e.g., paramedics, registered nurses) who do not have prescribing rights to administer and/or supply specified medicines."[3] Prior to 2011, when a group of diabetes nurse specialists were given prescribing rights over a very limited number of medications, the only nurses who were eligible to prescribe a wide range of drugs were registered nurse practitioners.[4] A Cochrane review of 46 international studies (37,337 participants) demonstrated that non-medical prescribers, such as nurses and pharmacists, were as effective as usual care medical prescrib-


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ers across a range of domains. An earlier systematic review of 17 empirical studies reported that non-medical prescribing was accepted and viewed positively by patients and professionals.[5,6] Concern for public protection against drug misuse resulted in governments developing medicines regulation legislation from the nineteenth century onwards, and by the twentieth century, legislation restricted prescriptive authority to a small number of occupational groups, such as medical practitioners, dentists and vets.[5] Towards the end of the twentieth century, non-medical prescribing was introduced into many Western countries. Notably, UK nurses have been prescribing for decades.[7] In the UK in 2015, over 28,000 nurses were able to prescribe the same medications as doctors, on the provision that it is within their level of experience and competence.[8] A major concern for low-income countries, and high-income countries such as New Zealand, is safe and timely access to medications for populations with acute and chronic diseases.[5] Nurses comprise the largest group of health professionals in New Zealand and are perfectly placed to prescribe medications, yet currently only 1% are registered with the Nursing Council of New Zealand (NCNZ) as nurse practitioners or nurse prescribers.[9] In New Zealand, children of Māori and Pacific descent are important populations at high risk of a serious disease, acute rheumatic fever (ARF).[10] ARF as a sequelae to group A beta haemolytic *Streptococcus* (GABHS) infection has all but disappeared in high-income countries.[11] However, in New Zealand, high rates of ARF persist among Māori and Pacific children living in lower socioeconomic areas in the North Island.[10] In response to this health issue, the New Zealand Government's Ministry of Health funded a school-based rheumatic-fever prevention programme that commenced in 2012. In one Auckland district health board, the programme was designed to utilise health teams consisting of registered nurses and health workers based in 61 primary and intermediate schools. The programme is delivered in schools that were assessed as high risk for children developing ARF based on a range of criteria, including incidence of rheumatic fever, demography and hospitalisations. The programme is named Mana Kidz.[12]

## Mana Kidz

The Mana Kidz programme comprises a network of primary health and community health organisations and is currently led by the National Hauora Coalition, a Māori primary health organisation.[12] The nurses within the health teams perform daily assessments of children presenting with sore throats, skin infections and other child health issues. Mana Kidz was first piloted in a school in South Auckland and subsequently expanded to the remaining 60 schools that were predominantly classified as decile one (most deprived) in the Counties Manukau District Health Board (CMDHB) area. By 2016, the programme had reached approximately 24,000 children aged 5–12 years, 40% of whom identified as Māori and 50% as Pacific Island.[13] The healthcare assistants within the teams provide outreach services to families to deliver medicines and address other healthcare needs of the children. RNs administer medicines under a standing order directive. The RNs in Mana Kidz undertook education that consisted of workbooks addressing the assessment and differential diagnosis of tonsillitis and skin conditions and the use of standing orders. A senior nurse educator skilled in public health and care of children and employed by Counties Manukau District Health Board facilitated these education events. Access to the Heart Foundation guidelines and algorithm for sore throat management were provided.[14] A pre- and post-intervention study examining the effect of the Mana Kidz programme illustrated a 58% reduction in the number of children developing ARF two years after implementation of the programme.[15]

The following reports an audit[16] conducted to establish the adherence of nurses' documentation to guidelines developed for the Mana Kidz programme.

## Aim

To examine the documentation of RNs against a best practice audit tool (Table 1) when standing order directives were used to supply medicines to primary and intermediate school children (5–12 years) who were at risk of ARF.

**Table 1:** Audit tool illustrating 14 statements agreed by the quality group.

| Example of medication audited | Medication cephalexin | Medication amoxicillin | Medication flucloxacillin |
|---|---|---|---|
| 1. All entries identifiable with signature and discipline or electronically identifiable | | | |
| 2. All entries dated and timed | | | |
| 3. All entries in chronological order | | | |
| 4. Clinical history documented thoroughly and accurately | | | |
| 5. Nursing Assessment documented completely and accurately | | | |
| 6. Communication with students, family and other professionals documented | | | |
| 7. Change of condition is documented | | | |
| 8. All lab results are followed up | | | |
| 9. Weight entered in database/student record | | | |
| 10. Referrals are accurately documented and followed up | | | |
| 11. Medications are administered within 24hrs of result being received * | | | |
| 12. Administration of medications is recorded (including date and person administering) | | | |
| 13. Discharge letter is complete and accurate | | | |
| 14. Adherence checks are complete | | | |
| **Totals** | | | |

# Method

Using a structured audit tool that detailed important clinical information, the notes of RNs were examined to compare information they collected on a patient management system with the information on the audit tool (Table 1). The audit tool development utilised a consensus approach, with a quality group of qualified professionals that met during 2013 to formulate the Manual of Operations and Standing Orders.[17] The group comprised two general practitioners, one nurse practitioner, one RN educator, a practice manager and a quality adviser from CMDHB. This quality group identified the need for standardisation of auditing across the programme. They reviewed the tools being used at that time and were quickly able to identify one for testing in late 2013. The change management model, Deming's Plan-Do-Study-Act (PDSA) cycle,[18] was also implemented with four versions of the tool trialled over a period of six months. The final version has been in use from July 2014. This audit comprised examining the notes against the 14 statements agreed by the quality group (Table 1). Statement 4 (line 4, Table 1), which specifically relates to assessment of a sore throat, refers to documentation of a comprehensive assessment of the child's throat for tonsillar exudate, cervical lymph nodes and temperature. These clinical signs can be formulated into the McIsaac score that was modified from the Centor score to estimate the probability of a GABHS tonsillitis.[19] Statement 8 (line 8, Table 1) refers to documenting a positive or negative throat swab result. Every child who was given antibiotics for a sore throat had a throat swab taken. This direction was stated in the standing order. Statement 9 (line 9, Table 1) refers to documentation of the child's current weight to ensure that the correct dose of antibiotic is administered. Statement 14 (line 14, Table 1) required documentation that adherence to antibiotics for a sore throat was checked at day five and day 10. Each listed medication was scored against the 14 statements as follows: complete=1, partly complete=2, not completed=3 and not applicable=1. A perfect score was 14 and the worst score possible was 42. RJ (author) issued the standing orders and reviewed all of the audits as the medical practitioner in the audit team.

## Ethics

Massey University's Human Ethics Committee granted approval for this project under a low-risk audit category due to the anonymised nature of the data.

## Sample size

Forty-seven RNs' notes were audited by seven senior nurses and a medical practitioner. The number of medications administered by these RNs using standing order directives and examined by the audit team ranged between four and ten. At the start of their employment with the Mana Kidz programme, nurses were audited every month. This frequency reduced to every three months, providing they produced satisfactory scores on the audit tool (Table 1). The number of medications audited was a pre-determined percentage of the number of medicines administered by the nurse. Figure 1 demonstrates the range of medications reviewed within each audit.

# Results

A sample of 47 RNs' documentation relating to the administration of 939 medications using standing order directives were examined and scored by seven senior nurses and a medical practitioner against the audit tool (Table 1). The scores were divided into four quartiles, with the top two quartiles demonstrating best practice in adherence to safety standards for the administration of medication. Audits were conducted between July 2014 and July 2017, and the 939 documented medications were allocated to 112 audits. Within this timeframe, some RNs were audited more than once. Figure 1 demonstrates the distribution range of medications administered by the RNs per audit, with the smallest number being two audits consisting of four medications, and the largest number of audits was 34 with eight medications. In this sample, the scores ranged between 14 and 25. For each of the 112 sets of documentation, the mean score was calculated. Mean scores were then allocated to quartiles as demonstrated in Figure 2. The highest-quality scores of between 14 and 16 were allocated to quartile 1: 91 (81%) of the sets met this standard. Seventeen sets (15%) met quartile two scores of between 17 and 19, and three sets scored in the quartile 3 range of between 20 and 22. One documentation set met the quartile 4 score.

# Discussion

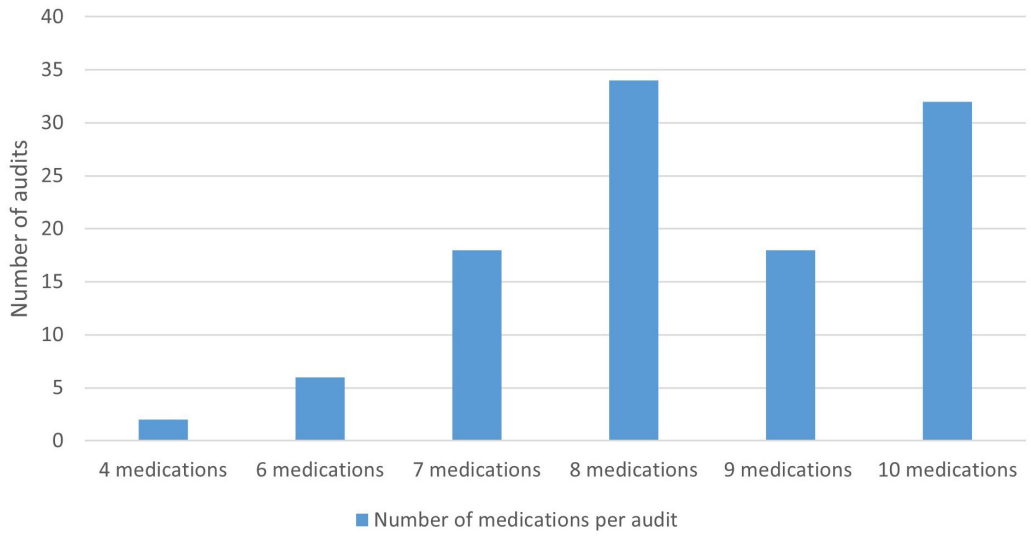
## Strengths and weaknesses

The strengths of this study include the compilation of an audit tool by a team with different professional backgrounds and expertise who met frequently to modify iterations of the tool following its use in practice. This is the first international study that examines nurses' documentation of using standing orders to supply medicines to children. A weakness of this study was that, rather than following the Delphi process, the development of the audit tool used a consensus approach. Additionally, there were no inter-rater reliability measures undertaken, although cross-checking with the medical professional occurred for those nurses whose audit scores were allocated to quartiles 3 or 4.

This audit demonstrates that the majority of RNs working using standing order instructions adhered to best practice standards when administering medications for children. RNs working for Mana Kidz are usually public health nurses, and a number identify as Pasifika and Māori. A re-audit of the four RNs who initially scored in the quartile 3 to 4 range demonstrated an improvement in all of their scores to within the quartile 1 range following supervision by a senior nurse. Supervision comprised sitting individually with the RNs and peer reviewing cases to highlight areas that needed attention. Additionally, supervision included site visits to the clinic for the supervisor to role model best practice and adherence to guidelines. This study supports international literature from England and Scotland [20,21] demonstrating the appropriateness and safety of nurse prescribing. Both medical practitioners and nurses highlighted the contribution to public health by nurse prescribers in a Scottish study. Antibiotic stewardship with more careful targeting of microbial drugs was an area where nurse prescribers potentially addressed medical practitioner over prescribing. Furthermore, the public show considerable confidence in nurse prescribing. Importantly, the Scottish study of surveys, case studies and interviews did not identify any issues that would affect patient safety.[20]

Within New Zealand there has been a significant, demonstrable improvement in child health, with a reduction of 58% of children developing ARF in the two years following implementation of the Mana Kidz programme.[15] In light of this important finding, policymakers and healthcare providers have a duty to commit resources to the expansion of RN prescribing. Currently only 441 RNs and 481 nurse practitioners are certified by NCNZ to prescribe medications.[22] This number represents less than 2% of the registered nurses and nurse practitioners in New Zealand. Nurses are the largest group of healthcare profes-

**Figure 1:** Illustrates the number of audits and distribution of medications per audit.



sionals in New Zealand, and utilising them to prescribe medications would potentially improve health outcomes for all population groups, not just children at risk of contracting ARF.

Barriers to nurse prescribing include limited support from both nursing and medical employers and a complete lack of financial remuneration for nurses willing to take on the added responsibility of prescribing. Additional constraints include access to prescribing training and mentors (medical and nurse practitioners) willing to supervise nurses during their prescribing practicum. A postgraduate diploma in RN prescribing has been available at a number of New Zealand universities since 2017, and yet, as of 9 July 2021, there are still only 441 nurse prescribers registered with NCNZ.

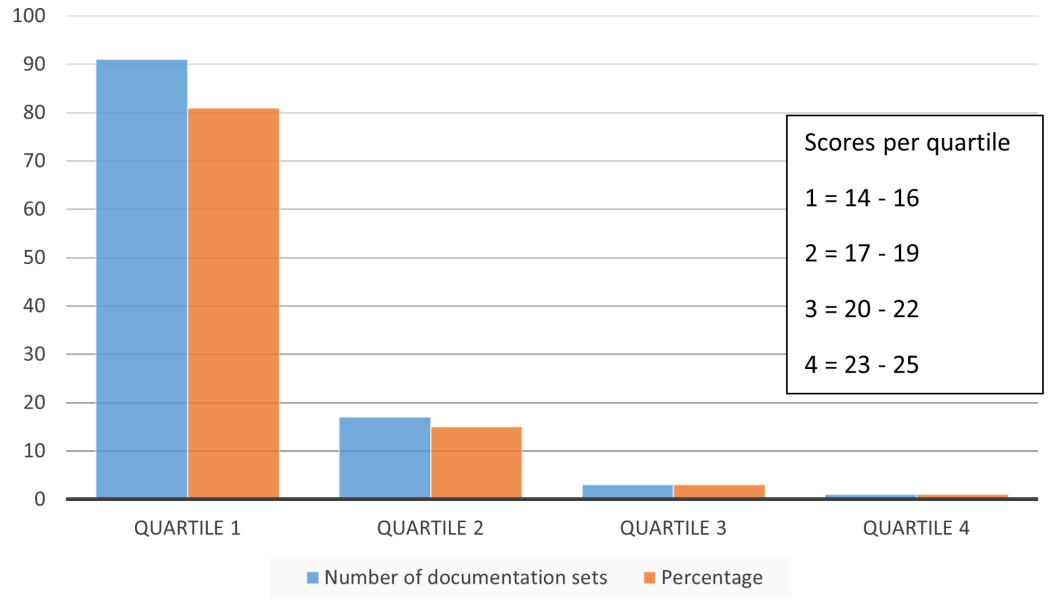
Standing orders provide a vehicle for nurses to prescribe medications. However, this system is labour intensive and onerous for the medical and nurse practitioners who issue them. New Zealand's Medicines (Standing Order) Amendment Regulations 2011[23] stipulate:

> *"If a standing order does not require the countersigning of charted treatments, or requires countersigning less frequently than once each month, the issuer must, at least once each month, audit a sample of the charted treatments of patients to whom medicines have been administered or supplied under the standing order."*

A recent New Zealand study exploring organisational views of the use of standing orders in general practice concluded that there was suboptimal understanding of the legislation. Additionally, the same study highlighted a lack of standardisation of standing orders, insufficient education of some nurses and that some general practitioners did not understand their responsibilities regarding the issuing of standing orders.[24]

The unnecessary workload that standing orders generate for the issuer prohibits medical and nurse practitioners from engaging in supporting nurses to prescribe. Our audit has demonstrated that nurses safely adhere to policy and guidelines when prescribing medications. Nurses should be supported and encouraged to become RN prescribers through further postgraduate study. Most importantly, nurses who are able to access and supply medications could potentially improve patient outcomes.

**Figure 2:** Number of documentation sets in each quartile. One documentation set contained between 4 and 10 medications.



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# Clinical outcomes of campylobacteriosis: a case series analysis of hospitalisations associated with the Havelock North *Campylobacter* outbreak

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## ABSTRACT

**AIM:** In August 2016, a large waterborne campylobacteriosis outbreak occurred in Havelock North, New Zealand. This analysis describes the clinical complications of cases admitted to hospital as a result of acute infection, identifies risk factors for hospitalisation and compares deaths between hospitalised and non-hospitalised cases. Hospital admissions with post-infectious sequelae were excluded as they are the subject of a separate analysis.

**METHODS:** A case series analysis was undertaken by reviewing the electronic medical records of 933 residents of Hawke's Bay District Health Board with probable and confirmed campylobacteriosis linked to the Havelock North *Campylobacter* outbreak.

**RESULTS:** A total of 67 hospital admissions, among 58 individuals, are described. Pre-existing comorbidity and advanced age were significant risk factors for hospital admission in univariate analysis. Dehydration (74.1%), electrolyte imbalance (35.8%) and acute kidney injury (27.6%) were common among hospitalised cases. The proportion of hospitalised cases that died within one year was significantly higher when compared to deaths among non-hospitalised cases (OR 5.0, 95% CI: 2.3–10.7), although this trend was not statistically significant after adjusting for age and comorbidity (OR 2.3, 95% CI: 0.96–5.3).

**CONCLUSIONS:** This study highlights the serious health impacts that occurred from a campylobacteriosis outbreak of this magnitude.

*Campylobacter* infection is a major cause of enteric illness (campylobacteriosis) worldwide. In developed countries, it remains the leading cause of culture-confirmed bacterial gastroenteritis,[1] and although campylobacteriosis is a self-limiting illness for most, serious complications, including haemorrhagic colitis and bacteraemia, are known to occur.[1]

The association between campylobacteriosis and post-infectious sequelae, including Guillain–Barré syndrome, have been widely described in the literature, including in New Zealand.[2] However, studies that focus on short- and medium-term clinical outcomes associated with campylobacteriosis are often limited by small sample size or rely on diagnostic information coded within routinely collected administrative health datasets.[3–6]

In August 2016, a large waterborne *Campylobacter* outbreak occurred following contamination of the reticulated, unchlorinated water supply in Havelock North, a town of approximately 14,000 residents in the Hawke's Bay Region. *Campylobacter jejuni* was implicated through epidemiological and microbiological investigation.[7] The Havelock North *Campylobacter* outbreak

(HNCO) has been described in detail elsewhere.[7,8] In brief, contamination of the ground water supply likely arose following a heavy rainfall event that resulted in infiltration of sheep faecal matter into the Heretaunga Plains aquifer from an agricultural field adjacent to the twin bore heads that supplied drinking water for the Havelock North township.

It is estimated that the HNCO resulted in between 6,260 and 8,320 people becoming unwell with symptoms of campylobacteriosis, including 953 residents or visitors to the area who had physician- or laboratory-confirmed illness. At the time of the outbreak, 42 hospitalisations were reported to the Hawke's Bay public health unit (HBPHU) linked to the outbreak.

This retrospective case series aims to (1) describe the clinical complications related to acute infection that resulted in hospitalisation and were attributable to the HNCO, (2) identify risk factors for hospitalisation among campylobacteriosis cases and (3) investigate the association between hospitalisation and all-cause mortality at both eight weeks and one year.

# Methods

## Case identification

As campylobacteriosis is a notifiable disease in New Zealand, physicians and laboratories are required by law to report all cases to the public health unit (PHU) responsible for the geographical location of the case. Standardised demographic and clinical information from all reported cases, including whether cases are linked to a known outbreak, are stored in the national notifiable disease surveillance database (EpiSurv). The Hawke's Bay District Health Board (HBDHB) is responsible for providing or funding the public healthcare services for the approximately 165,000 residents of Hawke's Bay and has a PHU responsible for the same population.

Consistent with the case definitions used in other studies of the HNCO, probable cases were defined as individuals who reported exposure to the Havelock North reticulated water supply during the likely period of *Campylobacter* contamination (5–12 August 2016) and subsequently developed onset of clinician-confirmed diarrhoea during the outbreak period (7–24 August 2016). In addition to these criteria, confirmed cases were required to have a faecal specimen that was positive for *Campylobacter*. The methodology for defining the outbreak period and case definitions for the HNCO has been described in more detail elsewhere.[7]

Individuals included in this case series were identified in two ways. Firstly, all probable and confirmed cases of campylobacteriosis that had a residential address within the HBPHU area and were linked to the HNCO were extracted from EpiSurv. This process identified 930 individuals for inclusion in this case series. Twenty three of the 953 cases linked to the HNCO in EpiSurv were excluded because their usual residential addresses were outside of the HBPHU area.

In addition to these 930 included cases, active case finding identified a further three probable cases to form a case series of 933 individuals (204 confirmed cases and 729 probable cases). Active case finding was undertaken to identify any hospitalised cases that were not notified to HBPHU at the time of the outbreak and therefore not captured by EpiSurv. This search was done by manually reviewing all inpatient admissions to HBDHB healthcare facilities between 7–31 August 2016 that listed *Campylobacter* enteritis, or a related complication, as the primary reason for admission based on International Classification of Disease (ICD) coding. A list of ICD codes used for active case finding is available in the supplementary material.

## Clinical data extraction

A qualified research nurse reviewed the electronic medical records of all 933 individuals in this case series. This review included all available hospital discharge summaries, specialist outpatient clinic letters, referrals to specialist services and laboratory results. Records from general practice visits are not held by HBDHB and were not reviewed.

Age, sex, ethnicity and Charlson Comorbidity Index (CCI) were manually extracted for all cases. The date of death of those who were deceased at the time of review was also extracted. Prioritised ethnicity was used to categorise cases into one of three groups,

Māori, Pacific Peoples or New Zealand European and Other, according to the Ministry of Health Ethnicity Data Protocols. CCI is a standardised measure of comorbidity based on ICD coding and produces a comorbidity score that has been validated to predict mortality across a range of health research settings.[8] A score of 0 indicates no comorbidity and scores above 0 correlate with higher predicted mortality risk. CCI scoring in this study was based on a review of documented comorbid diagnoses in hospitalisation and outpatient clinic records using a 10-year review period, from August 2007 to August 2016, with weightings assigned as outlined by Sundararajan et al.[8]

Hospital-based electronic medical records for admissions among cases that occurred within the approximate eight-week period following the HNCO (7 August–31 September 2016) were then reviewed in detail to identify those relating to campylobacteriosis. Hospital admissions were defined as emergency department or inpatient service events that lasted for more than three hours.

All hospital admissions that listed symptoms or complications of campylobacteriosis as the primary reason for admission were classified as attributable to the HNCO. Admissions were considered partially attributable if symptoms or infective complications were present but not the primary reason for admission. Post-infectious sequelae (eg, Guillain–Barré, reactive arthritis) were excluded as they are the subject of a separate analysis. Two confirmed cases had hospital admissions (one admission each) that were deemed not attributable to the HNCO and were excluded from analysis as they had systemically recovered from their acute infection at the time of admission and there was clear documentation within their clinical notes that the reason for admission was not related to their recent acute infection.

