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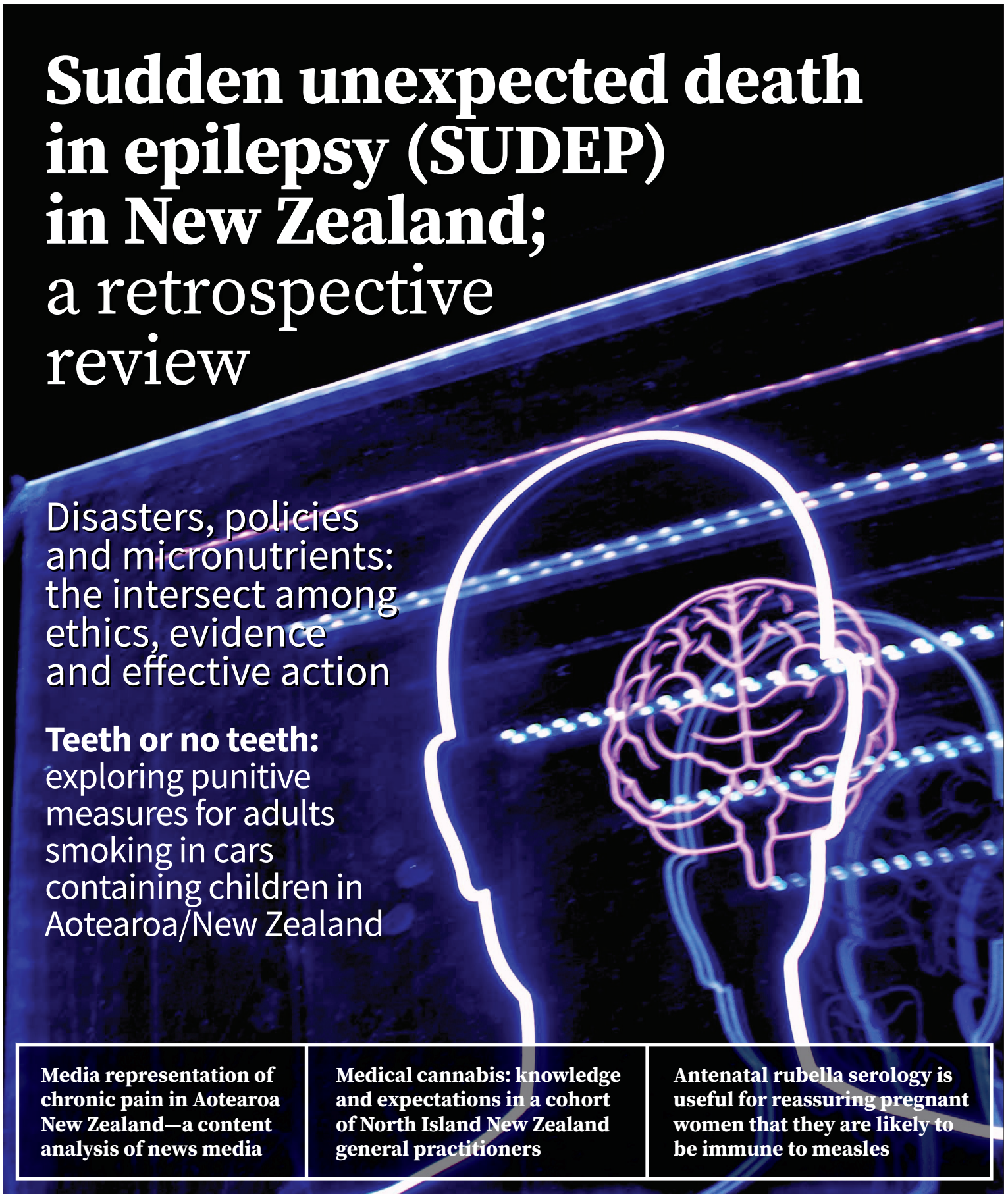

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Medical cannabis: knowledge and expectations in a cohort of North Island New Zealand general practitioners

Karen Oldfield, Irene Braithwaite, Richard Beasley, Allie Eathorne, Giles Newton-Howes, Alex Semprini

GPs are reporting that patients are asking them about medical cannabis prescriptions, mainly for symptoms relating to pain, cancer and palliative care, as well as reporting that patients are using illicit cannabis to self-manage conditions such as pain and anxiety/depression. Small numbers of GPs report that they have attempted to prescribe medical cannabis products, however the majority have concerns about the general use of cannabis as a medicine based on the lack of good evidence for use in the scientific literature and the confusing regulatory process currently in place for prescribing in New Zealand. GPs in the survey reported they would be likely to prescribe a cannabis product that is both regulated and has gone through clinical trials in specific medical conditions. With the upcoming implementation of the Medical Cannabis Scheme it is important that educational programmes emphasising evidence (both for and against use), medico-legal and practical elements of prescribing are in place to support the GPs to have informed discussions with their patients.

Trends in length of stay following acute coronary syndrome hospitalisation in New Zealand 2006–2016: ANZACS-QI 32 study

Tom Kai Ming Wang, Corina Grey, Yannan Jiang, Rod Jackson, Andrew Kerr

This study reports on trend in the length of 185,962 hospitals stay for heart attacks in New Zealand from 2006–2016. The length of hospital stay has fallen gradually over time for all age-groups, gender, ethnic group and types of heart attack. The factors that are associated with longer hospital stay include older age, female sex, Māori or Pacific ethnicities, going to a rural hospital initially, not having heart procedures or having heart surgery.

Stage at diagnosis for Māori cancer patients: disparities, similarities and data limitations

Jason Gurney, James Stanley, Chris Jackson, Diana Sarfati

In this study, we combined the best available data on stage of cancer at diagnosis for Māori and European/Other New Zealanders. We compared the two ethnic groups and found that while Māori are less likely to be diagnosed with early stage at diagnosis for several commonly-diagnosed cancers, this is not the case for all cancers. In our paper we talk about the weaknesses of our national cancer registry in terms of allowing us to monitor stage at diagnosis for Māori (and non-Māori) patients.

Sudden unexpected death in epilepsy (SUDEP) in New Zealand; a retrospective review

Mary Brennan, Shona Scott, Peter Bergin

Sudden unexpected death in epilepsy (SUDEP) has come to prominence in New Zealand over recent months because patients on lamotrigine have been required to change to the Logem brand, and several patients have apparently died shortly after changing brands. We have conducted a retrospective study of coroners' reports of SUDEP, which occurred prior to this enforced brand change. We identified 166 cases over a 10-year period (2007–2016), with a maximum of 26 cases occurring in 2013. Two-thirds of patients who died were aged between 15 and 45. We suspect that not all cases have been identified, and we are now undertaking a prospective study to learn more about risk factors for SUDEP.

Impact of human papillomavirus vaccination on rates of abnormal cervical cytology and histology in young New Zealand women

Carrie RH Innes, Jonathan A Williman, Bryony J Simcock, Phil Hider, Margaret Sage, Kieran Dempster-Rivett, Beverley A Lawton, Peter H Sykes

Cervical cell abnormalities are caused by persistent human papillomavirus (HPV) infection. Our study investigated the rate of cervical cell abnormalities in young New Zealand women. We found that women who had had the human papillomavirus (HPV) vaccination prior to 18 years were nearly a third less likely to be diagnosed with cervical cell abnormalities when aged 20–24 years. In this study, Māori women were less likely to be vaccinated but, if they were, vaccination offered similar protection for both Māori and non-Māori. This study confirms that HPV vaccination will offer protection against cervical cancer and