For all attributable and partially attributable hospital admissions the following information was collected: date of admission, primary and secondary reasons for admission (ICD coded), length of stay (days) and prevalence of the following complications (yes/no): dehydration, electrolyte disorders, acute kidney injury, bacteraemia, acute lower-gastrointestinal bleeding, colitis and requirement for intensive care unit (ICU) support. The research criteria used to define these conditions are included in supplementary material.

### Statistical analysis

Risk factors for hospitalisation were first investigated with univariate analysis using Pearson chi-square statistic. To account for interaction between risk factors, adjusted odds ratios (OR) were calculated using a multivariable logistic regression model. Risk factors that were significant in univariate analysis were included, with age (categorical) and CCI (categorical) included in the final model.

The proportion of hospitalised cases that experienced specific complications (eg, dehydration) were calculated on a per-case rather than per-admission basis, meaning cases that were admitted twice with the same complication counted once in the numerator. Confidence intervals (CI) around proportions were calculated using the two-sided exact (Clopper–Pearson) binomial method.

Multivariate logistic regression, adjusted for the confounding effects of age and CCI, was used to investigate whether hospitalisation from campylobacteriosis was associated with all-cause deaths at eight weeks and one year post outbreak.

Interaction terms were initially included in all multivariate models but did not substantially alter the pattern of model outputs, so they were removed. Data analysis was undertaken using IBM SPSS Statistics 22. Statistical significance for all tests were set at the ≤0.05 level.

### Ethics

This study was approved by the New Zealand Health and Disability Ethics Committee (18/NTA/155) with locality approval granted by HBDHB.

## Results

### Risk factors for hospitalisation

Of the 933 individuals included in this case series, 58 patients were admitted to Hawke's Bay hospital with complications of acute infection that were attributable or partially attributable to the HNCO. This number equates to a risk of hospitalisation with acute illness among reported cases of

6.2% (95% CI: 4.8–8.0). Table 1 compares the demographic characteristics of hospitalised and non-hospitalised cases. Hospitalised cases were significantly older with a higher level of comorbidity, when compared with non-hospitalised cases.

Age and CCI were both highly associated with the risk of hospitalisation in univariate analysis. Using multivariate analysis to adjust for the effect of age demonstrated that, in comparison to those with a CCI of 0, the risk of hospitalisation was approximately 2.9-times higher in those with a CCI of 1 or 2 and approximately 4.7-times higher in those with a CCI of 3 or more (Table 2). There was also a trend towards increased risk of hospitalisation with advanced age, although after adjustments for CCI in multivariate analysis, this association was not statistically significant.

### Acute complications requiring hospitalisation

Dehydration (74.1%), electrolyte disorders (35.8%) and acute kidney injury (23.9%) were common complications among cases admitted to hospital (Table 3).

Based on Kidney Disease: Improving Global Outcomes (KDIGO) scoring, seven of the 16 cases that were hospitalised with an acute kidney injury were classified as stage 1, three were classified as stage 2 and six were classified as stage 3. Two cases, one with pre-existing chronic kidney disease, required renal replacement therapy with dialysis.

Five cases were admitted with lower gastrointestinal bleeding, one of which was classified as severe (haemoglobin drop of >30gm/L); all resolved without endoscopic or surgical intervention. Of the cases that developed bacteraemia (n=5), none experienced serious end-organ sequelae (eg, endocarditis).

Two patients required support within ICU, which equates to a probability of needing ICU support if hospitalised of 3.4% (95% CI: 0.4%–11.9%). There was one inpatient death as a result of an acute stroke event which occurred 10 days into an admission for the management of diarrhoea, dehydration and frailty.

### Hospitalisation events

A total of 67 hospitalisation events were attributable (n=55) or partially attributable (n=12) to acute infectious complications of campylobacteriosis related to the HNCO. This total included nine re-admission events. Figure 1 shows the date of admission for all hospitalisations, with the majority (85.1%) occurring within the outbreak period, 7–24 August.

Length of stay varied significantly; of the 55 hospital admissions that lasted over 24 hours, the median length of stay was three days (interquartile range: four days). The longest hospital admission was 111 days, with the prolonged length of stay driven by multiple complications following pancolitis and multi-organ failure.

### Deaths

HBPHU received reports of four deaths in which campylobacteriosis was found to be a contributing cause of death (two in hospitalised cases, two in non-hospitalised cases). Unadjusted all-cause deaths were higher among hospitalised cases when compared to non-hospitalised cases; although this was not statistically significant at eight weeks (OR 3.9, 95% CI: 0.8–18.7), it was at one year (OR 5.0, 95% CI: 2.3–10.7).

After adjustments for the confounding effects of age and CCI, this trend remained, although it was not statistically significant at either eight weeks (OR 1.5, 95% CI: 0.28–7.8) or one year (OR 2.3, 95% CI: 0.96–5.3).

## Discussion

We describe 58 individuals who required hospitalisation due to acute illness in a case series of 933 people with probable or confirmed campylobacteriosis arising from a large waterborne outbreak. Key findings of this study include that age and comorbidity were significant risk factors for hospitalisation; dehydration and associated acute kidney injury were common among hospitalised cases; and unadjusted all-cause deaths were higher at eight weeks and one year among hospitalised cases compared to non-hospitalised cases.

Our finding of 58 individuals hospitalised is an increased estimate from previous publications about the HNCO, which report 42 people hospitalised.[7] Although not directly comparable as our analysis only includes HBDHB residents and includes both attributable and partially attributable hospitalisations, it is likely that the reliance

**Table 1:** Demographic characteristics of hospitalised cases, compared to non-hospitalised cases, in a series of 933 probable and confirmed campylobacteriosis cases.

| | Hospitalised cases, n (% of row total) | Non-hospitalised cases, n (% of row total) | Total cohort, n |
|---|---|---|---|
| **Sex** | | | |
| Female | 25 (5.1) | 464 (94.9) | 489 |
| Male | 33 (7.4) | 411 (92.6) | 444 |
| **Ethnicity** | | | |
| Māori | 6 (6.0) | 94 (94.0) | 100 |
| Pacific peoples | 1 (7.1) | 13 (92.9) | 14 |
| New Zealand European and Other | 51 (6.2) | 768 (93.8) | 819 |
| **Age*** | | | |
| <5 | 1 (1.7) | 59 (98.3) | 60 |
| 5–14 | 2 (1.9) | 102 (98.1) | 104 |
| 15–34 | 6 (3.3) | 174 (96.7) | 180 |
| 35–64 | 15 (5.9) | 240 (94.1) | 255 |
| 65–84 | 20 (8.4) | 217 (91.6) | 237 |
| 85+ | 14 (14.4) | 83 (85.6) | 97 |
| **Charlson Comorbidity Index*** | | | |
| 0 | 27 (3.8) | 691 (96.2) | 718 |
| 1-2 | 17 (12.2) | 122 (87.8) | 139 |
| 3+ | 14 (18.4) | 62 (81.6) | 76 |
| **Total** | **58 (6.2)** | **875 (93.8)** | **933** |

*Age and Charlson Comorbidity Index were both associated with hospitalisation (Chi-square test of association p=0.001).

**Table 2:** Risk factors for hospitalisation in series of 933 probable and confirmed campylobacteriosis cases.

| | **Adjusted OR for hospitalisation, OR (95% CI)**** |
|---|---|
| **Charlson Comorbidity Index** | |
| CCI=0 | Reference |
| CCI=1–2 | 2.9 (1.4–5.9) |
| CCI=3+ | 4.7 (2.0–10.7) |
| **Age** | |
| 0–34 years | Reference |
| 35–64 years | 1.9 (0.8–4.4) |
| 65–84 years | 1.8 (0.7–4.4) |
| 85+ | 2.3 (0.8–6.6) |

**CCI adjusted for age, and age adjusted for CCI.

**Table 3:** Proportion of cases and admissions with specific complications in a series 58 hospitalised campylobacteriosis cases.

| | **Number of hospitalised cases** | **Number of admissions** | **Proportion of hospitalised cases affected, % (95%CI)** |
|---|---|---|---|
| Dehydration | 43 | 45 | 74.1 (61.0–84.7) |
| Electrolyte disorders | 21 | 24 | 35.8 (24.5–48.5) |
| Acute kidney injury | 16 | 16 | 27.6 (16.7–40.9) |
| Bacteraemia | 5 | 5 | 8.6 (2.9–19.0) |
| Acute lower-gastrointestinal bleeding | 5 | 5 | 8.6 (2.9–19.0) |
| Colitis | 3 | 3 | 5.2 (1.1–14.4) |
| **Total** | **58** | **67** | |

**Figure 1:** Hospitalisations (N=67) attributable or partially attributable to HNCO, showing date of admission or readmission, 7 August–30 September 2016.

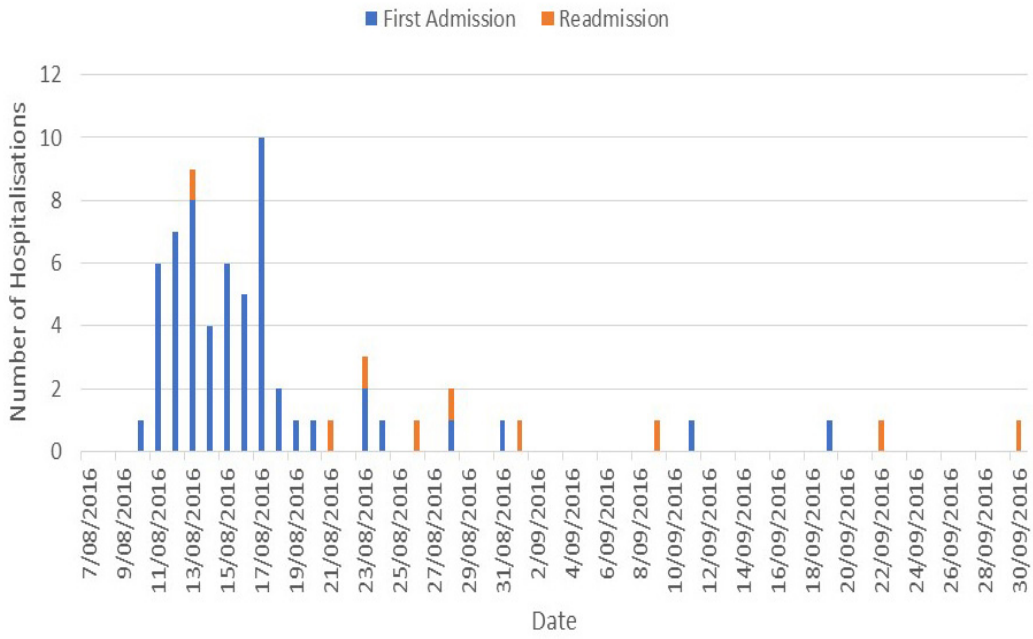


**Table 4:** All-cause deaths at eight weeks and one year in series of 933 probable and confirmed campylobacteriosis cases.

| Hospitalised | Died within eight weeks | Died within one year*** |
|---|---|---|
| Yes (n=58) | 2 (3.4) | 10 (17.2) |
| No (n=875) | 8 (0.9) | 35 (4.0) |
| **Total (n=933)** | **10 (1.1)** | **45 (4.8)** |

*** Includes those who died within eight weeks.


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on passive notification data in previous publications have underestimated the burden of hospitalisations associated with the outbreak.[7,9]

A unique feature of this waterborne outbreak is that the majority of the outbreak cohort are likely to have been exposed to *Campylobacter* in their drinking water supply over several days prior to chlorination of the water supply and the issuing of a boil water notice.[10] However, the proportion of cases hospitalised in this outbreak cohort (6.2%) is broadly similar to the 5.4% of cases that were reported as hospitalised in a national analysis of notified campylobacteriosis cases in New Zealand between 1999 and 2003.[11]

Patient comorbidity was a strong predictor of hospitalisation in this study. Those with a CCI score of three or more were approximately five-times more likely to be hospitalised in comparison to those with a CCI score of 0. Older age was also a strong predictor of hospitalisation, although the effect size is potentially underestimated in this analysis given active case finding was undertaken in residential care facilities during the HNCO, meaning it is possible that more complete case finding and a greater proportion of mild illness was captured in the over 65 cohort. A large Swedish study of notified sporadic *Campylobacter jejuni* cases found that those over 60 years of age had approximately double the risk of hospitalisation and that underlying patient comorbidity increased the risk by approximately four times.[6]

Of note was the relatively low proportion of hospitalisations among children in this outbreak (1.8% of those <15 years were hospitalised). This proportion is half of that reported in a previous population study of campylobacteriosis notifications in New Zealand between 1997 and 2015 (which found that 3.6% of cases in children <15 years were hospitalised).[12] It is unclear whether this disparity relates to differences in case notification procedures, better access to primary care treatment or less-severe clinical disease among children during this well-publicised outbreak.

The complications and hospitalisations described in this analysis confirm that campylobacteriosis can result in serious illness. Approximately one quarter (27.6%) of hospitalised patients had an acute kidney injury on admission, with dehydration being a significant underlying factor in most cases. This finding emphasises the importance of proactive fluid management of medically vulnerable individuals as part of campylobacteriosis outbreak response measures. During the HNCO, general practices serving the Havelock North population initiated phone triaging services for those experiencing gastroenteritis symptoms.[9] Data manually collected during the outbreak indicated that gastroenteritis-related general practice consultations (phone and in-person) peaked early in the outbreak, at 289 consultations per day, before rapidly declining over the first week.[9] General practices were able to provide intravenous fluid rehydration for those more seriously affected, and it is likely that without the significant response from both general practices and community pharmacies the number of individuals requiring hospitalisation would have been higher.[9,13]

We estimate *Campylobacter* bacteraemia occurred in 7.5% of hospitalised cases (0.5% of total reported cases), although this may well be an underestimate given that not all cases received blood cultures. This proportion compares to crude estimates of between 0.4% and 1% of notified cases in Sweden, 0.3% in Finland and 0.4% in Denmark.[14–16] Although traditionally associated with individuals who are elderly or immunocompromised, bacteraemia is known to occur in otherwise healthy individuals.[1,16] In our cohort, all patients with diagnosed bacteraemia were over 80 years of age.

To our knowledge, this is the first publication to compare all-cause deaths among cases hospitalised with campylobacteriosis to non-hospitalised cases at eight weeks and one year. Hospitalisation in this context is a proxy for severity of illness, although it is also heavily influenced by factors such as age and comorbidity, which were found to significantly affect the risk of hospitalisation.

In this cohort, the unadjusted risk of death at one year among hospitalised cases was approximately five times that of non-hospitalised cases. Although the trend towards excess deaths in hospitalised cases remained

after adjustments for age and CCI score, this trend was not statistically significant. However, utilising hospitalisation as a proxy for severity of infection in this analysis likely underestimated the true effect difference, given there were a small number of deaths that were directly attributable to campylobacter infection in individuals who died without being hospitalised (two deaths in non-hospitalised cases occurred in residential care settings).

These findings raise the possibility that campylobacteriosis, traditionally thought of as a self-limiting illness, can have persisting impacts on mortality in medically vulnerable populations. There are biologically plausible mechanisms, such as increased frailty following acute illness, that may mediate poorer medium-term survival following severe systemic infection.[18] Increased all-cause mortality has been described among domestically acquired campylobacteriosis cases in Sweden, compared to the general population at one month post notification (SMR 2.9, 95% CI: 1.9–4.0), although this effect decreased over time and no significant differences were apparent in mortality rates at one year (SMR 1.0, 95% CI: 0.9–1.1).[19]

## Strengths and limitations

This study was able to follow a cohort of outbreak-associated cases of campylobacteriosis to generate a robust estimate of the acute infectious complications that arose. Strengths include the large, well-defined outbreak cohort and utilising a comprehensive review of electronic hospital records to estimate the frequency of complications rather than relying on diagnostic coding in administrative health datasets. The design of the case series is a key limitation. Ideally, analysis of deaths would have been undertaken by comparing cases and controls, rather than comparing hospitalised and non-hospitalised cases. In addition, health records for admissions in private hospitals or public hospitals outside HBDHB were not able to be reviewed. Although the impact of this has been minimised by limiting this case series to HBDHB residents (who are less likely to seek healthcare outside of HBDHB), it is possible some hospital admissions may have been missed.

It would be useful to investigate the long-term consequences of campylobacteriosis in more detail using New Zealand's large datasets of notified and hospitalised cases. This analysis could generate suitable comparison populations to better quantify the population health impact of this common enteric pathogen. Such an analysis would allow the health and economic benefits of investing in improved safety of the water and food supply to be further quantified.

# Conclusion

This study provides a comprehensive analysis of the acute infectious complications that resulted in hospitalisation attributable from a large campylobacteriosis outbreak. It demonstrates the serious health impact that campylobacteriosis can have in medically vulnerable individuals and highlights the importance of public health measures to prevent exposure to this organism.

# Supplementary Material

**Supplementary Table 1:** ICD-10-AM codes used to search for non-notified cases of campylobacteriosis associated with the HNCO that were hospitalised, based on hospital admissions 7–31 August 2016.

| |
|---|
| **Gastroenteritis** |
| A04.5 Campylobacter enteritis |
| A04.9 Bacterial intestinal infection |
| A09* Other gastroenteritis and colitis of infectious and unspecified origin |
| A08.4 Viral intestinal infection, unspecified |
| A08.5 Other specified intestinal infections |
| **Potential complications of gastroenteritis** |
| E86 Volume depletion |
| N17* Acute kidney injury |
| J69.0 Aspiration pneumonia |
| R50* Fever of unknown origin |
| K59.3 Megacolon |
| A41.9 Sepsis, unspecified. |
| R57.2 Septic shock. |
| O60* Premature labour |
| **Known post-infectious sequelae of campylobacteriosis** |
| M02 Reactive arthritis |
| G61.0 Guillain-Barre syndrome |
| K58 Irritable bowel syndrome |

**Supplementary Table 2**: Research definitions.

| Condition | Extent of audit | Research criteria: |
|---|---|---|
| Acute lower gastrointestinal bleeding | Review of clinical notes and endoscopy results | Documented clinical diagnosis of lower gastrointestinal bleed within four weeks of symptoms of active infection (ie, diarrhoea). All bleeds in setting of confirmed acute infection, irrespective of potential underlying chronic pathology such as haemorrhoids or diverticulosis were included. |
| Severe lower gastrointestinal bleeding | Review of clinical notes and endoscopy results | A subset of those with a documented clinical diagnosis of lower gastrointestinal bleeding, which also had a haemoglobin drop of >30gm/L (either from baseline level or between admission haemoglobin and lowest haemoglobin during admission). |
| Colitis | Review of imaging and/or endoscopy result and/or histology | Documented clinical diagnosis of colitis or Endoscopy report documenting presence of mucosal inflammation with or without compatible histology or abdominal imaging consistent with colonic inflammation. |
| Toxic mega colon | Review of imaging and clinical notes | Documented clinical diagnosis of toxic mega colon or non-obstructive colonic dilation greater than 6cm reported on AXR or CT imaging with signs of systemic toxicity. |
| Dehydration | Review of clinical notes | A clinical diagnosis of dehydration at admission or discharge or documentation that intravenous fluid bolus was given on admission. |
| Electrolyte disorders on admission | Review of laboratory results | Hypokalaemia <3.5mmol/L<br>Hyponatremia <135mmol/L<br>Hypernatremia >145mmol/L |

**Supplementary Table 2**: Research definitions (continued).

| Condition | Extent of audit | Research criteria: |
|---|---|---|
| Acute kidney injury | Review of laboratory results | Acute kidney injury definition: KDIGO's serum creatinine criteria for acute kidney injury:<br><br>Stage 1: Increase in SCr of ≥0.3mg/dL (26.52umol/L) within 48 hours or increase in SCr 1.5 to 1.9 times baseline which is known or presumed to have occurred in the prior seven days<br><br>Stage 2: Increase in SCr to 1.0 to 2.9 times baseline<br><br>Stage 3: Increase in SCr to 3.0 times baseline or increase in serum creatinine to ≥4.0mg/dl (≥353.6umol/l) or Initiation of renal replacement therapy<br><br>*Operational definition of baseline creatinine:* The baseline Cr is an *outpatient* reading within 365 days of the current admission date; if multiple pre-hospitalization values are available, the one closest to the date of hospital admission will be used. If an outpatient pre-hospitalization value is not available during the 365 days prior to admission date, the lowest Cr value obtained during the current hospitalization should be taken as the baseline. |
| Bacteraemia | Review of laboratory results | *Campylobacter* species isolated from blood culture |

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# Repeated laparoscopies for pelvic pain: doing the same thing over and expecting a different outcome?

Karen Joseph


## ABSTRACT

**BACKGROUND:** Pelvic pain is a common and burdensome condition for women and the healthcare system. Surgery is a common treatment approach; however, as this is not always successful many women receive repeated procedures, often with diminishing benefits. In order to try and reduce the frequency of this high-cost, low-value approach, the New Zealand endometriosis clinical care pathway recommends that multidisciplinary review is undertaken prior to a third operation.

**AIMS:** To quantify the current practice of repeated laparoscopic procedures, informing the requirement for multidisciplinary meeting capacity.

**METHODS:** A retrospective audit was undertaken of the elective gynaecological laparoscopies performed for pelvic pain within the Canterbury District Health Board in the 2019 calendar year. De-identified data were also obtained from private insurance providers for the same time-period.

**RESULTS:** Of the women receiving a publicly funded laparoscopy, 34% had previously undergone at least one similar procedure (range 1-7). Although the data from the private sector have limitations, these also demonstrate a high number of repeated procedures – particularly for those residing in the Canterbury region.

**CONCLUSIONS:** Despite being recognised as low-value, high-cost care, repeated laparoscopies are common management for women with pelvic pain, suggesting that further investment into multidisciplinary services is required.


Chronic pelvic pain (CPP) afflicts around one in four New Zealand women[1] and is commonly attributed to endometriosis, despite around half of those women affected not having demonstrable lesions.[2] Surgery to locate and treat this presumed endometriosis is often seen as the mainstay of management for CPP. Data from New Zealand's largest health insurer reported that, in 2015, surgery for endometriosis was the most common procedure for female claimants aged 21–35 and was one of the top three procedures for women under 50.[3]

This approach is extrapolated from oncological practice of lesion reduction; however, in direct contrast to malignancy, there is a well-recognised lack of correlation between lesion status and prognosis.[4] In addition, the symptoms experienced are the same as the symptoms experienced by the 40–60% of women with CPP in whom lesions are not demonstrated.[2,5] Lesions are also commonly seen in women who do not suffer pelvic pain.[6]

The evidence base supporting surgical management of pain attributed to endometriosis is currently lacking. Some authors are questioning the practice, particularly given risks and costs associated with surgery.[7,8] The recently released Australian Endometriosis Clinical Practice Guideline rates the evidence for the recommendation "[c]onsider laparoscopy to diagnose and treat people with suspected endometriosis" as "very low - any estimate of effect is very uncertain."[9]

Within the limited literature, there is an indication of a "law of diminishing

returns"—that is, a lower likelihood of benefit with subsequent operations.[8,10] Repeated surgery is cautioned against in international guidelines.[9,11,12] However, this remains a common practice in New Zealand. An unpublished 2014 Endometriosis New Zealand patient poll found a mean number of four surgeries per respondent, with a range of 1–25 operations per respondent.[13]

In order to address this high-cost, low-value practice,[8] the 2020 Ministry of Health clinical care pathway Diagnosis and Management of Endometriosis in New Zealand recommends that "[c]linicians considering a third or more laparoscopy on a patient should seek the opinion of a multidisciplinary meeting [MDM]."[14]

An audit of numbers of repeated laparoscopies within the Canterbury District Health Board (CDHB) and in the private sector in New Zealand was undertaken to establish current practice. The results will inform capacity requirements for pelvic pain MDMs and provide a baseline to establish whether any change in practice occurs over time.

# Methods

Prior to commencement of data collection, the Health and Disability Ethics Committee confirmed the audit status of this work as out of scope for requiring review.

As COVID-19 pandemic restrictions have likely skewed the most recent data on healthcare usage, the 2019 calendar year was selected as a convenience sample to provide representative audit data.

## Populations

The CDHB provides services to a population of 578,000 within north and central Canterbury, New Zealand. This includes 288,000 females, of whom 134,000 are within the reproductive age group (15–49).[15] A monthly pelvic pain MDM was established in 2016 and includes clinicians from the gynaecology, physiotherapy, pain management, emergency and mental health departments. The MDM is a forum for clinician collaboration in the management of complex pelvic pain presentations, with an average of six patients discussed at each meeting.

Over 35% of New Zealand women aged 15–49 had private health insurance in 2019, with the highest rates in the Auckland, Waitematā and Capital and Coast DHB regions.[15]

## Data collection

### CDHB data

Elective operating theatre list records were obtained from the CDHB Women's Hospital surgical waitlist office for all elective gynaecology surgical procedures that were performed between 1 January and 31 December 2019. Procedures that were listed as laparoscopy for the investigation or treatment of pelvic pain were identified.

A hand search of the electronic patient records, including operation notes, clinic letters and past admission notes, was undertaken for each individual identified. The following variables were collected: National Health Index number, indication for procedure, number of previous laparoscopic procedures for pelvic pain (including indication for and funding of these) and whether the case had been reviewed at the CDHB pelvic pain MDM pre-operatively.

### Private sector data

The major health insurance companies funding surgical procedures were approached and asked for data on number of procedures performed within the same time-period.

De-identified data were obtained for the number of individual members having a pelvic laparoscopy in 2019, including whether they had already received funding for a similar procedure by the same funder in the previous five years. Data were provided for policyholders residing within the Canterbury postal area and those resident in the rest of New Zealand.

## Post hoc analysis

Post hoc calculation, as described in the *Results* section, was undertaken with MedCalc Software (MedCalc Software bv, Ostend, Belgium). The relative risk, its standard error and 95% confidence interval were calculated according to Altman.[16]

Adjustment for confounding factors was not possible owing to the limitations of the data available.

# Results

## CDHB data

There were 203 elective laparoscopies performed by the CDHB Women's Health Service for the indication pelvic pain in 2019. Eight were removed from data

analysis, leaving a total CDHB dataset of 195. Reasons for exclusion were: the procedures were part of a planned staged operation (4), listed indication also included infertility (3) and missing operative note (1).

Of the remaining 195 individuals, sixty-six (34%) had already undergone a similar procedure for pelvic pain, with a range of 1–7 past surgeries (Figure 1). For thirteen of the 66 women, this had been a previous "diagnostic only" procedure, and of these thirteen, no pathology was found in nine, who were therefore again left without operative intervention. Fifty-three of the women had already had at least one previous treatment laparoscopy for their pelvic pain.

The 66 women undergoing a repeat laparoscopy in the CDHB had already received a combined total of 109 procedures. Sixteen of these women were identified as having had at least one procedure in the private sector, with a range of 1–6 privately funded procedures. Overall, 30% of the previous procedures had been privately funded.

None of the 195 women had been discussed at the CDHB pelvic pain MDM prior to their 2019 operation.

## Private sector data

Two of the four major providers of private surgical insurance, Southern Cross and UniMed, were able to provide de-identified data for analysis within the required time frame of the audit. Combined, these two providers represent the majority of the market.

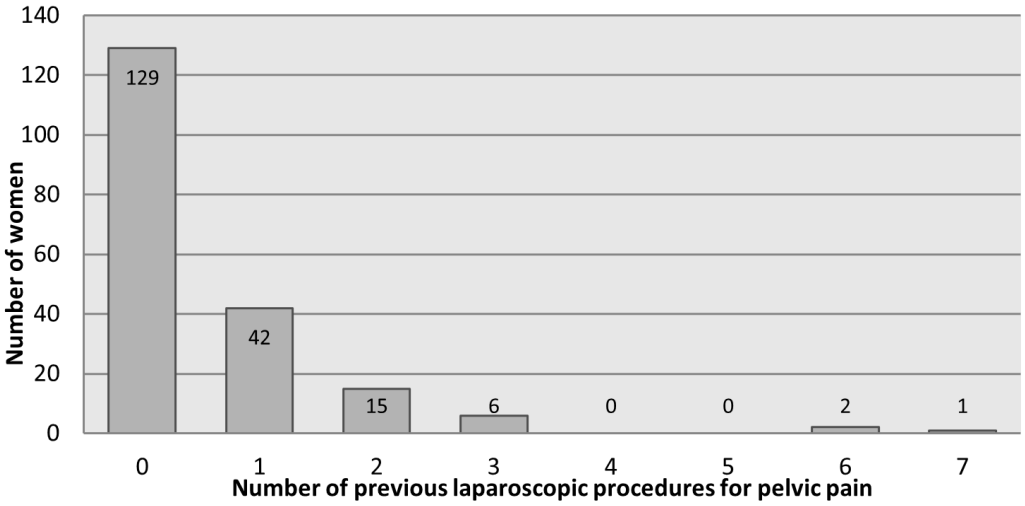
In the 2019 calendar year, 262 policyholders residing in Canterbury underwent a total of 274 pelvic laparoscopies. Of these 262 women, twelve individuals (4.6%) had undergone two procedures in 2019, and 70 (27%) had received funding from the same insurer for at least one previous pelvic laparoscopy within the preceding five years. Indication for surgery for each individual was not available, but the majority (61%) of procedures in the whole cohort were listed as being "endometriosis surgery."

When reviewing the data provided, an unexpected finding was made of a disparity between those living within the Canterbury region and the rest of the country (Figure 2). The relative risk of having already undergone a previous pelvic laparoscopy in the preceding five years for those residing in Canterbury, versus those outside it, was calculated.

The 1,064 women residing outside of the Canterbury area who had a privately funded pelvic laparoscopy in 2019 were significantly less likely to have a had a second procedure in that year (RR 6.1 (95% CI 2.52–14.75) P=0.0001) or to have already undergone a similar procedure funded by their policy in the previous five years (RR 2.4 (95% CI 1.82–3.08) P<0.0001).

Differences between data from the DHB and private insurance cohorts were not analysed, as the datasets are not comparable.

**Figure 1:** Number of previous laparoscopies for pelvic pain within the CDHB cohort.



# Discussion

This audit set out to estimate the number of additional cases that will need to be accommodated in the CDHB pelvic pain MDM in order to comply with the recommendations of the Ministry of Health clinical pathway.

None of the 24 women who underwent their third or greater surgical procedure within the CDHB cohort were discussed at the pelvic pain MDM. Although, notably, the recommendation to do so was not published until March 2020—after the timeframe of this audit, this forum was available for discussing non-surgical alternatives to a further operation. These data suggest that each monthly meeting will need to accommodate an extra two cases for discussion. Although it is difficult to estimate the number of those in the private sector who would need similar provision, it seems likely that the numbers could be similar, as there were sixteen women who appeared to meet this criterion from the limited dataset available.

The data from the private insurers are limited owing to the de-identified nature and shorter timeframe of inclusion of past procedures, and because the indication for the surgical procedure was not available. Despite these limitations, the unanticipated finding of a more than double relative risk of Canterbury women having had prior surgeries compared to the rest of the country is striking and warrants further investigation.

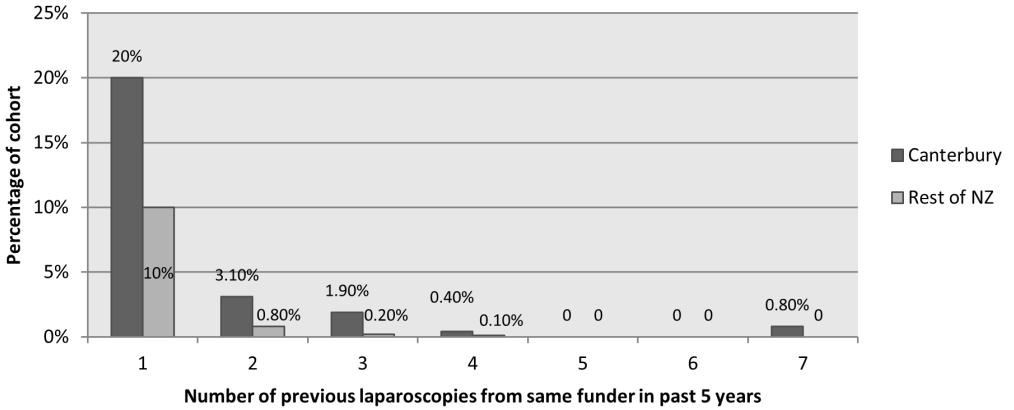
## Future research directions

The recurrence of symptoms following laparoscopic treatment of pelvic pain and subsequent repeated surgical procedures is well recognised in the literature. Laparoscopic treatment of endometriosis fails to improve pain symptoms in 20–54% of cases.[8,17,18] Of those who do obtain benefit from surgical intervention, up to 93% have a recurrence of pain.[19] Cohort studies have shown the repeat surgery rate for those with endometriosis to be 50–60% by five to seven years,[19,20,21] with an average interval of under two years.[10,17] Around half of these women go on to receive multiple procedures.[20]

Variation in practice of repeated surgeries has been recognised and may be related to a number of variables in patient characteristic, services available and gynaecologist decision-making. However, this variation in practice is often not based on evidence.[22–24] Review of the literature identifies some possible factors that may contribute to these discrepancies and inform further research.

The most significant factor influencing the likelihood of having a repeat procedure is the age of the woman at the first operation, with younger age predicting probability of a repeated procedure in the future.[20,21] Rates of repeated procedures have been reported as over 70% in those who are less than 30 years old at primary surgery.[20,21] The reason for this has not been established. However, notably, younger age is also a risk factor for persisting pain following surgery for endometriosis.[25]

**Figure 2:** Percentage of the private insurance cohort who already had prior laparoscopies funded by the same insurance provider in the previous five years by number of previous procedures in past five years.



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Endometriosis New Zealand delivers the Menstrual Education programme to school students "to improve adolescent knowledge of menstrual health and endometriosis." Outcomes published include an observed relationship between the number of years that the education programme has been running in Canterbury and the numbers of young women aged under 20 undergoing laparoscopic surgery and subsequent follow-up in the Endometriosis and Pelvic Pain Coaching Clinic, which is run by the holder of the intellectual property of the Menstrual Education programme.[26] If this observed relationship were to be confirmed, this could suggest there is a relationship between delivery of this programme and reduced age at first laparoscopy. It may then follow that this programme is a possible contributor to the discrepancy of repeated procedures in the Canterbury region, where it has been running the longest.

Psychosocial factors have also been shown to be predictors of healthcare usage and outcomes. Although around one in five adults in New Zealand live with chronic pain, not all seek healthcare equally. Those with high levels of symptom-related anxiety and catastrophic worry about pain are more likely to present for care.[27] In those with CPP, psychosocial factors including depression, anxiety and catastrophic worry correlate with increased pelvic pain severity and persisting pain following surgery for endometriosis.[2,18,25,28] It is possible that this combination of increased healthcare consulting behaviour, augmented pain experience and reduced benefit from surgery could result in increased likelihood of repeated surgical procedures.

A 2019 Ernst & Young report commissioned by the CDHB reported a significantly higher rate of "mood/anxiety disorder" in Canterbury compared to the national average.[29] Possible reasons for this finding include that the last decade has seen a disproportionate number of stressors on the local population, including natural disasters and a terrorist attack.

An audit in the CDHB gynaecology clinic found a strikingly high level of catastrophic worry about pain among the women referred for review of CPP—a level higher than those of similar groups in the published international literature.[30] Reasons for this discrepancy are unclear as there is no such difference between this variable in those seen in the population of the CDHB pain clinic and international norms, despite the shared environmental milieu. Regardless of the reasons behind this finding, it does represent a potentially modifiable risk factor for poor outcomes for those living with pelvic pain and resultant delivery of high-cost, low-value care in the region.

A study investigating decision-making by gynaecologists identified that a strong predictor for being referred for a surgical procedure for CPP was having had prior abdominal or pelvic surgery. This finding highlights the significance of the decision for the primary procedure.[23] Younger age was also associated with an increased chance of being booked for a surgical procedure, another factor that compounds the impact of gynaecologists' decision-making on the trajectory of the woman's future care.

An observational study in Australia reviewed the predictors of gynaecologists deciding to arrange surgery for women attending a gynaecology clinic for CPP. The strongest predictor of clinicians' decisions to operate was randomisation to a clinic with advanced endoscopic skills rather than one with additional pain management skills.[24] Notably, the percentage of patients in whom endometriosis lesions were identified was the same in each cohort despite the differing operative rate.

Currently, the health-cover benefits of the major insurance companies will fund (repeated) surgical interventions but not comprehensive pain management input. Although the CDHB does have a specialist pelvic pain clinic run by a Pain Medicine Physician, this clinic has a very limited capacity. This means that the services available to women with CPP, both publicly and privately funded, are mainly delivered by endoscopic surgeons rather than by clinicians with additional pain management skills.

## Limitations of study

The data for this study were obtained retrospectively and relied on existing records, which in many cases were limited in detail. For the women in the CDHB cohort,

the nuances of decision-making for undertaking a repeat operation may not have been appreciable in the electronic records. This audit also only identified those who received an elective procedure, whereas during the audit timeframe some women were likely to have undergone a similar procedure on an urgent operating list not captured in this dataset, and so the totals may be an underestimate.

It is not possible to compare the data for the two cohorts, as the data available from the private sector are non-equivalent. The insurance providers were only able to provide de-identified data, so the indication for performing the laparoscopy was not provided, meaning that some of the procedures were likely to have been performed for indications unrelated to pain. As this would be expected to be the case with the data collected from all regions in New Zealand, the discrepancy is still notable.

It is also not possible to establish whether the women in the insurance-funded cohort had previously received a laparoscopy from the same funder more than five years earlier, or funded by a different provider. Of note, 30% of the prior procedures received by the CDHB cohort had been privately funded, which suggests that women commonly access surgery via multiple funding streams. Thus the data for the insurance funded cohort may be an underestimate.

## Conclusions

Despite being recognised as low-value care, the practice of repeated laparoscopies is common in both the private and public gynaecology sectors. Further prospective research, including detailing clinician and patient decision-making rationale and data collection within other public hospitals, is required to further explore the practice of repeated laparoscopic procedures for pelvic pain in New Zealand.

The limited data available suggest that this practice may be more common in Canterbury than elsewhere in New Zealand. More research is needed to understand these findings and to identify modifiable risk factors for the delivery of high-cost, low-value care. The literature identifies a number of interlinked risk factors, including younger age at first surgery and lack of specialist pain management and psychosocial interventions, which have the potential to interact into a cascade of poor outcomes from surgery and repeated operations.

International and local research has identified the need for further training in pain management skills for gynaecologists.[31] The investment in such training and in the development of a multidisciplinary services has the potential to address some of the factors contributing to the current practice and provide an alternative care pathway.

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# A broken neck: outcomes from conservative management of C2 fractures in older adults

Krystina V Common, H Carl Hanger


## ABSTRACT

**AIM:** To describe the management, complications and functional outcomes of older patients who sustain fractures of the second cervical vertebra (C2).

**METHODS:** Retrospective review of consecutive patients aged 65 years and older. All patients admitted with the clinical discharge code of S12.1 (fracture of second cervical vertebra) to Christchurch Hospital, New Zealand, over five years were included. Outcomes of mobility, domicile and mortality (inpatient, 30 days, one year and two years) were recorded, as well as all complications from injury and from treatment.

**RESULTS:** Sixty-four patients (26 male, 38 female) with a mean age of 80.6 years were included. On admission, 89% of patients lived at home, 25% used a mobility aid and the median Charlson Comorbidity Index score was 2.0. All patients were managed conservatively (non-surgically) with majority immobilised in a rigid collar (46, 72%). Thirty-seven (58%) received inpatient rehabilitation. Complications were common, with medical (n=39 (61%)) and collar complications (37 (58%), mainly pain and pressure related) the most frequent. Mortality was 9% in hospital and 22% at one year. Of the 57 patients living in their own homes prior to fracture, 43 (75%) were able to return home. More patients required a mobility aid on discharge compared with on admission (25% vs 70%, Chi square=43, p<0.0001).

**CONCLUSIONS:** C2 fractures in older people cause substantial morbidity and loss of function in older patients. Despite the majority needing inpatient rehabilitation and complications related to the collar or immobility being common, three-quarters of patients were still able to return home. Walking ability declined and most needed some walking aid post fracture.


Cervical fractures can occur in patients of any age. However, in older adults the force required to cause these injuries may be much less than in younger patients.[1] Factors inherent to the older adult such as frailty, medical comorbidities and medications can all lead to an increased risk of falls. The risk of fracture itself is also increased due to osteoporosis[2] and degenerative changes in the cervical spine.[3] Studies have also shown that, despite a decreasing number of neck injuries in patients under the age of 65, there is an increasing incidence in patients aged over 65 years.[4,5]

In all age groups, C2 is the most frequent location for a fracture in the upper cervical spine. This is particularly so in patients aged over 80.[6,8] The two most common types of C2 fracture are through the dens (type II or III odontoid) and body of C2 (hangman) fractures, and all are unstable.[7,8] Although these injuries can be caused by high-energy impacts such as motor vehicle accidents, low-energy injuries such as falls are the most common mechanism of C2 fractures in older people.[7,8]

The management of C2 fractures is stabilisation to prevent neurological injury and promote bony union. The three main methods used are (1) rigid cervical collar immobilisation, (2) halo-vest immobilisation and (3) surgical fixation. The decision between these options depends on fracture and patient characteristics, but there is a lack of consensus, especially in older patients, as to the best treatment option.[3,5,9,10] Although use of surgical fixation may be increasing over time, rates

of non-union, complications and mortality are variable and there are concerns about operating on comorbid and frailer older patients.[3,11–15] Complications of management include non-union (which can be associated with sudden death) and neurological complications from instability as well as postoperative and comorbid medical issues.[3] Complication rates reported from any management vary widely, from 21% to 44%,[3,7,15–18] and no treatment modality seems better.[3,5,9,10] In our centre, most of these patients are managed conservatively with external immobilisation, and very few are having surgical fixation.

Our clinical experience is that older patients with C2 fractures are very frail, have comorbidities and become functionally compromised by their immobilisation with a rigid cervical collar. The complications of rigid collar use appear to be infrequently reported.[11,15,18,19] Therefore, we chose to review the management, complications and functional outcomes of consecutive older patients with odontoid (C2) fractures.

# Methods

The study was carried out at Christchurch Hospital, the sole acute hospital in Canterbury, New Zealand, with a catchment population of 520,000 people. It was a retrospective review of the management and outcomes of all patients aged 65 and over who were discharged with an ICD-10 discharge code of S12.1 (fracture of second cervical vertebra) from Christchurch hospital over five years (1 January 2009 and 31 December 2013 inclusive). All patients were initially managed and followed-up by the orthopaedic spinal team. The clinical records (both electronic and paper) were reviewed by a single clinician (KC), and data regarding mechanism of injury, comorbidities, complications, discharge location, requirement for rehabilitation and mobility and mortality outcomes were collected. Outpatient clinic notes were accessed via the electronic patient management system (Health Connect South (HCS)). Mortality data (out to two years post fracture) were obtained from the same electronic record (HCS), which is linked to the National Mortality Database using each patient's unique National Health Index number.[20]

Low-impact injuries were defined as a fall from standing height or less. High-impact injuries were defined as a fall from greater than standing height or other trauma, such as injuries sustained in motor vehicle collisions.

A Charlson Comorbidity Index (CCI) score was calculated for each patient.[21]

Complications were recorded and categorised into one of six categories:

1. Complications directly related to the injury (pain, transfusions, other injuries)
2. Direct neurological damage from the injury (intracranial events, cord or nerve impingement)
3. Fracture fixation or collar problems (poor compliance, swallowing difficulties, pressure injuries from the collar)
4. Medical complications (infections, cardiac problems, incidental scan findings, malignancies, endocrine abnormalities),
5. Immobility-related complications, such as constipation, deep vein thrombosis/pulmonary embolism (DVT/PE) or pressure areas not from collar
6. Psychological problems (Delirium, depression, anxiety)

Data that were not normally distributed are presented as medians and interquartile ranges, and Chi-square analyses were used for comparisons of categorical data.

The New Zealand Health and Disability Ethics Committees (HDEC) advised that formal ethics approval was not required as the review was considered a retrospective audit. The Māori Health Team (Te Komiti Whakarite) at Christchurch Hospital, New Zealand, also reviewed the study plans and gave consent.

# Results

A total of 69 patients were identified as having the discharge S12.1 code. Five patients were excluded from final analysis: two patients because they did not have a C2 fracture, and three because the relevant paper notes could not be obtained. This left a total of 64 patients whose medical notes were analysed in full. Full patient characteristics are shown in Table 1. Patients had a mean age of 80.6 years and were

predominantly of European ethnicity (95%). Forty percent had high-impact injuries and 60% of patients had low-impact falls. All patients were managed conservatively with a non-operative method of fixation. The majority (72%) were managed in a rigid cervical collar. Of those in the collar and brace system, one was managed in a halo-vest immobiliser and traction for a short duration, but this was stopped due to delirium and they were converted to a rigid collar, whereas the others were in the Aspen®CTO system only. Thirty-seven patients (58%) had inpatient rehabilitation associated with this injury (13 orthopaedic geriatric rehabilitation unit, nine spinal unit and nine older persons health rehabilitation unit, six in other district health boards (DHBs)).

Table 2 demonstrates the outcomes in this group of patients. The most frequent complications were medical (60%) or complications directly arising from the use of a collar (58%).

The most frequent medical difficulties were lower-respiratory infections (14 (22%)), and four (6%) had respiratory distress/needed intubation. Urinary retention (7 (11%)) and falls (6 (9%)), with two (3%) patients sustaining additional fractures, were next most frequent issues.

Collar complications were predominantly pressure related: early reddening or irritation (n=8 (13%)), established pressure areas under chin (n=4 (6%)) or on chest (n=3 (5%)), difficulty eating (n=9 (14%), with one requiring nasogastric tube) and discomfort/pain (n=21 (33%)). Pain from the collar was severe enough that six abandoned the hard collar, and a further two patients attempted intermittent self-removal. Difficulty walking or participating in rehabilitation was reported in four patients (6%) with a hard collar.

Constipation (11 (17%)) was the most frequent immobility-related problem. No cases of venous thromboembolism were recorded, and there were two pressure injuries (not related to the collar).

Seven patients sustained direct neurological injuries, all of which (except one) were as a result of high-energy injuries. Five of these seven patients died as a direct result of the severity of their intracranial injuries. Delirium (psychological complication) occurred in at least 12 patients (19% of all patients).

The majority (75%) of patients who were living at home prior to their fracture were able to discharge to their own homes from either their acute inpatient stay or their time in rehabilitation. Of those patients who were originally admitted from residential care, only one patient died, and the remainder were able to return to their residential care facility. There were six new admissions to residential care, although one of these patients only stayed for short-term care until their collar was removed and then they were able to return home.

Six patients (9%) died during their inpatient stay: five of these sustained significant neurological injuries as a result of high-energy impacts, and one had multiple medical comorbidities and recurrent falls. These patients all died within 10 days. Fourteen patients had died at one year (22%) and 21 by two years (33%).

Significantly more patients required a mobility aid on discharge than on admission (Chi square=43, $p<0.0001$). Sixty percent of patients required a walking frame on discharge and only 14% were able to walk independently (without an aid) on discharge, whereas 67% were documented to be independent walkers on admission. Four patients were discharged home from hospitals outside of the Canterbury area, so their final discharge mobility is unknown.

All patients alive at discharge (and in region) were followed in outpatients until their fractures were stable. At six months, three patients had bony non-union recorded, but all three were thought to have fibrous union and were stable.

# Discussion

The key findings in this observational study were that all patients were managed conservatively, mortality at one year was 21.9%, which is similar or better than other studies,[3,8,11,15,17] and complications were very common.[3,7,15,18] Most older people needed further inpatient rehabilitation, in part because of the rigid collar fixation and in part because of comorbidities. Sixty-seven percent walked independently without an aid prior to their injury, but the majority required some walking aid after discharge.

**Table 1:** Patient characteristics.

| | |
|---|---|
| **Number of patients** | 64 |
| **Gender** | |
| Male | 26 (41%) |
| Female | 38 (59%) |
| **Age (years) mean (SD)** | 80.6 (7.3) |
| **Ethnicity** | |
| European | 61 (95%) |
| Māori/European | 2 (3%) |
| American/European | 1 (2%) |
| **Charlson Comorbidity Index** | |
| Median | 2.0 |
| (IQR) | (1.0–3.0) |
| **Mechanism of injury** | |
| High-energy impact | 26 (41%) |
| Low-energy impact | 38 (59%) |
| **Acute treatment unit** | |
| Orthopaedic trauma unit | 48 (75%) |
| Intensive care unit | 7 (11%) |
| Acute general medical / coronary care | 4 (6%) |
| Oncology | 3 (5%) |
| Surgical specialty unit# | 2 (2%) |
| **Type of fracture** | |
| Odontoid type I | 2 (2%) |
| Odontoid type II | 22 (34%) |
| Odontoid type III | 26 (41%) |
| Hangman's body C2 | 2 (3%) |
| Pathological | 1 (2%) |
| Not classified | |
| *Not known* | 6 (9%) |
| *Multiple fractures* | 4 (6%) |
| *Complex C2/C3* | 1 (2%) |
| **Management of C2 fracture** | |
| Halo Immobiliser | 1* (2%) |
| Collar + brace | 9 (14%) |
| Rigid collar | 46 (72%) |
| Soft collar | 6 (9%) |
| No collar | 2 (3%) |

# Plastic surgery or maxillofacial unit with multiple trauma.

* Patient initially treated with halo immobiliser then changed to rigid collar.

**Table 2:** Patient outcomes.

| | **Premorbid** | **After discharge** | |
|---|---|---|---|
| **Domicile** | | | |
| Home | 57 | 43 | |
| Low-level residential care | 7 | 4<br>9 | |
| High-level residential care | | 6<br>2 | |
| Died | | | |
| Not known | | | |
| **Mobility** | | | |
| Independent, no aid | 43 | 9 | |
| Stick or crutches | 6 | 4 | p<0.0001 |
| Frame | 8 | 39 | |
| Immobile | 2 | 2 | |
| Unknown | 5 | 4 | |
| **Complications** | | | |
| Neurological from injury | 7 (11%) | | |
| Immobility | 16 (25%) | | |
| Other Injury related | 20 (31%) | | |
| Psychological | 26 (41%) | | |
| Collar related | 37 (58%) | | |
| Medical complications | 39 (61%) | | |
| **Length of stay (days)** | **Acute** | **Rehabilitation** | **Total** |
| Mean | 10 | 23 | 23 |
| Median | 8 | 21 | 16 |
| IQ range | (5–11) | (12–32) | (8–30) |
| **Mortality** | | | |
| Inpatient | 6 (9%) | | |
| At 30 days | 6 (9%) | | |
| At one year | 14 (22%) | | |
| At two years | 21 (33%) | | |

A rigid collar is an important treatment modality in the management of C2 fractures, but poor compliance can lead to non-union, which is associated with sudden death.[3] Previous studies have suggested that halo fixation is poorly tolerated in older people and concluded that rigid cervical collars are better tolerated.[3,6,14] Halo fixation was not tolerated by one patient in our cohort. Most of our patients were managed conservatively in a rigid collar, which is thought to be better tolerated. Despite this, nearly two-thirds (58%) of our cohort suffered a complication related to their collar, including difficulty eating and pressure areas as well as intolerance leading to poor compliance. The collars also created physical limitations on patients, such as being unable to look down to see their food or feet. This appeared to impact their ability to carry out activities of daily living (ADLs) such as walking, toileting and washing. Many older adults rely on visual cues for walking, and so rigid immobilisation of the neck can impact their ability and their confidence to walk. This may be one reason why there is an increased need for a walking aid on discharge, as was seen in our cohort of patients. The longer length of stay (mean 23 days, range 1–99 days) demonstrates the time it takes for patients to overcome their acute injury and learn how to manage their ADLs, injuries, collar cares and pain sufficiently to manage in the community.

A small proportion (six) of our patients were managed with a soft collar only. Although this is not recognised as a standard management strategy, three of these patients were still alive at two years despite having a soft collar as their only treatment. Soft collars may be a management option, but only in very select older adults who cannot tolerate more rigid immobilisation. Soft collars do not limit swallowing or mobility as much as rigid collars and so might reduce complications.[3]

Nearly 60% of our patients sustained their injury as a result of a low-energy impact, which is consistent with previous studies.[3,4,14] Although more patients sustained their injuries from a low-impact accident, very few of these patients (2%) had any neurological complications compared with 23% who sustained their injuries from high-energy accidents. Four out of these six patients sustained their injuries from motor vehicle accidents.

There is a lack of consensus over the management of C2 fractures in the elderly population.[1,3,5,10,15,22] While there is a trend for increased surgery for selected patients,[10] this trend is not universal[5] and most studies show the majority of older people are still treated non- surgically. Surgical approaches may have benefits of better immobilisation and higher bony union rates, but there can also be an increased risk of ICU admission and need for a feeding tube. There are concerns that an operative approach increases the early mortality rate compared with non-operative management, but this has not been demonstrated consistently.[3,14] For these reasons, surgery has tended to be for carefully selected patients—often those who are younger and with multi-trauma or less stable fractures.[8] In older patients, the risks of surgery are higher, in part due to comorbidities, and reports suggest conservative management may give similar longer-term outcomes.[3,12,23] This current non-comparative study does not address the surgery versus no surgery debate, but it does describe functional outcomes of conservative management of C2 fractures, including mobility and domicile, as well as highlighting some issues with rigid collar immobilisation.

The complication rate was high in this cohort as all patients had at least one complication during their inpatient stay. Documented complication rates vary enormously, from 0% to 91%, for non-operative management strategies.[3] Most recent studies report complication rates in the range of 35% to 46% of patients,[7,15,17,18] rates that are lower than those found in our study. There is no consistent approach for assessing complications, which makes it difficult to compare rates between studies. However, complications are clearly common in older patients who have a C2 fracture, regardless of treatment approach (surgical or conservative).

The mortality rates were 9% at 30 days and 22% at one year for our cohort of patients, which are comparable or better than other reported mortality rates.[3,8,11,15,16,23–25] Functional dependency pre-fracture was the main predictor of mortality in one study,[16] whereas increasing

age and comorbidities were predictors in others.[11,17,24] The unadjusted median CCI score of 2.0 found in our study predicts a one year mortality rate of 21%, which is similar to our one year mortality rate.[21] These data, together with the New Zealand paper by Chan et al,[11] suggest that late mortality (at one year) for older C2 fracture patients may be predicted more by their comorbidities and less by the C2 fracture itself. This is similar for other frailty fractures, such as femoral neck fractures, where frailty and comorbidities influence longer-term survival.[26]

As with other retrospective studies, there are limitations. It was a single-centre study and all patients were managed non-surgically. Inpatient rehabilitation occurred in three different units on two geographic sites, both of which are separate from the acute admitting hospital. There was less-frequent orthopaedic input in the older persons health unit at time of the study. Since then, all three units have moved to the same campus, with easy access to both orthopaedic and spinal input. Retrospective review of notes may underestimate complications, such as falls or delirium, if they were not accurately recorded at the time. Also, if discharge coding was different to S12.1, then some C2 fractures may have been missed. Three patients' notes could not be accessed, which resulted in a slightly smaller cohort than planned. However, in mitigation of these shortcomings, this is a comprehensive review of a five-year cohort of older patients with a C2 fracture that included a longer follow-up period (two years) and recorded complications and functional outcomes such as mobility and domicile, as well as use of rehabilitation services. Bony union was not consistently recorded in outpatient records and so could not be formally assessed, but all surviving patients were followed until their fractures were stable.

This study has shown that conservative management of C2 fractures in older patients has a significant impact on patients. All patients suffered from at least one complication. Nearly three in five patients required inpatient rehabilitation, and a similar number had collar-related complications. Functional limitations, such as increased need for walking aids, were very common post fracture and rehabilitation.


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# Is not fasting before cardiac catheterisation better than fasting? A systematic integrative literature review

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## ABSTRACT

**AIM:** To synthesise international evidence about not fasting before cardiac catheterisation.

**METHODS:** We used a systematic, integrative literature review and applied quality assessment criteria.

**RESULTS:** Nine of 1,535 articles met the inclusion criteria. Critique and analysis of the literature revealed three themes: (1) Fasting before coronary angiography and angioplasty is associated with perceived risk management, not actual risk management. (2) Not fasting before coronary angiography and angioplasty is considered safe and beneficial for the patient when compared to the risks of fasting. (3) Current practice, evidence and guidelines are inconsistent.

**CONCLUSION:** Ongoing concerns regarding not fasting before cardiac catheterisation are related to perceived risk, not actual risk. Indeed, this review indicates that not fasting may optimise patient experience. Further large-scale research is needed in this area to support policy and practice change to a patient-centric fasting protocol.


Coronary artery disease (CAD) is the leading cause of death internationally and the second leading cause of death in New Zealand.[1,2] The disease carries a significant health burden and affects more than 170,000 individuals across New Zealand.[3] Cardiac catheterisation is the gold standard test for diagnosis of coronary artery disease.[4] This procedure is minimally invasive and usually completed under conscious sedation. In recent years, the risks associated with this procedure have decreased substantially due to the development of equipment, peri-procedural care and operator experience.[5] Accordingly, diagnostic angiography is commonly completed as an outpatient procedure, with many elective angioplasties following the same trend.[6]

Historically, patients undergoing coronary angiography and angioplasty have been required to fast in preparation for this procedure.[7,8] However, scholars have questioned the evidence base for this practice, with some centres changing guidelines to remove fasting altogether.[9,10] Concerns regarding eating before procedures relate to the possible increased risk for pulmonary aspiration, a serious event that can lead to pneumonia, respiratory compromise and death.[11,12] However, fasting patients for an extended period could put patients at higher risk of other complications, including hypotension, contrast-induced nephropathy and hypoglycaemia.[5,13] Allowing patients to eat and drink before coronary angiography positively affects the individual's experience, improves patient satisfaction and reduces anxiety.[14–16] In this context, we aimed to synthesise current international evidence about not fasting before cardiac catheterisation.

## Methods

We used an integrative review to synthesise current evidence about not fasting before coronary angiography and

angioplasty. The integrative method is the broadest type of review, allowing the inclusion of studies with diverse methodologies, including both empirical and theoretical publications.[17,18] This systematic approach facilitates an in-depth analysis and captures varied perspectives on a topic without the focus on hierarchical evidence types.[17,18]

Searches were carried out via title, subject and keyword using the following online databases: MEDLINE, Scopus, the Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus), Cochrane and Web of Science. The search terms listed in Table 1 captured variations of the terms "non-fasted," "fasted," "before," "coronary angiography" and "coronary angioplasty." Terms were combined using Boolean operators. Inclusion and exclusion criteria are listed in Table 2.

The initial search yielded 1,531 papers. After the removal of duplicates and screening by title and abstract, seven studies remained and were screened by full text. Four papers were added through reference checking and screened. Of these 11, nine studies were included in the review (Figure 1).

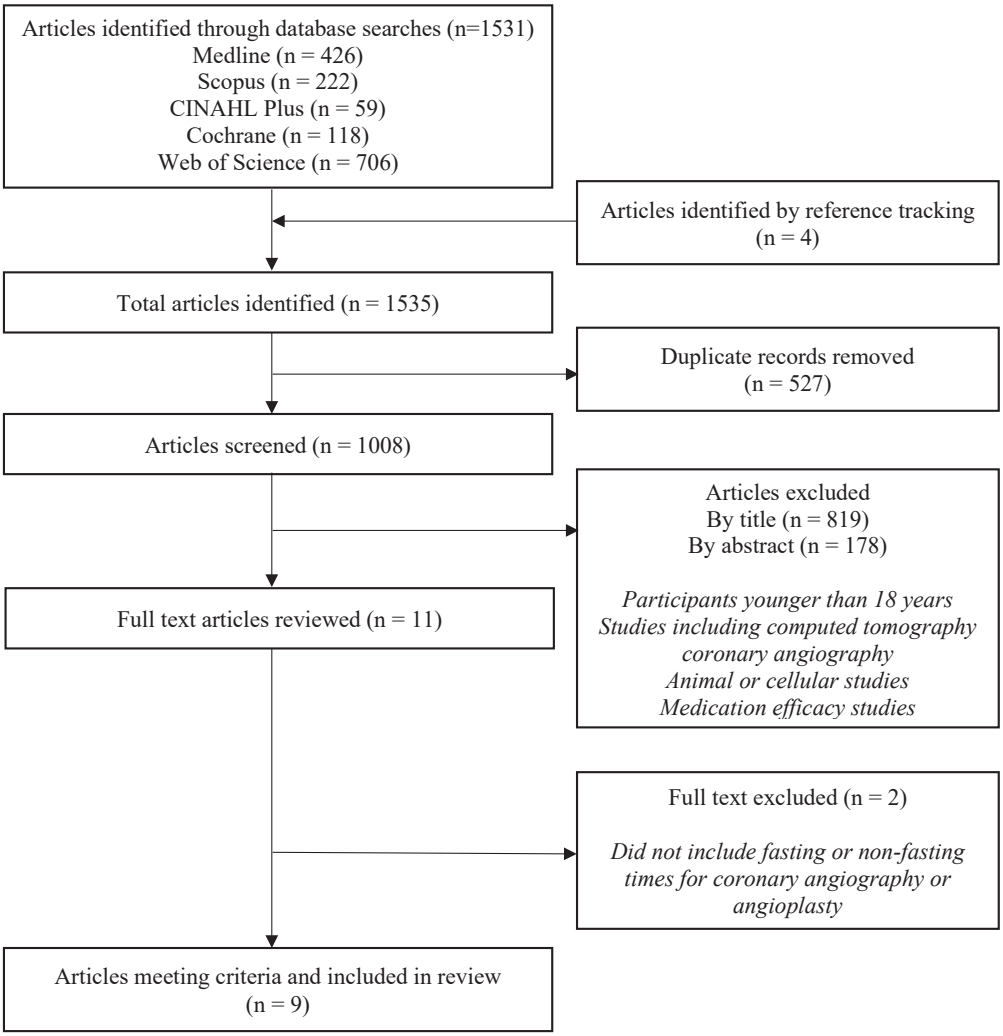
Data extraction was completed using a standard pro forma and included: relevance to the research question, study design and limitations.[19] Studies were then assessed for quality and methodological rigour (Table 3). For research reviews, no gold standard for quality scores exists; the diversity of methodologies means criteria for quality assessment are variable.[17] We chose the quantitative assessment tool developed by Hawker et al[20] to assess empirical studies and abstracts. This tool evaluates each section of the study, including abstract, research aims and background, methodology and sampling, data collection and analysis, ethics and bias and research findings. Overall, the quality of available evidence was low. The quality of evidence published by Hamid et al[9] and Bacus et al[14] were rated as fair. The abstracts from Mishra et al[15] and Li et al[21] were rated as poor as they did not provide sufficient information to accurately assess some article sections using the evaluation tool. The opinion pieces, study protocols and nursing guidelines were considered grey literature and were not formally scored for quality.[22]

**Table 1**: Search terms.

| Non-fasted | Fasted | Before | Coronary angiography and angioplasty |
|---|---|---|---|
| Unfasted | Fasting | Prior | Coronary angiogra[a] |
| Fed | Fast | Pre-procedur[a] | Cardiac angiogra[a] |
| | Starve | Preprocedur[a] | Coronary catheteris-[b]ation |
| | Starved | | Cardiac catheteris[b]a-tion |
| | Nil by mouth | | Coronary arteriogra[a] |
| | Nil-by-mouth | | Cardiac arteriogra[a] |
| | NBM | | Angioplasty |
| | Nil per o[a] | | Percutaneous coronary intervention |
| | Nil-per-o[a] | | |
| | NPO | | |

[a] different endings expanded during search; [b] different spelling applied during search.

**Figure 1:** Flowchart of literature selection process.





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The process of thematic data analysis followed the six-phase approach outlined by Braun and Clarke: familiarisation with data, generating initial codes, searching for themes, reviewing themes, defining and naming themes and producing the report.[23] Data from all studies were extracted and coded. Codes were catalogued and grouped in Microsoft Excel to allow for identification of themes. This theme-based approach to data extraction allowed information from a variety of sources to be compared and combined.[24]

# Results

Of the nine studies included in this review, there was one retrospective observational analysis of a data registry,[9] one prospective observational study[14] and two abstracts of randomised controlled trials from conference proceedings.[15,21] There were three opinion pieces (two of which provided commentary on other studies included in this review),[16,26,27] one published clinical guideline[28] and one record from a clinical trials register.[25] Three studies discussed both coronary angiography and angioplasty[14,21,25] and five studies discussed coronary angioplasty only.[9,16,26–28] One study did not outline whether included participants underwent coronary angiography or angioplasty.[15] Seven studies commented on the incidence of outcomes associated with fasting or not fasting.[9,14–16,21,25,26] Of the four empirical studies, one was completed in the United Kingdom,[9] one in New Zealand,[14] one in Singapore[21] and one in the United States of America.[15] The planned study, found on the clinical trial registry, will be completed in the United Kingdom.[25]

Two full-text empirical studies were identified, one with 1916 participants involved[9] and the second with 1,030 participants.[14] Abdelaziz[25] has indicated an intention to complete a randomised controlled trial involving 600 participants. Their study outline hypothesises that there will be no difference in the incidence of procedural complications between non-fasted and fasted groups and that the non-fasted groups will have a lower incidence of hypoglycaemia and hypotension.[25] This is similar to Hamid et al[9] and Li et al,[21] who aimed to show the safety of not fasting before coronary angiography and angioplasty. Three studies concluded that their results demonstrated the safety of this practice.[9,15,21]

Thematic analysis identified the following three themes related to not fasting before cardiac catheterisation:

- Fasting before coronary angiography and angioplasty is associated with perceived risk management, not actual risk management.
- Not fasting before coronary angiography and angioplasty is considered safe and beneficial for the patient when compared to the risks of fasting.
- Current practice, evidence and guidelines are inconsistent and further study is required.

**Table 2**: Inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Papers published in English. | Papers not published in English. |
| Papers including participants aged >18 years inclusive. | Papers including participants younger than 18 years. |
| Studies relating to coronary angiography or coronary angioplasty. | Computed tomography coronary angiography and magnetic resonance coronary angiography. |
| Meta-analysis, literature reviews, opinion pieces, letters, commentaries, conference proceedings, clinical trials, practice guidelines, policy statements. | Grey literature not captured in included online databases. |
| Papers published on or before 21 May 2020. | Papers published after 21 May 2020. |

**Table 3:** Evidence on not fasting before cardiac catheterisation.

| Author, year, country, quality | Type of literature | Setting and sample | Focus and aims of each study | Data related to not fasting before cardiac catheterisation |
|---|---|---|---|---|
| Abdelaziz, 2018,[25] United Kingdom,<br>quality: poor | Registered protocol for a randomised control trial.<br>Clinical trials registry. | Teaching hospital.<br>Anticipated 350 participants.<br>All patients 18 years and over undergoing elective coronary angiography or angioplasty.<br>All elective patients at this hospital were given the opportunity to participate. | Aim is to show there is no difference in potential complications between fasting and non-fasting groups.<br>The author hypotheses that there will be a lesser incidence of hypoglycaemia and hypotension and greater patient satisfaction, improved catheter lab efficiency and associated financial benefits in the non-fasting group.<br>Outcomes measured will include the incidence of nausea, vomiting, abdominal pain, emergency intubation and aspiration within 8 hours.<br>Secondary outcome measures will include hypoglycaemia, hypotension, patient satisfaction, and chest infection. | Current fasting practices before coronary angiography and angioplasty are not based on studies.<br>Previously, fasting practices were based on guidelines for general anaesthesia.<br>Emergency procedures carry the most risk and are done without fasting patients.<br>There is no reported complication rate for emergency procedures, where patients are not fasted. |
| Aguilar-Nascimento and Fergi, 2015,[26] Brazil, quality: poor | A commentary of Hamid et al.[9]<br>Published in a peer-reviewed journal. | N/A | Brief context provided and the findings of Hamid et al[9] are discussed, with some integration of references from other sources.<br>Endorses the findings of Hamid et al.[9]<br>A strong recommendation is made for further research in this area. | Agreement that data suggests fasting is not necessary for angioplasty.<br>Preoperative fasting increases insulin resistance and gluconeogenesis.<br>Agreement that prolonged fasting causes dehydration and increased risk of acute renal failure.<br>Highlights the necessity for a revision of fasting protocols for angioplasty. |
| Bacus et al, 2020,[14] New Zealand, quality: fair | Prospective, observational study.<br>Single-centre. | Public hospital.<br>1,030 consecutive patients over six months undergoing elective coronary angiography or angioplasty.<br>2017–2018. | Aimed to assess current practice and quantify duration of fasting and the rate of fasting related complications. | There was a wide variation in fasting practice within the single institution.<br>The fasting duration was much longer than anticipated.<br>Patients fasted up to 24 hours (mean=11.6 hours), and only 11% received pre-hydration.<br>The rate of vomiting was low, and no aspiration events occurred.<br>The author claims the data supports the need for further research in this area.<br>Measured outcomes: hunger (47.1%), headache (11.6%), hypotension (6%), hypertension (4.1%) nausea (3.9%), arrhythmia (1.3%), hyperglycaemia (0.8%), vomiting (0.8%), vasovagal syncope (0.8%), hypoglycaemia (0.7%), aspiration (0%). |

**Table 3:** Evidence on not fasting before cardiac catheterisation (continued).

| Author, year, country, quality | Type of literature | Setting and sample | Focus and aims of each study | Data related to not fasting before cardiac catheterisation |
|---|---|---|---|---|
| Hamid et al., 2014,[9] United Kingdom, quality: fair | Retrospective observational analysis of a data registry. | Two district general hospitals.<br>1,916 consecutive patients undergoing angioplasty.<br>2010–2013. | To demonstrate that percutaneous cardiac catheterisation does not require prior fasting.<br>No patients were required to fast before their procedure. | The incidence of intraprocedural endotracheal intubation, aspiration pneumonia and on table death was zero.<br>Authors claim that their study shows that patients do not need to be fasted before coronary angioplasty procedures.<br>Patients undergoing urgent angioplasty following acute myocardial infarction are not fasted and the need for emergency intubation or cardiac surgery for such patients is rare.<br>Reducing fasting times could arguably reduce acute kidney injury in this patient cohort, avoiding associated extended hospital stays and economic and health implications. |
| Hamid et al., 2014,[16] United Kingdom, quality: poor | An author's reply to the commentary reported by Wijeyeratne, Wendler.[27]<br>Commentary/authors reply.<br>Internally peer-reviewed. | N/A | To raise awareness regarding not fasting before angiography and angioplasty. | There is a difference in fasting protocol between institutions, for the same procedure.<br>Concerns for increased risk of pulmonary aspiration in non-fasted patients are most likely unfounded.<br>Patients undergoing emergency angioplasty procedures do not fast and there is no reported excess of peri-procedural pulmonary aspiration on the British Cardiovascular Intervention Society national registry.<br>When patients are not fasted, radial access for procedures may be easier and less sedation induced hypotension may occur. |
| Li et al, 2017,[21] Singapore, quality: poor | Article abstract from conference proceedings.<br>Randomised control trial. | General hospital.<br>515 patients.<br>Randomisation to overnight fasting or limited-fasting group at referral for outpatient angiography. | To show that routine cardiac catheterization is safe in non-fasted patients. | More patients in the limited fasting group required sedation than the overnight fasting group due to anxiety or radial spasm.<br>More patients required fluid bolus for hypotension in the overnight fasted group (4% vs 9.4% p=0.02).<br>Two patients in the overnight fasting group reported nausea post procedure unrelated to sedation use.<br>No incidence of vomiting or SaO2 <92% in either group. |

**Table 3:** Evidence on not fasting before cardiac catheterisation (continued).

| Author, year, country, quality | Type of literature | Setting and sample | Focus and aims of each study | Data related to not fasting before cardiac catheterisation |
|---|---|---|---|---|
| Rolley et al., 2011,[28] Australia/New Zealand, quality: poor | Nursing clinical practice guidelines.<br>Guidelines created following a literature review, a consensus development workshop and a modified Delphi technique. | N/A | To present a set of nursing clinical practice guidelines for individuals undergoing angioplasty together with a summary of the evidence to support the recommendations. | Based on available evidence, it is not justifiable to routinely fast patients undergoing angioplasty.<br>Fasting should be on a case-by-case basis and based on clinical judgement.<br>The grade of this evidence is "N," meaning no consensus was achieved regarding the recommendation.<br>Fasting is widely implemented due to theoretical considerations and potential risk. |
| Mishra et al., 2019,[15] United States of America, quality: poor | Article abstract from conference proceedings.<br>A single centre, prospective, randomized study.<br>Preliminary analysis | 253 inpatients.<br>Up to December 2018. | The fasting group and non-fasting group had similar rates of contrast induced nephropathy (3% vs 4%), peri-procedural.<br>hypotension (3% vs 0.8%), aspiration pneumonitis (0 vs 0.8%), nausea/vomiting (4% vs 8%), hyperglycaemia (7% vs 2%), hypoglycaemia (0.8% vs 2%) and 30-day mortality. For all outcomes p=not significant.<br>The non-fasting group had higher patient satisfaction scores (4.3±0.08 vs 4.1±0.09, p=0.039).<br>The non-fasting group had lower cost of index hospitalisation (9,693 USD±878 vs<br>13837 USD±1,470, p=0.016) | Not fasting is associated with improved patient satisfaction and reduced cost of care when compared to traditional fasting practices.<br>The incidence of adverse outcomes were similar between fasting and non-fasting groups. |
| Wijeyeratne et al, 2014,[27] United Kingdom, quality: poor | A commentary on Hamid et al.[9]<br>Commentary/letter to the editor.<br>Internally peer-reviewed. | N/A | The aim of this commentary is unclear. | There is no clear evidence to support the current practice of fasting before invasive cardiac procedures.<br>The paper by Hamid et al[9] serves to raise awareness.<br>Wider applicability of research by Hamid et al[9] may be limited due to study methods.<br>Fasting before cardiac procedures appears to have come from fasting guidelines for general anaesthesia. The theoretical risk is that sedation may depress cough and swallow reflexes.<br>There are no consensus guidelines in this area and the evidence base is poor. More robust evidence would, therefore, be crucial to establish best practice and promote consistency. |

## Theme 1: fasting before coronary angiography and angioplasty is associated with perceived risk management, not actual risk management

The benefits of fasting found in this literature search are centred around mitigating the possible risks associated with not fasting. Fasting is thought to reduce the risk of vomiting, bronchial aspiration and resulting pneumonia.[9,14,26] However, Hamid et al[16] suggest that the increased risk of aspiration in unfasted patients is unfounded. There is also a perceived benefit of fasting due to the possibility of proceeding to emergency surgery and the need for general anaesthesia.[9,28] For this reason, patients routinely fast from four to eight hours before coronary angiography.[9,14,26] Hamid et al[9] claim that the benefits of fasting before coronary angiography and angioplasty are not evidence-based, as little evidence exists. Hamid et al[16] suggest that the risk associated with not fasting has been overstated and that those who fast may be at greater risk of complications. Interestingly, individuals presenting with an acute requirement for angioplasty did not fast before the procedure.[16] Further, there are limited reports of excess peri-procedural pulmonary aspiration or related complications during emergency coronary artery bypass grafting in the unfasted patient.[16,25]

## Theme 2: not fasting before coronary angiography and angioplasty is considered safe and beneficial for the patient when compared to the risks of fasting

Coronary angiography is considered a safe procedure, which brings into question the need for fasting in preparation.[26] In one study involving 1,916 angioplasty patients over three years, only two patients (0.1%) required subsequent emergency coronary artery bypass grafting surgery.[9] Also, none of the patients in this population fasted, and yet none required intubation during the angioplasty procedure and there were no episodes of aspiration pneumonia. Similarly, Bacus et al[14] reported that, among 1,030 elective coronary angiography and angioplasty patients, there were no episodes of aspiration. Mishra et al[15] recorded one episode of aspiration pneumonitis in the non-fasting group of 253 inpatients, and this did not represent a statistically significant difference between the non-fasting and fasting groups. The outcomes of small-scale studies demonstrate that reducing or eliminating fasting before coronary angiography and angioplasty may be safe. However, further studies are needed to explore this.[9,21,26]

The benefits of not fasting before cardiac catheterisation are mostly perceived rather than evidence-based. Scholars hypothesise that allowing patients to eat and drink up to the time of their procedure will increase their level of hydration, reduce the risk of contrast-induced nephropathy, improve vascular access and reduce peri-procedural hypotension and hypoglycaemia.[9,14,16,21] Fasting-related procedural delay and cancellation is thought to significantly impact patients and optimal health resource allocation.[14] These delays can be avoided, and hospital stays potentially shortened, if patients are allowed to eat pre-procedure.[9,16,25] Scholars also predict that non-fasting patients may be less anxious before their procedure.[16] Following preliminary analysis, Mishra et al[15] reported that non-fasting patients had a significantly higher patient satisfaction score and a lower cost of index hospitalisation compared to the fasting group.

Pre-procedural fasting is associated with risk and possible complications. In a randomised trial, patients that were allowed to eat up to two hours before angiography had a lower incidence of hypotension requiring a fluid bolus (4% vs 9.4%) and a lower incidence of nausea (0% vs 0.8%) when compared to those who had fasted overnight.[21] However, patients that were fasted for less time also required a larger dose of sedation (6.8% vs 2.6%) as a result of anxiety or arterial spasm.[21] Mishra et al[15] compared patients who fasted solids from midnight and clear fluids from two hours before the procedure to patients who were allowed to eat and drink until the time of the procedure. There was no statistically significant difference between the two groups for incidence of adverse events, such as peri-procedural hypotension, contrast-induced nephropathy, hypoglycaemia, hyperglycaemia, nausea,

vomiting and 30-day mortality. In the study completed by Bacus et al[14] , 47% of patients with a mean fasting time of 11.6 hours reported feeling hungry, and 11.6% reported headaches. Prolonged periods of fasting is thought to increase insulin resistance, potentially exacerbating the metabolic response following trauma.[16] Additionally, patients who are fasting may be less likely to take their morning medication, including anti-hypertensives, leading to poorly controlled hypertension.[9] Bacus et al[14] reported eight episodes of hyperglycaemia and seven episodes of hypoglycaemia, suggesting that this may have been due to missed medications and prolonged fasting. Fasted individuals, particularly the older age group, are at risk of dehydration, hypoglycaemia and contrast-induced nephropathy.[9,26] Such complications could lead to a prolonged hospital stay with economic and health implications.[9]

### Theme 3: current practice, evidence and guidelines are inconsistent and further study is required

Data available in this review indicate there is an inconsistency in practices between institutions. In New Zealand, one hospital guideline recommended fasting patients for four to six hours.[14] The practice in two district general hospitals in the United Kingdom was that no patients were fasted in preparation for cardiac catheterisation.[9] In Singapore, standard practice in one hospital was to fast patients from midnight for both elective and in-hospital cardiac catheterisation.[21] The duration of fasting within a New Zealand institution was variable, with patients fasting anywhere between zero and 24 hours before their procedure.[14] The mean fasting time of 11.6 hours was greater than anticipated considering the maximum recommended duration for fasting was six hours.[14] In emergencies, however, angioplasty is performed urgently without any fasting restrictions.[9,26] Current practice in this context is based on limited scientific evidence and may have developed from fasting guidelines for general anaesthesia.[9,14,16,25–27] According to Wijeyeratne et al,[27] the evidence base relating to this practice and the optimal period of fasting has been "exceedingly slow to develop."

Authors of papers included in this review claim that there are no available fasting guidelines specific to coronary angiography and angioplasty.[9,16,26] Instead, information and opinion identified in this review suggest that practice is based on local hospital and health board guidelines, which are considered inconsistent and unsubstantiated.[9,25,27,28] Protocols and guidelines such as this require revision.[26] Clinical nursing guidelines for angioplasty published in 2011 state that, given the available evidence, routine fasting for coronary angioplasty "is not justifiable; fasting should be based on clinical judgement on a case-by-case basis."[28] However, the grade of this recommendation was documented as low, and consensus among the panel of clinical experts had not been reached. Clinicians are encouraged to "follow local policy and procedures."[28]

Although both Hamid et al[9] and Mishra et al[15] suggest that their research demonstrates patients do not require fasting before coronary angioplasty, this review identified that there is consensus on the need for further study.[9,16,21,26,27] Future research should involve larger cohorts and multiple centres in randomised controlled trials in order to support interventional cardiologists to change from their current practice.[9,16,21,26,27] Studies currently underway aim to record the incidence of outcomes related to fasting and not fasting, such as contrast-induced nephropathy, hypotension, nausea, vomiting, emergency intubation, aspiration pneumonia, hyperglycaemia, hypoglycaemia and patient satisfaction.[15,25]

## Discussion

Overall, analysis of the nine papers in this review identified limited evidence about not fasting before cardiac catheterisation. Thematic synthesis revealed that, although not fasting in this context is generally considered to be safe, there is still concern with implementing this practice in a clinical setting. This review identified that the potential for vomiting and pulmonary aspiration are two significant concerns associated with not fasting before coronary angiography and angioplasty. Vomiting, nausea and allergic reactions were once common complications of angiography due to the hypertonic nature of first-generation

contrast dye.[29] In some reports, reactions to contrast dye occurred in over 50% of cases.[30] Such reactions could be why fasting was once a relevant choice for cardiac catheterisation. However, contrast dye used today is low-osmolality and non-ionic, and the reported rate of vomiting is low (0.8%).[5] Similarly, the risk of requiring emergency surgery has reduced significantly in recent years and is reported at around 0.14% in the contemporary setting.[31] These diminishing risks question the necessity of this practice.[14]

Although there is limited recent evidence to support fasting in this context, this practice continues to be widely enforced and supported by healthcare professionals. The recommendation of fasting before cardiac catheterisation is based on perceived risk, and it does not acknowledge the potential risk associated with fasting. It may be that physicians are more concerned by rare events with potentially severe outcomes than the possibility of more common adverse events with lesser effects from not fasting. For example, the perceived risk of aspiration causing serious harm for a small number of individuals may be over-emphasised in the context of the general wellbeing and comfort of the majority of patients. Although this is understandable, it limits the opportunity to foster the potential safe and beneficial outcomes of not fasting in this context. Indeed, in the randomised controlled trial by Mishra et al,[15] unfasted patients reported higher satisfaction scores following cardiac catheterisation compared to those who fasted.

Research in other fields does not show a connection between not fasting and vomiting or aspiration when patients receive conscious sedation. In a study of cerebral angiography by Kwon et al,[32] there was no statistical difference in nausea and vomiting between fasting and non-fasting groups, and there were no cases of pulmonary aspiration among 2,554 patients. The overall incidence of nausea and vomiting was low, reported at 1.05%. Similarly, a systematic review of various procedures involving conscious sedation found no episodes of aspiration in unfasted patients undergoing procedures other than endoscopy.[33] Research regarding procedural sedation in the emergency department has shown no association between fasting duration and the incidence of vomiting and other complications.[12,34,35] Indeed, current recommendations for conscious sedation in the emergency department state that fasting is not required when verbal contact is maintained.[36]

The overall quality of evidence included in the review was assessed as poor when compared to empirical evidence, as it is based predominantly on expert opinion.[22,37] However, the quality of grey literature is variable, and its inclusion can be important in reducing publication bias and providing contextual factors.[38] The low quality of evidence identified by this review limits understanding of the safety of not fasting and its future utility. Further, there is no consensus among experts for recommendations in this area and practice varies greatly between and within hospitals.[9,14,21,25,26,28] Indeed, current guidelines and local practices may not be based on scientific evidence. We argue that further investigation into the risks and benefits of not fasting before cardiac catheterisation is warranted.

# Conclusion

This is the first systematic review to synthesise evidence about not fasting before coronary angiography and angioplasty. It has revealed limited evidence regarding this practice. Thematic analysis of nine studies demonstrates that current fasting practices are based on managing perceived risk and that not fasting before angiography is generally considered safe and beneficial for the patient. Due to the gap in knowledge that exists regarding this topic, there is significant potential for future research, both locally and internationally. Future multicentre randomised controlled trials will build a reliable and robust knowledge base on this topic. It appears that the ongoing concerns around not fasting are related to perceived risk, rather than actual risk. However, further research is needed in this area to support policy and practice change on a large scale.

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# The assessment of competency and coercion in the End of Life Choice Act 2019

Jane Casey, Sandy Macleod

**ABSTRACT**

The eligibility criteria of the End of Life Choice Act 2019 specify the person must be competent to make an informed decision about assisted dying. The patient must initiate the conversation about assisted dying, and then it is incumbent on health professionals to perform a skilled exploration of the person's suffering and rationale. The legal standards for competence must be met. Common mental health and cognitive disorders that may impact on decision-making must be recognised. The context and the authenticity and consistency in choice are important elements. Education and training of involved health practitioners is required to ensure the assessment process is robust. A comprehensive approach is necessary to determine the autonomy of the decision and for the protection of the rights of the individual.

The matter of medically assisted dying can be difficult to discuss in a dispassionate way. For doctors it may raise many conflicts: the duty to preserve life yet the duty to relieve suffering, the duty to respect patient autonomy yet the duty to do no harm. In psychiatric practice, there is the issue of suicide prevention. And clinicians have their own family, religious and cultural foundations and life experiences, which inform perspectives on this complex topic.

The fact of this matter is that assisted dying will become lawful in New Zealand from 7 November 2021. The End of Life Choice Act 2019 (the Act) will give people who experience unbearable suffering from a terminal illness the option of asking for legal medical assistance to end their lives, and clinicians across the health and disability sector will be asked about assisted dying.[1]

## Eligibility criteria

A person must meet all of the criteria to be eligible for assisted dying (Figure 1). Importantly, a person cannot access assisted dying solely because they are suffering from a mental disorder or mental illness, have a disability or are of advanced age.

A discussion on the challenges of accurate prognosis or the definition of *advanced state* or *unbearable suffering* is beyond the scope of this paper. However, as noted in the First Annual Report on Medical Assistance in Dying in Canada (2019), suffering is closely tied to loss of autonomy and loss of ability to engage in meaningful life activities or perform activities of daily living.[2] It has been recognised for decades that the request for medical assistance in dying is usually motivated by multiple interactive factors, including both physical and psychological suffering and a desire to control the circumstances of one's death.[3]

## Medical practitioner cannot initiate discussion

According to Section 10 of the Act, a medical practitioner cannot initiate a conversation that is *in substance* about assisted dying. This concept was introduced in the supplementary order paper by Mr David Seymour, Member of Parliament for Epsom, as a safeguard similar to what is in place in Victoria, Australia. This

prohibition overrides the right to be fully informed where Right 6(1b) of the Code of Health and Disability Services Consumers' Rights (the Code) states that a person has a right to the information that a reasonable person in their circumstances would expect to receive, including "an explanation of the options available." Doctors will need to be mindful in the exploration of a person's suffering, as Section 10 of the Act limits frank discussion regarding future management. It raises issues for how a clinician responds to a patient expressing the wish to die or hasten their death and/or suicidal ideation. Discussion around suicide may be important and indeed preventative. It may be challenging to navigate when a patient asks about all the treatment options without specifically asking about assisted dying. Once the person directly enquires about assisted dying, Right 6 of the Code applies in full.

Research suggests that it is generally the well-educated who seek medically assisted dying.[4] Therefore, Section 10 may discriminate against groups who are not aware of this option or are in some way constrained, shamed or fearful. The importance of the doctor–patient relationship and delicate skill in the exploration of the issues cannot be understated. Time needs to be taken to enable a person-centred conversation in trust but without influence. This will protect against suboptimal decisions, clinician distress or, in the worst-case scenario, being subject to proceedings by the Health and Disability Commissioner.

If a medical practitioner with a conscientious objection is asked by a person about assisted dying, they have certain responsibilities under the Act. Once the Section 11 request is made, the attending medical practitioner has to undergo certain steps in the process. These are detailed in the Act and on the Ministry of Health website.

## Assessment of competency

Inherent to the eligibility criteria is the assessment of competency. In the Code and common law, there is the presumption of competence. However, under the Act, there is no presumption; the person requesting assisted dying must be assessed and found competent to make an informed choice and be competent at the time the medication is administered. Under Section 6, "competent" requires the person to be able to understand, retain and use or weigh information as part of the process of making the decision, and then communicate the decision (Figure 2). These legal standards for competence should be well familiar to clinicians. They form the backbone to the assessment of informed consent as outlined in the seminal paper of Appelbaum & Grisso.[5]

Under Section 11, the attending medical practitioner is further required to *do their best to ensure that the person expresses their wish free from pressure from any other person by conferring with other health practitioners who are in regular contact with the person; and conferring with members of the person's family approved by the person*. If it is suspected on reasonable grounds that a person is not expressing their wish free from pressure from any other person, under Section 24 the attending medical or nurse practitioner is required to take no further

**Figure 1:** Section 5 Meaning of person who is eligible for assisted dying.

a. be aged 18 years or over
b. be a citizen or permanent resident of New Zealand
c. suffer from a terminal illness that is likely to end their life within 6 months
d. be in an advanced state of irreversible decline in physical capability
e. experience unbearable suffering that cannot be relieved in a manner that the person considers tolerable
f. be competent to make an informed decision about assisted dying.


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action and to inform the patient of the same.

Assessing a person's capacity to decide to bring forward their death and then ensuring that the request is an autonomous wish, freely expressed without coercion, requires a skilled and considered approach to assessment. Given the gravity and finality of the decision, there needs to be certainty. The involved health practitioners will need to develop skills and allow time for this task-specific assessment of capacity to decide. The assessors will also need to be aware of their own issues where it has been shown that those with a previous bias against assisted dying are more likely to deem a person incapable than those who were neutral or accepting of the option.[6]

There will be questions around patients' understanding of the underlying condition, the available treatments and the prognosis, the access to palliative care and other end of life care options. Of note, under Section 33, an advance directive cannot provide for assisted dying. However, a previously thought through advance care plan may facilitate discussion on important aspects, such as significant others and spiritual needs. The understanding of the legal process, the medication and procedure, the effect and possible complications and the impact on family and friends will be discussed. The length of time that assisted dying has been considered, the consistency of the expressed wish, the option to change their mind or withdraw at any time and a review of the decision at intervals will be necessary. This educative process by the attending medical practitioner, performed in tandem with the comprehensive assessment, will take place over time and may involve several consultations. This is followed by a second assessment and opinion by an independent medical practitioner. If competence is not established to the satisfaction of either medical practitioner, a third opinion must be obtained from a psychiatrist. This lengthy process is essential and must be robust, yet it may be difficult for some with a terminal illness to endure.

Most standardised tests of competency focus upon the procedural aspects of the capacity to decide. The NICE Capacity and Consent Tool provides guidance on criteria to use when assessing decisional mental capacity.[7] The MacArthur Competence Assessment Tool for Treatment is widely used with validity across a variety of populations.[8] The Aid to Capacity Evaluation, developed to help clinicians systematically evaluate capacity when a patient is facing a medical decision, has the potential to be adapted for this clinical domain.[9] Although useful, assessment tools have their limitations. Self-identity and decision-making capacity are dynamic and change with the individual's network of relationships, and their cultural and social context. This may be particularly relevant for Māori, tikanga Māori and taha whānau principles. A relational autonomy approach, which promotes understanding and incorporating a person's interpersonal context, is used to assesses authenticity, consistency and social dimensions with the decision to be made in line with the person's values, commitments and beliefs and in continuing interactions with others.[10]

**Figure 2:** Section 6 Meaning of competency.

In this Act, a person is competent to make an informed decision about assisted dying if the person is able to—

a. understand information about the nature of assisted dying that is relevant to the decision; and
b. retain that information to the extent necessary to make the decision; and
c. use or weigh that information as part of the process of making the decision; and
d. communicate the decision in some way.

## Comorbid conditions that may impact on competency

In a terminally ill patient, there are potential comorbid cognitive and mental health disorders that require recognition. They are, in essence, any condition that may impact on attention, memory, executive function, reasoning and judgment. The presence of a mental illness or cognitive disorder does not automatically preclude decision-making capacity, yet there needs to be careful assessment to determine that competency is preserved.

Depression may be comorbid with terminal illness and compound feelings of hopelessness and burdensomeness. In patients with cancer with a poor prognosis of <3 months life expectancy, the presence of depression has been shown to be associated with requests for euthanasia.[11] However, the request may depend on one's state, with the expressed wish for euthanasia in depressed older people mostly being resolved upon treatment for depression.[12] The presence of other mental illnesses that may impact on capacity, such as a psychotic or substance use disorders, need to be recognised and teased out. Delirium is a common, if not inevitable, complication of dying. The diagnosis of delirium in the medically frail may be difficult and confounded by patient discomfort, anguish, restlessness, fatigue and drowsiness. Even within cognitive fluctuations—so-called "lucid intervals"—underlying higher cortical functioning is likely to be subtly impaired.[13]

Older patients with comorbid cognitive impairment may initiate a request. Mild or even moderate cognitive impairment does not necessarily preclude the capacity to decide. In this situation, there would be a careful assessment of cognition with a focus on working memory and frontal executive function. Exploring aspects of autobiographical memory are important in the assessment of authenticity and consistency in the expressed wish.[14] In disorders of the frontal lobe, bedside tests of verbal fluency, trail-making and clock-face tests can be performed, but it is abstract thinking and the ability to reason or use and weigh relevant information that are vital in the evaluation of judgment. It is important to ensure that retained language function is not confabulation or masking deficits in underlying conceptual thinking, as seen in frontal lobe dysfunction. [15]

The presence of aphasia may hamper the assessment, and a speech-language therapist may be required to facilitate communication. Moreover, there needs to be careful screening, as there is increasing evidence that the higher-level executive skills of judgment, flexibility, planning and foresight can be affected in association with aphasia.[16]

Cancer-related cognitive decline (CRCD) associated with the diagnosis and/or treatment is a more subtle disorder of cognition, compared to other neurodegenerative disorders. In these patients there can be deficits in memory, attention, executive function and speed of processing information. The rates of CRCD may vary from 10–50%, depending on the variables, including the cancer type and therapy. The mechanisms are not fully understood, and symptoms can persist long after the therapy.[17]

## Protection against coercion

This is perhaps the most difficult aspect in the process of assessment. Article 16 of the United Nations Convention on the Rights of Persons with Disabilities mandates the right of freedom from exploitation, violence and abuse. It is now considered to be routine in all capacity assessments to assess the "freedom" of the decision. Under Section 11(h) of the Act, the attending medical practitioner is required to *do their best* to ensure that the person expresses their wish free from pressure from any other person. This is arrived at by conferring with health practitioners, such as medical colleagues, nurses, social workers and others who are in regular contact with the person, and by conferring with members of the person's family *approved by the person*. If ever there was a decision that had to be autonomous, it should be the request to end one's life, yet discussion and family consultation would seem crucial in most cases.

One question to consider will be whether the person requesting assisted dying contemplated the potential adverse impact

of their death on their loved ones. Families may report feeling pressured to accept a relative's wish for assisted dying, especially if "threatened" with the alternative prospect of their suicide. The assessing health practitioner will become versed in relevant probing questions to discover who suggested the idea, who may benefit, whether the individual may feel like a burden or whether there are financial or other pressures. The individual must be assessed on their own, yet this may be challenging for the terminally ill due to the understandable physical presence of the attending whānau and carers (Figure 3).

Discussion with family allows for an opportunity to explore family perceptions, to screen for coercion and to resolve issues underlying the request. In family meetings, signs of possible coercion may be observed, such as individuals talking over the patient or the patient deferring to others.[18]

A considered and cautious approach is necessary to ensure that the request for assisted dying is free from coercion. Under Section 24 of the Act, if at any time the attending medical or nurse practitioner suspects on reasonable grounds that a person who has expressed the wish to receive assisted dying is not expressing their wish free from pressure from any other person, the health practitioner must take no further action under the Act and inform the person that they are doing so. Health practitioners may also need to consider their broader professional obligations in the situation where there are evident risks to a patient.

# Conclusion

The option of assisted dying will become available for New Zealanders. The End of Life Choice Act 2019 is person-centred, with the role of whānau and family being important yet guided by the patient. The eligibility criteria include the requisite competence to make this final decision and that the choice is voluntary. A comprehensive approach is essential in the assessment of capacity and vulnerability to coercion. Education, training and support for involved health practitioners is being rolled out by the Ministry of Health. The competency cell of Section 6 needs to be complemented with an assessment of the person's capacity for reflection; the impact of distorting influences, such as overpowering emotions, depression or other mental illness; and in certain conditions, a review of cognitive function. An assessment of psychosocial context is required to assess authenticity and consistency. A comprehensive approach to assessment of both the procedural and contextual elements is vital as a safeguard to protect the vulnerable in our society.

**Figure 3:** Questions on context and freedom of choice.

When did you first think of assisted dying as an option?
Did someone suggest assisted dying as an idea?
Are you requesting assisted dying for yourself or others around you?
If others, who will benefit from your assisted dying and how?
Are you feeling any pressure from others to request assisted dying?
Do you feel you may be a burden to others?
Do you have any significant financial concerns?
Do you have any concerns for your family after you die?
Is there anything we need to know that you don't want your family or others to know?

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# What are the long-term outcomes for New Zealand survivors of critical illness?

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## ABSTRACT

The COVID-19 pandemic has drawn considerable attention to the survival journey and recovery of patients post critical illness. A decade ago, the Society of Critical Care Medicine described the prolonged adverse health effects after a critical illness as the "post intensive care syndrome" (PICS). Evidence is emerging from Australia around the impact critical illness has on disability, mental health, cognitive function and health-related quality of life for patients this side of the world. For example, one study has shown that disability was highly prevalent in survivor's six-month post hospital discharge, with 50% having mild disability and 25% with moderate to severe disability. Currently it is unknown what the survival journey is like for patients in New Zealand; how we should best measure outcomes for our population; and how we should support Māori and Pasifika patients post critical illness. Research is needed in every aspect of PICS in New Zealand. In 2022, the much-anticipated Survivorship of Patients Post Long Intensive Care Stay, Exploration/Experience in a New Zealand Cohort (SPLIT ENZ) study will explore important aspects of recovery and long-term outcomes for New Zealand survivors of critical illness.

The advent of the worldwide COVID-19 pandemic has highlighted two important considerations: firstly, that a high proportion of those with COVID-19 require intensive care, and secondly that COVID-19 is associated with long-term health consequences, so-called "long COVID."[1] Now, more attention has been given to the recovery journey of patients after a critical illness. Modelling from over a decade ago had already estimated that 50% more beds were needed by 2020, partly to accommodate an increasing proportion of those aged over 80 years of age needing ICU treatment.[2,3] Despite admitting and treating an increasingly complex group of patients, mortality (an indicator of success of ICU treatment) is the lowest it has ever been in Australasia. More than 90% of critically ill patients receiving ICU treatment survive to hospital discharge.[4] Although these increasingly complex patient cohorts are surviving ICU, they also endure the persistent burden of survivorship: poorer outcomes and lingering health issues. Attention is appropriately cast on the capacity of ICUs to accommodate an increasing proportion of complex patients, but it is critical that resourcing and ongoing management of critical illness does not just stop at the ICU doors.

Survival is clearly an important primary aim of intensive care. However, there is a growing emphasis on long-term outcomes for ICU survivors. Poor mental health and functional disability are common and persistent in up to a quarter of patients in the year following ICU treatment.[5] Marra et al,[6] for example, showed that cognitive dysfunction, depression, anxiety or physical impairments are common after discharge, with 64% of ICU survivors experiencing poor outcomes at three months. Even at 12 months post discharge, these poor outcomes persisted for 56% of ICU survivors.[6] This collection of adverse health effects is labelled "post intensive care syndrome" (PICS).[7] Caregivers of patients also experience their own poor health, known as "PICS-family" (PICS-f): complicated grief responses, post-traumatic stress disorder (PTSD), depression, sleep disturbances and fatigue are components of this.[8–10]

This viewpoint aims to explore the existing literature on PICS, with particular attention


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on the New Zealand perspective. We identify under-researched areas of the post-ICU survivorship journey and important avenues for future research to address gaps in the literature.

## Long-term outcomes following ICU: international perspective

Since PICS was first conceptualised nearly a decade ago by the Society of Critical Care Medicine, a growing body of evidence and knowledge has developed.[7] Early studies highlighted that patients with respiratory failure and the acute respiratory distress syndrome (ARDS) have significant persistent morbidity, with poor quality of life, functional, cognitive and mental health issues for up to five years after discharge from an ICU.[11] This likely reflects these patients having the highest acuity, which requires long durations of mechanical ventilation and time spent in ICU (over three weeks for half of patients).

Two important international studies[5,6] report health outcomes in patients after discharge from ICU treatment in a broader range of conditions.

Jackson and colleagues[5] explored the prevalence of depression, PTSD and functional disability in around 800 ICU survivors. This cohort was comprised of patients who received more than 72 hours of mechanical ventilation or who were in ICU for five or more days and received treatment for respiratory failure or shock. The group was followed up three and 12 months after discharge. After three months, 37% of the cohort reported depressive symptoms, which were still present in 33% of the cohort after 12 months. The authors reported that depression was predominantly driven by physical rather than cognitive symptoms. After three months, 32% of patients reported deficits in activities of daily living, and after 12 months, 27% reported these deficits. Mental health and functional problems were associated with older age, but the authors were unable to identify an association between mental health and functional disabilities and delirium while in ICU. The ANZICS TEAM trial, a multi-centre, randomised controlled phase III study of early activity and mobilisation in patients expected to require prolonged mechanical ventilation, aims to improve these outcomes.[12]

The study by Marra and colleagues[6] reported a multi-centre cohort of 406 patients treated in an ICU. This study has been crucial in our understanding of the impact of critical illness on new impairments, as, unlike Jackson's study,[5] Marra and colleagues actively excluded a large proportion of patients with known pre-ICU baseline impairments in Activities of daily living (ADLs) or cognitive dysfunction. Although there are inherent difficulties in quantifying pre-existing conditions, such as cognitive dysfunction and mental health issues, before a critical illness,[13] the authors were able to exclude a third of the patients. The major impetus was to highlight how critical illness contributes to the development of new disability and new PICS issues. Three months after discharge, between 25% and 33% of patients had new cognitive impairments, functional disabilities or depression, and for many these problems persisted after 12 months. Although most patients were assessed as having problems in one PICS domain (39% and 35% after three and 12 months respectively), a substantial proportion of patients had problems in two domains (19% and 16% after three and 12 months respectively), and problems in all three domains were reported in 6% and 4% after three and 12 months. Development of PICS was associated with older age, higher pre-illness clinical frailty scores, a longer duration of mechanical ventilation, ICU delirium and more comorbidities.

## Long-term outcomes following ICU: Australian perspective

There are some important studies emerging from Australia that are starting to generate a greater understanding of the survival journey for patients in the Southern hemisphere. Haines et al[14] reported five-year outcomes for 150 Australian patients recovering from critical illness. The mortality

after five years was 44%, with about half of the deaths within one year of discharge. This estimated mortality is consistent with international literature.[15] For survivors, most of the recovery occurred in the first year after discharge. However, there was a substantial burden of PICS associated with reduced quality of life and poor mental health physical function.

Hodgson et al's[16] report on disability used the World Health Organization's (WHO's) Disability Assessment Schedule 2.0 (WHODAS) to map PICS to the WHO International Classification of Functioning, Disability and Health (ICF). The study evaluated disability after six months in 262 Australian survivors of ICU treatment. Disability was highly prevalent in survivors after six months: 50% had mild disability and 25% had moderate to severe disability. Those with moderate to severe disability had a longer duration of mechanical ventilation and were more likely to have a history of depression and anxiety. The authors suggested that WHODAS could be an important comprehensive tool by which to measure PICS in future studies. WHODAS may also provide an efficient and effective tool for measuring and quantifying PICS, which would be useful to both clinicians and researchers. There are currently only single domain tools to quantify PICS (over 250 tools exist) , with wide variations in outcome measures reported in PICS research.[17]

Heydon et al[18] reported on the health-related quality of life, activities and needs of 50 survivors and their families. The study participants were assessed for PICS using the EQ-5D-5L, the Functional Activities Questionnaire and a novel "needs" questionnaire regarding healthcare service usage and socioeconomic status. The authors reported that participants had a decline in their health outcomes and a modest improvement after three months. There was also an increase in healthcare-service usage in the three-month period after discharge. The most frequent self-reported unmet need among these patients was for mental health support.

Return to work, return to study, and reintegration into social aspects of life are severely affected after discharge from ICU. Return to work is of major concern for patients and their families, and it has societal and community effects. Two of the studies discussed reported that between 30% and 61% of patients were still unable to return to work three and six months after ICU discharge.[18,19]

## Long-term outcomes following ICU: New Zealand perspective

Although Australia and New Zealand share some cultural and health-system similarities, there is little research more specific to New Zealand. The small number of studies regarding New Zealand patients focus more narrowly on long-term mortality[20,21] or the ICU experience of patients, families and staff.[22,23] There is no published research addressing the needs, or the best ways of supporting, Māori or Pasifika patients, either during ICU or once home recovering from a critical illness. It is also uncertain as to the most appropriate and useful specific outcomes for Māori or Pasifika patients and their whānau/fono; although instruments such as the EuroQol may be suitable, it would be useful to explore more specific relevant outcomes, as has been done in the context of stroke research in New Zealand. [24]

Research about PICS in New Zealand could quantify survival and disability in order to ensure follow-up resources equitably, but also provide important local information about the expectations and needs for patients, clinicians and their family and whānau. Generating future research into specific resources and strategies to improve health outcomes for patients after critical illness would be vital. This could include post-discharge ICU follow-up clinics or peer-support groups for those who are experiencing PICS in New Zealand.

A research project beginning in 2022 (SPLIT ENZ: Survivorship of Patients Post Long Intensive Care Stay, Exploration/Experience in a New Zealand Cohort (ETHICS Id no:21/NTA/107)) will explore the New Zealand survivorship journey and the extent of disability and PICS, with a view to highlighting the needs of critically ill patients treated in New Zealand.

## Major points

- International evidence highlights the profound effect that critical illness has on recovery, quality of life and disability for ICU survivors.
- Risk factors for worse outcomes include older age, frailty, number of comorbidities, prolonged mechanical ventilation and a history of mental health disorder.
- Australian research also identifies low return-to-work rates after ICU discharge.
- Mental health support is likely an unmet need after ICU discharge.
- High-quality studies evaluating the recovery journey of New Zealand survivors of ICU treatment are needed.

## Conclusion

The COVID-19 pandemic and an increasing number of complex critically ill patients has brought greater attention to the capacity of our ICUs to admit and manage our sickest citizens. For those lucky enough to be discharged from the ICU, the journey is not over. Attention is urgently needed on the under-researched areas of the survivorship journey, the extent of disability and PICS. In 2022, the SPLIT ENZ study will explore exactly this—long term outcomes, level of disability and the recovery journey of New Zealanders—and highlight the specific needs for these patients during their journey. This will hopefully contribute to, and stimulate further research into, specific resources and strategies that will improve health outcomes in the future for New Zealand critically ill patients.

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# Cannabis hyperemesis syndrome in type 1 diabetes: sheep in a wolf's clothing?

Parvathy Chandra

Cannabis is the most commonly used illicit drug in New Zealand. New Zealand's use of cannabis peaked during lockdown, according to data published by the New Zealand Drug Foundation, making New Zealand's rate of use of cannabis the highest in the Western world. Evidence from longitudinal studies carried out in Dunedin and Christchurch indicates that by the age of 25, 80% of New Zealanders will have tried cannabis at least once,[1] and after adjustments for age and gender differences, Māori are reportedly twice as likely to use cannabis compared to non-Māori.[2] Chronic cannabis use is well-known to be associated with severe adverse health outcomes affecting mental health, cognition and respiratory and gastrointestinal systems.[1] Cannabis hyperemesis syndrome (CHS) is a condition that leads to recurrent episodes of vomiting and abdominal pain that occurs in long-term users of marijuana. Diabetic gastroparesis (DGp) affects about 40% of patients with type 1 diabetes and commonly occurs in people who have had diabetes for over ten years alongside other established microvascular complications.[3] Typical symptoms include early satiety, nausea, vomiting and weight loss, which result in frequent presentations to the emergency department (ED). The existing literature indicates that 10–30% of youth and young adults with type 1 diabetes report ever using cannabis.[4] Cyclical vomiting due to gastric dysmotility in diabetic patients who are also cannabis users is frequently misdiagnosed as DGp. Gastric emptying studies often cannot differentiate between the two conditions, as chronic cannabis use can result in varying degrees of delayed gastric emptying.[5] Autonomic dysfunction causing gastroparesis in type 1 diabetes is a devastating diagnosis. Traditional management strategies are generally unsatisfactory, and advanced treatment options like gastric neurostimulation are not readily available in many centres.

This case series will hopefully raise awareness about CHS among clinicians who frequently assess patients with type 1 diabetes presenting with cyclical vomiting and DKA.

## Case 1

A 31-year-old Caucasian male presented to the emergency department with abdominal pain, vomiting and diarrhoea. His past medical history included a diagnosis of type 1 diabetes at the age of two and proliferative diabetic retinopathy. He was on a basal-bolus insulin regime and had an Hba1c in the range of 58–64mmol/mol. He had a history of 15 presentations to ED in the past nine years with recurrent vomiting, at times associated with DKA. His symptoms were attributed to gastroparesis secondary to long-standing diabetes. An upper gastrointestinal endoscopy, barium swallow, CT abdomen and gastric emptying study were all normal. He was a cannabis user but denied any association between smoking cannabis and his symptoms of cyclical vomiting. With good support from the dieticians and diabetes team, he completely stopped cannabis use in 2019. He did not present to ED with cyclical vomiting, and reported quick recovery from infrequent episodes, until this year, when he unfortunately restarted smoking cannabis. Cyclical vomiting recurred and the diagnosis of CHS was confirmed.

## Case 2

38-year-old Māori woman with type 1 diabetes had multiple presentations to ED with vomiting and DKA. She had poorly

controlled diabetes for 28 years with a Hba1c of 112mmol/mol and a history of non-adherence to treatment. She had retinopathy, nephropathy and been labelled with DGp. She previously had normal upper-gastrointestinal endoscopy and abdomen X-rays. The gastric emptying study showed a long lag phase for gastric emptying and delayed initial emptying. Nasogastric tube feeding failed due to intolerance, and therefore she was treated with prokinetics and anti-emetics. During one of the presentations, a urine drug screen was requested, and the results were positive for cannabis. With the help of a multi-disciplinary team, she was educated on the adverse effects of cannabis use in type 1 diabetes and about the risks of DKA. This resulted in her successfully quitting cannabis, which helped improve compliance to treatment and dropped her Hba1c to 79mmol/L. Her symptoms resolved.

## Case 3

28-year-old Caucasian woman had 20 presentations to ED in the past year with cyclical vomiting and abdominal pain. She was diagnosed with type 1 diabetes at age 17 and had variable control and compliance to treatment. Her Hba1c ranges between 64–70mmol/mol but there were no microvascular or macrovascular complications of diabetes. She also had a chronic history of anxiety and depression and was previously under the care of community mental health services. She smoked cannabis frequently to help improve her appetite and weight. Due to erratic eating habits (munchies) without bolusing, she often got ketoacidosis, which resulted in further weight loss. With support from gastroenterologists, she was treated with nasogastric feeding along with prokinetics, antidepressants (sertraline, quetiapine, mirtazapine and fluoxetine) and dietary modifications. This failed to achieve remission of symptoms, and she continued to present to ED with vomiting and DKA. A gastric emptying study demonstrated markedly delayed emptying consistent with moderate to severe gastroparesis. A trial of haloperidol was considered but not commenced due to the risk of previously reported suicidal ideations. Despite multiple attempts with heavy input from dieticians, gastroenterologists, psychiatrists and the diabetes team, she could not quit cannabis and remains significantly symptomatic with cyclical vomiting and severe mental health issues.

## Discussion

Cannabis hyperemesis syndrome, once thought to be a rare condition, is becoming increasingly common due to the widespread availability of cannabis and a favourable public opinion about its healing effects on various medical conditions. Allen and colleagues reported the first published case series of CHS in Australia in 2004, which were followed by several other published case reports. The true prevalence of CHS in New Zealand is primarily unknown due to most cases often being misdiagnosed or not brought to medical attention. It may also be possible that some clinicians and cannabis users have not heard of CHS as a clinical entity and remain unaware of the diagnostic criteria and treatment options. Given the recent political shift for legalisation of cannabis in New Zealand, there is a renewed interest in understanding CHS.

CHS is an important differential diagnosis of cyclical vomiting syndrome. It should be considered in all cannabis users presenting with recurrent symptoms of abdominal pain, weight loss, intractable vomiting and compulsive bathing. Some studies report an average duration of 16 years of regular marijuana use before developing emesis symptoms.[6] In contrast, one study reported the development of an acute illness with multisystem involvement after a single injection of crude marijuana extract.[7]

The mechanism by which cannabis induces hyperemesis is currently unknown, which adds to the complexity of diagnosis. It is hard to fathom how a drug that is often used to treat intractable nausea can also cause such severe vomiting. A recent review has explored numerous potential explanations regarding various pharmacokinetic and pharmacodynamic factors of cannabinoids.[5] Tetrahydrocannabinol (THC), which is lipophilic with its widespread distribution, tends to sequester in fat and contributes to its long half-life and thus potential toxicity.[8] Another proposed explanation is that, in susceptible individuals, the pro-emetic effect of cannabis on the gut (eg, delayed gastric emptying) overrides its anti-emetic CNS

properties.[6] This hypothesis is supported by the demonstration of delayed gastric emptying on gastric emptying scintigraphy in some cases.[7]

CHS is typically characterised by a prodrome of early morning nausea and abdominal discomfort, during which patients may increase cannabis use to relieve nausea. A hyperemetic phase follows with intense and persistent vomiting, significant weight loss and compulsive warm bathing behaviour to alleviate symptoms. If complete cessation of cannabis is achieved, a recovery phase follows with a total resolution of symptoms within 12 hours to three weeks, and a normal eating pattern resumes.[9]

In 2009, Sontineni proposed initial diagnostic criteria for CHS, which Simonetto modified later, in 2012.[10] This was followed by many authors suggesting diagnostic criteria with varying degrees of overlap, which has resulted in inconsistency with the diagnosis. A recent systematic review summarises the published diagnostic criteria and proposes an individualised diagnostic approach that may increase sensitivity in identifying CHS patients.[11] Rome IV Diagnostic Criteria is widely used to assist in diagnosing CHS but is under-utilised in patients with diabetes.

1. Criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis and may be associated with pathologic bathing behaviour (prolonged hot baths or showers).
2. Stereotypical episodic vomiting resembling cyclic vomiting syndrome (CVS) in terms of onset, duration and frequency.
3. Presentation after prolonged excessive cannabis use.
4. Relief of vomiting episodes by sustained cessation of cannabis use.

Although a definitive duration of cannabis use is not well described, the diagnosis must be made in the setting of habitual cannabis use even if using for less than a year.[10]

Abstinence from cannabis has been shown to completely resolve symptoms of CHS in several studies.[10,12] In an emergency setting, the initial step is to exclude other conditions causing cyclical vomiting, including hyperemesis gravidarum, Addison's disease, DKA and psychogenic vomiting. If there is a history of cannabis use and the patient meets Rome IV criteria, a diagnosis of CHS can be made and rehydration should be commenced in a calm environment. Studies on the effectiveness of supportive therapy in the care of CHS patients are limited; however, intravenous antiemetics like ondansetron and topical capsaicin have been traditionally used to control symptoms in the acute phase.

Off-label use of haloperidol is proposed as a rescue medication in the acute treatment of CHS in multiple published case reports. A recent randomised triple-blinded crossover trial identified low-dose intravenous haloperidol (0.05mg/kg) superior to intravenous ondansetron 8mg in the emergency treatment of CHS.[13] Once acute treatment is completed, a multi-disciplinary team input consisting of endocrinologists, gastroenterologists, dieticians, addiction services and a mental health team is essential to provide adequate support to such patients in order to maintain abstinence.

# Conclusion

The above cases demonstrate the challenges faced by clinicians when trying to differentiate between two extremely similar conditions causing cyclical vomiting syndrome, cannabis hyperemesis syndrome and diabetic gastroparesis. CHS, if recognised, is a potentially reversible condition with cessation of use, as demonstrated in the first two cases, and should be considered before embarking on unnecessary and expensive investigations. Moreover, patients are erroneously made to believe that they have DGp, thus failing to acknowledge their cannabis addiction, which is a significant step towards education and de-addiction strategies. This case series might prompt clinicians to undertake a urine drug screen for all diabetic patients presenting with cyclical vomiting with or without DKA and use Rome IV criteria to reach the diagnosis of CHS. Further research in this field is needed to develop a better diagnostic tool to help distinguish between the two conditions, which in turn may facilitate quick and effective rehabilitation of patients.

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# Psychedelic and related medicines at the end of life

David B Menkes

The Assisted Dying Service[1] reflects the implementation last month of the End of Life Choice Act (EoLCA) 2019 and marks a turning point for medical practice in New Zealand. While we as a profession grapple with the implications of the new law,[2] it is timely to consider the range of options that may assist dying patients and their families.

Although unregistered and currently illegal in this country, the classical psychedelic psilocybin has shown encouraging results in two randomised crossover trials of patients with terminal cancer and associated anxiety and depression.[3,4] In contrast to conventional palliative pharmacotherapies, the clinical effects of psilocybin, including long-lasting symptomatic and quality-of-life improvements, are often apparent after a single supervised psychedelic experience. If validated in larger studies, these findings would suggest psychedelics will be an important addition to current therapeutic options at the end of life.

Compared to the serotonergic psychedelics psilocybin and LSD, methylenedioxymethamphetamine (MDMA, "ecstasy") is another unregistered illicit drug with somewhat different pharmacology and subjective effects and notably less hallucinatory. MDMA has been termed an "entactogen" because of its powerful tendency to suppress fear responses and promote feelings of openness and connection. Recent controlled trial data indicate the long-lasting efficacy of MDMA-assisted psychotherapy in relieving the symptoms of treatment-resistant post-traumatic stress disorder;[5] US Food and Drug Administration approval for this indication is currently being sought. Closer to home, a randomised controlled trial of MDMA for anxiety and depression in terminal illness, hosted by the universities of Auckland and Otago, is due to start in early 2022. A small, US-based pilot study has indicated the likely benefit of MDMA-assisted psychotherapy for this indication.[6]

Patients with terminal illness often encounter a variety of psychological and physical challenges, and these are generally well managed in palliative care. Nonetheless, concerns about the efficacy and tolerability of conventional palliative treatments have led patients and their families to seek additional options, including medically assisted dying. The future availability of psychedelic and related medicines may offer valuable alternatives to patients who might otherwise opt to pursue the EoLCA.


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# Supplies of Sera and Vaccines

1921

With the exception of such vaccines, e.g., influenza vaccine and autogenous vaccines, as are manufactured by the various Government Bacteriologists and can be obtained therefrom, the Department of Health has arranged to undertake the agency for New Zealand of the Commonwealth Serum Laboratories, whose product it has been carrying and distributing through the Hospital Boards for some time past. These products are obtainable, therefore, only through the Health Department, but to facilitate their distribution the Department has arranged to supply Hospital Boards therewith, from whom medical practitioners can obtain their supplies at the prices set out in the printed price list issued by the Commonwealth Laboratories. Medical practitioners requiring these products should apply to the Boards of their districts therefore, and if the Boards have not the sera in stock, then it can be supplied by the Department. Medical men should, however, avoid making it a practice of applying to the Department instead of to the Hospital Board, with the exception of those in the Wellington hospital district, who can be supplied by the head office of the Health Department instead of by the Wellington Hospital Board.

The Department's object in stocking these sera is to ensure that an adequate and fresh supply of sera is always available, and by keeping the main supplies in Wellington under proper conditions of cool storage, it can avoid the loss and expense that resulted in the past from stocks being held in varying quantities throughout the Dominion, and the consequent necessity for much writing-off of stale and expired stocks.

The present system enables stocks to be held by Hospital bBoards sufficient only for immediate requirements, which can be replenished from the Department's main stock. The Department, moreover, can always obtain fresh supplies within a week from the Laboratories in Australia, and therefore, there is no danger of stocks either being exhausted or being held in such large quantities as to become stale and have to be destroyed.

Though the Department does not refuse to supply chemists or others with sera, it is pointed out to medical practitioners that there is apparently nothing gained by a chemist, possibly in a small town, with only one medical man as a client, having to hold stocks of sera which may or may not be required, and in the latter eventuality having to be written-off, in which case the chemist would have to bear the loss unless he covered himself against loss by charging a sufficiently high price for the sera. Under the present conditions the Department bears the loss, if any, in regard to expired stocks, but avoids such contingencies owing to the facilities it has for disposing and renewing its stock.

**URL:**
www.nzma.org.nz/journal-articles/supplies-of-sera-and-vaccines

# The next phase in Aotearoa New Zealand's COVID-19 response: a tight suppression strategy may be the best option

Michael G Baker, Amanda Kvalsvig, Sue Crengle, Matire Harwood, Collin Tukuitonga, Bryan Betty, John Bonning, Nick Wilson

*First published in: 2021 Nov 26; 134(1546)*

On Tuesday 30 November and Monday 6 December (respectively), two corrections were applied to this manuscript:

- "August 17 2001" was changed to "August 17 2021" (page 10)
- Figure 2 was updated (page 10)

# He Pikinga Waiora Kimi Ora lifestyle programme: case study of a successful community-based Indsigenous diabetes intervention

Bridgette Masters-Awatere, Shemana Cassim, Jade Tamatea, Nina Scott, Chae Simpson, Cherie Paekau

*First published in: 2021 Nov 12; 134(1545)*

On Monday 6 December, one correction was applied to this manuscript:

- An acknowledgement of funding from the Healthier Lives National Challenge was added (page 76)

**URL:**
www.nzma.org.nz/journal-articles/erratum-11

# Abstracts for the 259th Otago Medical School Research Society PhD Speaker Awards, Wednesday 22 September 2021

## The effect of heat therapy and high-intensity interval training on fitness, blood pressure and osteoarthritis impact in patients with severe lower-limb osteoarthritis

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Osteoarthritis is a degenerative joint condition making traditional exercise painful and difficult to perform. Due to the lack of activity, osteoarthritis sufferers have lower fitness ($\dot{V}O_{2peak}$) and higher systolic (SBP) and diastolic (DBP) blood pressure, compared to those without osteoarthritis. The purpose of this study was to compare the effect of three low-/no-impact interventions on $\dot{V}O_{2peak}$, blood pressure and the subjective impact of osteoarthritis in patients with severe lower-limb osteoarthritis.

Ninety-three patients with severe knee or hip osteoarthritis awaiting total joint replacement were recruited from Dunedin Hospital. Participants were randomised to heat therapy (Heat; 20–30 min immersed in 40°C water followed by ~15 min light resistance exercise), upper-limb high-intensity interval training (HIIT; 6–8 x 60 s intervals on a cross-trainer or arm ergometer at 100% $\dot{V}O_{2peak}$, 60–90 s recovery) or home-based exercise (Home; 15–20 min light resistance exercise), for 36 sessions (3 sessions per week for 12 weeks).

Across the interventions, peak $\dot{V}O_2$ increased by 15% following HIIT (+2.9 [95%CI: +1.3, +4.4] $mL{\cdot}min^{-1}{\cdot}kg^{-1}$) but not Heat (+0.4 [-0.6, +1.3] $mL{\cdot}min^{-1}{\cdot}kg^{-1}$) or Home (-0.2 [-1.2, +0.8] $mL{\cdot}min^{-1}{\cdot}kg^{-1}$). The SBP and DBP had decreased following Heat (SBP -9 [-14, -3]; DBP -3 [-5, 0] mm Hg) and HIIT (SBP -6 [-9, -4]; DBP -2 [-5, 0] mm Hg), but not Home (SBP 0 [-3, +3;] DBP 0 [-2, +3] mm Hg). Osteoarthritis impact, as assessed by the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index questionnaire (0 (no impact)–96 (most impact)), was unchanged with Heat (-1 [-7, +5]), HIIT (+2 [-4, +8]) or Home (-2 [-7, +4]).

Upper-limb HIIT was effective for improving $\dot{V}O_{2peak}$ in patients who have difficulty performing lower-limb exercise. Heat and HIIT had potent anti-hypertensive effects, of similar magnitude to some pharmaceuticals, but neither intervention improved patients' subjective impact of osteoarthritis.

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## The preferences of people with rheumatoid arthritis for tapering biologic therapies

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Biologics are effective treatments for people with rheumatoid arthritis (RA) but are associated with adverse effects and are costly. Tapering of biologics is recommended when people with RA achieve remission but is not without risk of disease flare-up. Little is currently known about how the preferences of people with RA would influence their decisions to accept biologics tapering. This study aimed to assess the preference of people with RA for biologics tapering.

A total of 736 potential participants currently taking biologics or had stopped biologics due to medical reasons were recruited from Auckland, Wellington, Christchurch and Dunedin. Participants completed an online discrete choice experiment (DCE) survey, asking their preferences between three hypothetical treatment options with varying levels of four attributes: frequency of treatment, chances of known adverse effects, chances of regaining disease control and healthcare service-related features. DCE

data were analysed using a mixed logit model.

Of the 160 who responded, 142 complete responses were analysed. Frequency of biologic treatment was the most important treatment attribute influencing preference, followed by the chance of flare upon tapering. Time to see the rheumatology team after a flare was ranked the least important among the seven attributes. On average, people with RA were willing to accept between 25.3% to 50.2% increase in chance of disease flare in exchange for reducing the treatment frequency and chances of adverse effects (serious infection and skin cancer associated with biologic use).

This study shows that frequency of treatment and risk of disease flare was the most important determinant for people with RA when making hypothetical choices about tapering biologics. For these attributes, they were willing to accept a greater chance of flare in exchange for treatment benefits in the form of a reduction in dosing frequency and potential risk of adverse effects from continued use. These findings have implications for clinical practice and policy making about tapering.

## Effects of wearing face masks on cognitive functioning and mood states: a randomised controlled trial in young adults

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Despite significant public concern that wearing face masks can adversely affect the brain, and self-report evidence in healthcare workers that it is associated with impaired cognition, few studies to date have measured the impact of wearing the types of face masks commonly worn during the COVID-19 pandemic (surgical or cloth face masks) on cognition. In the present study, we investigated the effects of wearing a surgical face mask for prolonged periods (at least 8 hours) on neuropsychological functioning, including objectively measured cognition (basic visuomotor performance, inhibitory control, mental flexibility, selective attention, short-term and working memory and self-reported current mood states).

We tested 42 younger adults (18–36 years old) using a controlled counterbalanced crossover design with a 1-week washout. Participants were given a surgical face mask to wear for at least 8 hours throughout the day of testing. Paired-sample *t* tests assessing differences in cognitive variables of interest between the control and mask sessions revealed a difference in cognitive performance between the two sessions for the more challenging condition of a selective attention task, $t(41) = -3.18$, $P = 0.003$, $g = 0.33$, reflecting 5.4% worse cognitive performance (as evidenced by slower reaction-times) during the mask session. Additionally, paired-sample *t* tests comparing mood scale ratings between the control and mask sessions showed that participants reported feeling less happy, $t(41) = -2.53$, $P = 0.015$, $g = 0.41$, and more tense, $t(41) = 2.12$, $P = 0.040$, $g = 0.30$, during the mask session compared to no-mask control.

In summary, the current study revealed small but significant adverse effects of wearing a surgical face mask on neuropsychological functioning. This evidence of adverse effects in a university population signals that future research is needed to investigate the effects of wearing surgical face masks in vulnerable populations (eg, people with asthma and older adults).

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## Astrocyte-mediated trans-regional regulation of synaptic plasticity in the hippocampus

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The synaptic plasticity process of long-term potentiation (LTP) and long-term depression (LTD) is vital for memory formation and overall neural health. However, mechanisms must be in place to prevent pathologically excessive LTP and LTD. Such regulation comes partly through metaplasticity, whereby neural activity at one point in time influences later plasticity. We have discovered a unique trans-regional mode of metaplasticity in the hippocampus, whereby "priming" stimulation of inputs to the basilar dendrites of pyramidal cells in area CA1, inhibits later LTP at synapses in the middle molecular layer (MML) of the dentate gyrus, a neighbouring region ~800 microns away. As there are no known neuronal connections between these brain regions, we tested the hypothesis that the metaplasticity is in fact accomplished via astrocytic networks.

Intracellular astrocyte patch clamping and extracellular field potential recordings were conducted in the MML of acute hippocampal slices taken from young-adult male Sprague-Dawley rats and 2–7-month-old mice. The control and primed group sizes ranged from n = 6–9. In rat slices, $Ca^{2+}$ was buffered in patched astrocytes by dialysing EGTA intracellularly while recording local synaptic potentials in MML. Priming stimulation (2x100 Hz trains) in CA1 was delivered 15 min prior to MML LTP induction (4x100 Hz trains). Priming inhibited MML LTP compared to non-primed control (*t*-test, $t_{(13)}=4.4$, $P = 0.0007$), while buffering astrocytic $Ca^{2+}$ completely abolished this effect

($P$ = 0.73). The involvement of astrocytes was confirmed by a lack of LTP inhibition in $IP_3R2^{-/-}$ mice that do not display $Ca^{2+}$ release from astrocyte-specific inositol triphosphate receptor-2 ($IP_3R2$)-dependent stores ($P$ = 0.71, $t$-test). Further, we have shown that the glial cytokine tumour necrosis factor-alpha (TNFα), acting on TNFα receptor-1, is a critical signalling molecule.

Taken together, these data demonstrate a novel hippocampus-wide regulation of synaptic plasticity that is mediated by astrocyte-neuron communication. We propose that such metaplasticity plays an important role in hippocampal information processing while also homeostatically counteracting excitotoxicity under pathological conditions.

*Supported by the Health Research Council, Brain Research New Zealand and a New Zealand International Doctoral Scholarship.*

## Acute and chronic effects of nitric oxide exposure on cardiac arrhythmias

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Nitric oxide (NO) is a gaseous signalling molecule that regulates cardiac function by targeting calcium handling protein kinases such as calcium/calmodulin-dependent protein kinase II delta (CaMKIIδ). NO can alter CaMKIIδ activity in the heart and this leads to irregular heart rhythm (arrhythmias). Currently, it is unknown how the duration of NO exposure can affect cardiac function in the presence and absence of CaMKIIδ. This study was designed to determine how acute and chronic NO treatment affects cardiac arrhythmias in mice lacking CaMKIIδ.

To assess the effect of acute exogenous NO on arrhythmias, hearts from CaMKIIδ knock-out (KO) mice (n = 5) and wild-type (WT) C57BL/6 mice (n = 7), were isolated and perfused with S-nitrosoglutathione (GSNO), a NO donor for 10 minutes. In the chronic phase, WT (n = 5) and KO hearts (n = 5) were given GSNO-supplemented drinking water for 5 weeks. Thereafter, the hearts were isolated and perfused with GSNO.

Following acute GSNO treatment, there was no significant increase in arrhythmias in KO hearts compared to baseline (12.0 ± 4.8 vs 5.2 ± 3.2). However, the WT hearts developed arrhythmias (premature ventricular beats, bigeminy and trigeminy) with increasing GSNO concentrations compared to baseline (19.6 ± 6.8 vs 6.9 ± 2.3; $P < 0.05$). Chronic treatment of WT and KO hearts with GSNO led to an increasing trend in arrhythmias in both WT and KO isolated perfused hearts compared to baseline (WT = 25.2 ± 14.7 vs 8.4 ± 5.4; $P$ = 0.05, KO = 30.4 ± 11.3 vs 15.2 ± 4.0; $P$ = 0.08).

The responses of the mouse hearts to GSNO treatment depending on duration of treatment shows that WT hearts are more sensitive to acute NO and therefore increased arrhythmias. Additionally, KO mice are protected from arrhythmias during acute NO treatment. In the chronic phase of GSNO treatment, WT and KO mouse hearts are equally affected by GSNO treatment and the KO hearts showed increased susceptibility to arrhythmias. This suggests that CaMKII inhibition could attenuate cardiac arrhythmias only during acute NO exposure.

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## Phosphorylation of RyR2 by CK2 is anti-arrhythmic

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Cardiovascular disease is one of the leading causes of mortality in New Zealand and is responsible for one third of all global deaths each year. Among cardiac diseases, arrythmias are one of the most prevalent forms. The main mechanism of arrhythmia are inappropriate releases of $Ca^{2+}$ (termed $Ca^{2+}$ sparks) through ryanodine receptor 2 (RyR2), a sarcoplasmic reticulum-located channel that plays an essential role in cardiac excitation-contraction coupling, releasing the bulk $Ca^{2+}$ required for contraction. We have recently identified that RyR2 is phosphorylated by casein kinase 2 (CK2), and that *in vitro* loss of this phosphorylation increases $Ca^{2+}$ sparks. This project aimed to determine the role of CK2 phosphorylation of RyR2 *in vivo*. This was achieved using phospho-specific mutant mice, which expressed a variant of RyR2 unable to be phosphorylated by CK2 ($S2692A/S2693A^{++}$).

To determine whether loss of phosphorylation increases $Ca^{2+}$ sparks, line-scan imaging was performed on isolated cardiomyocytes from $S2692A/S2693A^{++}$ and wildtype controls. Cells isolated from $S2692A/S2693A^{++}$ animals exhibited 4.3 sparks/100 µm/s, which was significantly greater than in control animals' 2.9 sparks/100 µm/s (n = 45 cells, 8 animals per group respectively, one-way ANOVA, $P > 0.05$). Next, to determine whether this increase in $Ca^{2+}$ spark frequency translated to an increased risk of arrhythmias, electrocardiograms were recorded before and after a pharmacological stress trigger, an intraperitoneal injection of caffeine (120 mg/kg) and epinephrine (1.6 mg/kg). In control animals this procedure increased the heart rate but had little effect on arrhythmogenicity, with brief changes in sinus rhythm occurring in only 2 out of 9 animals. In contrast, $S2692A/S2693A^{++}$ animals experienced a significant increase (7 out of 10 animal) in severe and prolonged non-sinus rhythm (one-way ANOVA, $P > 0.05$).

Combined, these data show that phosphorylation of RyR2 by CK2 is essential for normal channel function and $Ca^{2+}$ release, and

that loss of phosphorylation increases $Ca^{2+}$ leak and the susceptibility of arrhythmia. Clinically, understanding the regulation of RyR2 function may offer a novel target for treatment of cardiac arrhythmia.

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## *In vitro* and *in vivo* evaluation of high-dose inhaled rifampicin powder formulations for tuberculosis treatment

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Despite the availability of oral and injectable drugs, tuberculosis (TB) treatment is hindered by suboptimal drug concentrations in the lungs and blood. Pulmonary delivery of anti-TB drugs may ensure sufficient drug concentration in the lungs and blood. This study reports on the *in vitro* and *in vivo* (rat) assessments of inhalable rifampicin formulations.

Four high-dose rifampicin powder formulations were prepared using spray drying and crystallization techniques. *In vitro* aerosolisation efficiency was evaluated using an artificial lung, the Next Generation Impactor. In *in vivo* assessments in Sprague-Dawley rats, repeated doses of formulations were administered by intra-tracheal insufflation or by oral gavage. Liver toxicity was evaluated by histopathology and alanine transaminase (ALT) assay in serum. Lung tissue was evaluated by histopathology. The pharmacokinetic study compared plasma concentration-time profiles of rifampicin after repeated intra-tracheal or oral administrations of powder formulations.

Amorphous and crystalline dihydrate powder formulations of rifampicin with high aerosolisation efficiency (lung dose ≥ 62.7%) were studied in rats (n = 6 per treatment group). Serum ALT levels were significantly lower after intra-tracheal administration compared to oral administration, suggesting lower hepatic effects from the pulmonary administration. Normal architecture of lung and liver histology after repeated intra-tracheal dosing indicated absence of toxicity. Intra-tracheal administration led to significantly higher peak plasma concentrations ($C_{max}$= 13.2 ± 1.7 µg/mL) and area under the plasma concentration-time curve (AUC = 193.1 ± 37.9 µg.h/mL) in a shorter time ($T_{max}$ = 4.5 ± 2.9 h) compared to oral administration ($C_{max}$ = 4.5 ± 2.3 µg/mL; AUC = 87.4 ± 64.7 µg.h/mL; $T_{max}$ = 7.5 ± 5.0 h) at the same dose ($P < 0.05$), suggesting faster and higher absorption of rifampicin into the systemic circulation.

Intra-tracheal delivery of rifampicin powder formulations to rats was safe and resulted in higher bioavailability than oral rifampicin. This study is a foundation for future clinical studies on inhaled rifampicin and the development of other inhaled anti-TB drugs.

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## Aryl hydrocarbon receptor ligands can modulate fructose-induced hepatic insulin resistance

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The increasing prevalence of hepatic insulin resistance, an underlying factor of non-alcoholic fatty liver disease and type 2 diabetes, necessitates the understanding of molecular pathways that could play a role in its development. The aryl hydrocarbon receptor (AhR), a transcription factor activated by a wide range of exogenous (environmental pollutants, phytochemicals) and endogenous (tryptophan derivatives) ligands, has been implicated in regulating insulin sensitivity by altering lipid metabolism, but research is conflicting regarding how different AhR ligands modulate this response, particularly in human cells.

Five AhR agonists, the tryptophan metabolite 6-formylindolo[3,2-b]carbazole (FICZ), synthetic agonist β-naphthoflavone (BNF), dietary phytochemical indole-3-carbinol (I3C), seaweed-derived 4,7-dibromo-2,3,-dichloroindole (4DBDCI) and prototypical AhR agonist 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) were tested in human HepG2 cells. Triglyceride levels were quantified via a kit and western blotting for the change in insulin-stimulated pAkt expression (normalised to total Akt) was used to measure insulin sensitivity. Data were analysed via one-way ANOVA with Bonferroni's post-hoc test (n = 3 per group).

No changes in triglyceride content in response to each compound were detected. However, in a hepatic insulin resistance model, FICZ prevented the fructose-mediated reduction of pAkt, producing 94.9 ± 10.5 (SEM) % of the vehicle control response, compared to fructose alone which produced 55.1 ± 5.6 (SEM) % of the vehicle control response ($P < 0.05$). BNF, I3C and 4DBDCI all increased the fructose-mediated insulin resistance, reducing pAkt expression to 20 – 25% ($P < 0.05$ vs fructose-only) of the vehicle control, while TCDD did not induce a change.

The protective effect of FICZ, as well as the compounding effect of BNF, I3C and 4DBDCI, against fructose-mediated insulin

resistance was independent of triglyceride accumulation and further investigation into the mechanism is therefore warranted. The contrasting effects on insulin sensitivity by these five compounds also warrants exploration into the complex activity of AhR agonists.

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# Abstracts for the 260th Otago Medical School Research Society Masters/ Honours Speakers Awards, Wednesday 3 November 2021

## An exploration of mental health promotion in Aotearoa New Zealand: A qualitative study

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Mental health promotion focuses on promoting positive mental health for individuals, communities and populations. In recent years mental health has reappeared on the Aotearoa New Zealand (NZ) political agenda. However, the current level of knowledge and reporting about mental health promotion action occurring is limited. This study therefore aimed to explore what health promotion practitioners are currently doing to address mental health in Aotearoa NZ, in terms of both content and practice.

Between May and December 2019, semi-structured interviews were conducted with fifteen health promotion practitioners employed at various health organisations in Aotearoa NZ. Participants were selected using a combination of maximum variation and snowball sampling methods. Data were thematically analysed using both inductive and deductive methods.

Health promotion practitioners reported undertaking a diverse range of mental health promotion programmes/projects in Aotearoa NZ, including, but not limited to, programmes focused on: developing personal skills, creating supportive environments, encouraging community action and activating messages from national initiatives at a local level. Participants reported undertaking a variety of processes and utilising various approaches in the planning and evaluation of their programmes/projects, for example needs assessment, equity and Treaty-based practice, collaboration and process evaluation. However, various factors, operating at the systems level, restricted them from being able to undertake "best practice" mental health promotion. In particular, participants reported operating within short-term and prescriptive contractual agreements, a tertiary-focused healthcare system, a fragmented field and a limited workforce, which created significant challenges for their mental health promotion practice.

This study highlights a number of potential opportunities for future mental health promotion action and practice in Aotearoa NZ. Findings highlight a critical need for system level action to create an environment that encourages and supports health promotion practitioners to undertake best practice mental health promotion in Aotearoa NZ.

*Supported by a University of Otago Masters Scholarship.*

## Vaccination, vaccine hesitancy and COVID-19 in New Zealand, 2018–2021.

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Vaccine hesitancy is considered a serious threat to public health, due to worldwide decline in vaccine uptake and resurgence of vaccine preventable diseases. With mass vaccination underway for coronavirus disease 2019 (COVID-19), opposition and reluctance could hinder success and therefore must be understood and addressed. This research aimed to understand attitudes towards vaccination and drivers of hesitancy within a New Zealand context from 2018 to today, with particular emphasis on the COVID-19 vaccine.

Literature searches were conducted in November 2020 and June 2021, to gather both historical and current research on vaccination attitudes in New Zealand and factors influencing vaccine hesitancy. Key words included coronavirus, vaccine hesitancy, vaccination, anti-vaccination, infodemic, misinformation and social media. Online and unpublished sources were also used, along with the *Otago Daily Times* (March 2020–February 2021) to provide a local perspective amidst a global pandemic.

Drivers of attitudes and vaccination hesitancy are multifacto-

rial. With social media now so prevalent, misinformation and the "anti-vax" sentiment can reach more people than ever before. The speed at which the COVID-19 vaccine was developed and approved for use has fuelled hesitancy, with safety appearing the predominant concern. Vaccine hesitancy can be overcome by actively addressing and correcting misinformation with scientifically backed messaging, that is tailored to local communities. Government and regulatory bodies must communicate transparently to the public to avoid confusion and overcome reluctance. Healthcare professionals also play an important role in fostering trust in vaccines within the communities they work in, but they must be well supported by the wider healthcare system.

Vaccine hesitancy is a clear threat to a successful vaccination campaign for COVID-19. Misinformation circulating both online and in person can influence decision-making surrounding vaccination. Hesitancy must be actively and publicly addressed in order to increase vaccine uptake.

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## Replication of a Māori and Pacific-specific T2D-risk variant within *JAZF1*

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Māori and Pacific individuals have a two times greater risk of Type II diabetes (T2D) compared to other population groups in New Zealand. This provides a unique opportunity to explore the hypothesis that some of this risk is attributed to genetic variation. Genome sequencing of 56 Māori and Pacific individuals led to the identification of a Māori- and Pacific-specific non-coding variant, *rs150587514*, in the first intron of the *JAZF1* gene. This variant is common in Māori and Pacific people (minor allele frequency (MAF) of >10%) but uncommon in other population groups (MAF <0.1%). *JAZF1* is a gene essential for β-cell function and insulin secretion. Previous unpublished work in 1,821 Māori and Pacific individuals found that the C risk allele conferred a 1.6-fold greater risk of developing T2D compared to those without the risk allele (OR = 1.63 [95% CI 1.27; 2.15], $p = 3.9 \times 10^{-4}$). The aim of the current work was to validate this association by genotyping an independent cohort of Māori and Pacific individuals to test the replicability of this previously identified association. An independent Māori and Pacific cohort were recruited through a partnership with the Ngāti Porou Hauora Charitable Trust. This resulted in a replication cohort of 478 Māori and Pacific participants. These individuals were genotyped using custom designed Taqman probes in a Taqman genotyping assay. Using these genotypes and corresponding phenotypic data, a logistic regression association analysis was conducted between *rs150587514* and T2D, with T2D as the outcome variable. The association between *rs150587514* and T2D risk was replicated, and the direction of effect remained consistent with the original analysis (OR = 2.07 [95% CI 1.27; 3.37], $p = 3.5 \times 10^{-3}$). Importantly, in combination with the original data, the association between *rs150587514* and T2D was strengthened (OR = 1.73 [95% CI 1.36; 2.19], $p = 6.2 \times 10^{-6}$). The meta-analysis of these two cohorts indicates that per *rs150587514* C-risk allele, Māori and Pacific individuals have a 1.7-fold greater risk of developing T2D. This is the first validated Māori- and Pacific-specific variant associated with an increased risk of T2D. This finding adds to our understanding of the genetic contribution to complex disease and has a potential long-term impact in precision medicine initiatives directed to Māori and Pacific communities, working to decrease the health inequities that exist in Aotearoa.

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## Infra-slow pink noise stimulation can increase default-mode network activity in individuals with early Alzheimer's disease

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Alzheimer's disease (AD), the most common form of dementia, is a significant and growing health challenge worldwide. Current available treatments for AD have poor efficacy. Decreased activity within default-mode network (DMN) has been demonstrated as a potential biomarker for tracking AD progression and is a recommended target for brain stimulation. This pilot study explored a novel high-definition transcranial infra-slow pink noise stimulation (HD-tIPNS) technique for increasing DMN activity in individuals with early AD.

The study was a double-blinded (participant and assessor) pilot randomised placebo-controlled parallel trial with two intervention arms. For treatment group (n = 9), HD-tIPNS targeting hubs of DMN [posterior cingulate cortex (PCC), pregenual anterior cingulate cortex (pgACC), left and right parahippocampal gyrus (LPHG and RPHG)] was delivered for a single session of 30 minutes. For sham group (n = 7), stimulation was applied for two minutes at the beginning and end of the session. Electroencephalographical data were collected at baseline and immediately post-intervention. Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to compute and compare current density (CD) at the PCC, pgACC, LPHG and RPHG for the infra-slow (0.01–0.1 Hz),

slow (0.2–1.5), delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12 Hz), beta1 (12.5–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz) bands.

When compared to sham group, the treatment group demonstrated increased CD in the PCC [slow ($p$ = 0.0411) and gamma ($p$ = 0.0315) bands], LPHG [slow ($p$ = 0.0111), beta2 ($p$ = 0.0454) and beta3 ($p$ = 0.0195) bands], and RPHG [slow ($p$ = 0.0222), beta2 ($p$ = 0.0317), beta3 ($p$ = 0.0132) and gamma ($p$ = 0.0136) bands].

These preliminary findings showed that a single-session of HD-tIPNS is capable of increasing DMN activity in individuals with early AD. Future research could evaluate the efficacy of multi-session HD-tIPNS for improving cognition in individuals with early AD.

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## Agmatine attenuates actin dynamic alteration and synaptic dysfunction in aged rats

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Cytoskeletal protein actin forms the morpho-functional platform at synapses (the communication points between neurons) and changes dynamically between monomeric globular (G-actin) and polymerised filamentous (F-actin) forms in response to neuronal activity. Such actin dynamics is essential for almost all aspects of synaptic physiology, including long-term potentiation (LTP). Synaptic dysfunction contributes to age-related cognitive decline, and agmatine supplementation attenuates memory deficits in aged rats. However, little is known how agmatine affects synaptic function. This study investigated the effects of long-term agmatine supplementation on cytoskeletal protein actin and synaptic function in aged rats.

The parahippocampal region was dissected from female Sprague-Dawley rats at 18 months of age following daily agmatine (agm) supplementation (50 mg/kg) via food chow for 14 weeks (aged-agm, n = 10), and rats at 4 months (young, n = 7) and 18 months (aged, n = 8) provided with normal food chow. Synaptosomes enriched with synaptic nerve terminals were prepared for the measurements of F- and G-actin via western blot and chemically induced LTP (cLTP) via a radioactive assay.

One-way analysis of variance revealed a significant difference between groups in the F-/G-actin ratio ($F_{2,18}$ = 13.39, $P$ = 0.0003), with a reduced F-/G-actin ratio in the aged group relative to the young group ($P$ < 0.001). Agmatine supplementation significantly increased the F-/G-actin ratio when the aged-agm and aged groups were compared ($P$ < 0.05). Moreover, there was also a significant difference between groups in cLTP ($F_{2,19}$ = 6.27, $P$ = 0.008), with reduced cLTP in the aged group when compared to the young group ($P$ < 0.05) and aged-agm group ($P$ < 0.01).

These findings demonstrate that agmatine supplementation significantly attenuated age-related alteration in actin dynamics and normalised cLTP deficits in aged rats, which underlie the anti-aging and memory enhancing effects of agmatine. Future research will explore the potential of agmatine in maintaining healthy brain aging.

## Estrogen receptor alpha activation stimulates the Coolidge effect but has no effect on the sexual refractory period of estrogen-deprived male rats

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Estrogen is involved in normal male sexual function and can exert its effects on cells by activating estrogen receptors (ERs) such as ERa and ERb. Here, we explored the role of ERa activation on the sexual refractory period (ie, the time when males cannot be sexually aroused after an ejaculation) and the Coolidge effect (ie, the shortening of the refractory period when a novel sexual partner is introduced after ejaculation). We investigated the effects of ERa administration on different parameters of sexual behaviours including mounting, intromission, and ejaculation in estrogen-deprived male rats.

Twenty-four sexually experienced male rats (8 per group) were treated for 29 days with: (1) saline (Control group), (2) aromatase-inhibitor (Fadrozole, 1 mg/kg) or (3) aromatase inhibitor daily with the addition of ERa agonist on the last day (ERa group, propyl pyrazole triol, 1 mg/kg). On day 29, all groups had a mating test with one female until reaching sexual satiety (30 minutes without ejaculation), and then exposed to a different female until a second sexual satiety.

On day 29, the Fadrozole group had similar mounting (3.0 ± 2.3) and intromission (18.0 ± 12.2) frequencies than the Control group. However, significantly lower ejaculation (1.3 ± 1.0) frequency and longer refractory period (725.9 ± 266.2 s) compared to the Control group ($p$ < 0.001 for all) was observed. The ERa group had significantly higher mounting frequency (16.6 ± 8.0) than the other groups ($p$ < 0.01 vs. Control, $p$ < 0.001 vs. Fadrozole) but had similar time to reach sexual satiety, intromission frequency and ejaculation frequency as the Fadrozole group.

Following introduction of the second female, the Fadrozole group had similar mounting and intromission frequencies but lower ejaculation frequency ($p$ < 0.05) than the Control group. The ERa group, however, had higher mounting frequency (5.9 ± 2.0) than the Fadrozole group ($p$ < 0.05).

In conclusion, estrogen plays a role in controlling the sexual refractory period and the Coolidge effect. Specifically, estrogen regulates the Coolidge effect through ERa activation.

This study will provide further pre-clinical evidence on the role of estrogen in male sexual function, which will be relevant to males who face estrogen deprivation.

## Evaluation of vascular endothelial growth factor-$A_{165}$ glycoforms in angiogenic assays

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Vascular endothelial growth factor-$A_{165}$ (VEGF-$A_{165}$) is the key mediator of angiogenesis which has been explored as a therapeutic agent to control angiogenesis and revascularisation of ischaemic tissues. Unfortunately, the use of VEGF-$A_{165}$ has failed to improve angiogenic outcomes in clinical trials, despite showing promising results in vitro and in vivo. We propose that these failures occurred due to therapies using VEGF-$A_{165}$ lacking appropriate glycosylation. The aim of this project was to test the angiogenic capacity of differentially glycosylated isoforms (glycoforms) of VEGF-$A_{165}$.

Chemically synthesised (unglycosylated), *Escherichia coli*-produced (unglycosylated) and human embryonic kidney (HEK)293 cell-produced (glycosylated) forms of recombinant human VEGF-$A_{165}$ were evaluated in *in vitro* angiogenic assays. A Ba/F3 bioassay was employed to quantify cell proliferation upon VEGF receptor (VEGFR)-2 binding at varying doses of VEGF-$A_{165}$ glycoforms. A Matrigel® assay was utilised to assess endothelial cell tube formation at varying doses of VEGF-$A_{165}$ glycoforms. A barrier assay was used to measure Evans blue-conjugated BSA leakage through an endothelial cell monolayer in response to 25 ng/mL of each VEGF-$A_{165}$ glycoform. Three replicates were conducted for each assay.

VEGFR-2 receptor binding of the VEGF-$A_{165}$ glycoforms induced similar dose-dependent upregulation of cell proliferation, increasing $E_{max}$ by 2.37 to 3.54-fold compared to control. All VEGF-$A_{165}$ glycoforms did not produce a dose-response curve for parameters of endothelial tube formation evaluating cell migration. All VEGF-$A_{165}$ glycoforms at 25 ng/mL induced a 2.79- to 3.24-fold increase in leakage compared to assay control on the endothelial cell monolayer. No significant differences were detected between VEGF-$A_{165}$ glycoforms in any assay (Brown-Forsythe and Welch ANOVA).

These findings show that the chemically synthesised VEGF-$A_{165}$ is biologically active and suggests that glycosylation may modulate the angiogenic capacity of VEGF-$A_{165}$. However, further studies are needed to determine if the VEGF-$A_{165}$ glycoforms exhibit differences in pharmacokinetics that may impact their utility as treatments for vascular diseases.

## Dissecting the receptor signalling events responsible for the immune suppressive and immune stimulatory effects of IL-10

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Interleukin 10 (IL-10) is a dynamic cytokine produced by most adaptive and innate immune cells. Although IL-10 is known as a potent anti-inflammatory cytokine, it can also stimulate the activity of B cells, cytotoxic T cells, natural killer cells and mast cells. This has hindered the use of IL-10 as a therapeutic in immune mediated diseases. This project aimed to identify IL-10 mutants that exhibit signalling bias to develop as selective anti-inflammatory therapies. We hypothesised that structurally guided human IL-10 mutants with altered receptor affinity could bias IL-10 signalling towards therapeutic immune suppressive pathways.

Peripheral blood mononuclear cells (PBMC) derived from two healthy donors were stimulated with wild-type human (h)IL-10 or receptor-selective mutant IL-10s. PBMC were stained for cell surface markers such as CD14 as well as intracellular phosphorylated (p) proteins pAKT1 and pSTAT3. Phospho-flow cytometry was used to detect phosphorylated proteins in specific cells, with changes in the geometric mean fluorescence intensity (gMFI) measured.

Stimulation of CD14+ monocytes with hIL-10 induced a mean (± SEM) pSTAT3 gMFI of 324 ± 37. Similarly, the IL-10 mutants induced mean gMFIs ranging from 307-331 ± 12-3. However, the IL-10 mutants displayed differential pAKT1 activation in CD14+ monocytes with mean gMFIs of 1,317-1,456 ± 2-21 which was substantially reduced compared to that induced by hIL-10 with a gMFI of 2,427 ± 271.

The differential pAKT1 gMFI with retention of pSTAT3 between the mutants and hIL-10 suggests that though changes to receptor affinity may not affect the JAK-STAT3 pathway, PI3K-AKT1 signalling could be subject to manipulation. This could provide a mechanism of decoupling the immune stimulatory and immune suppressive activity of IL-10 which would contribute to improved IL-10 therapies for immune mediated disease.

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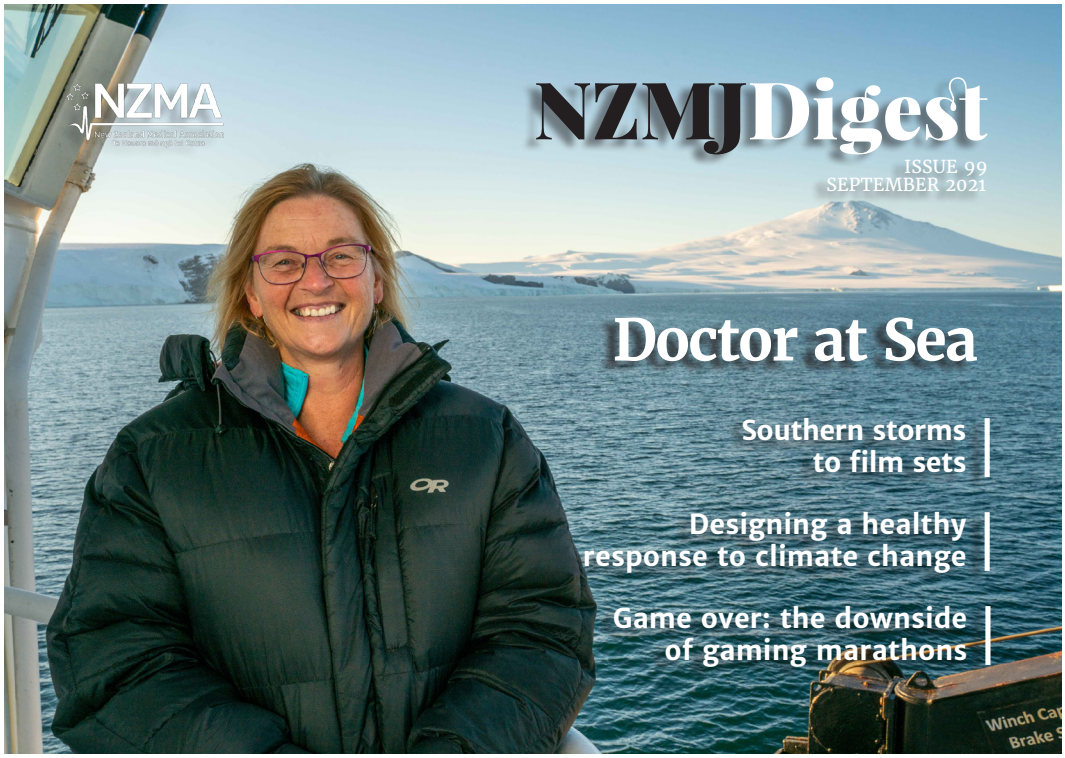


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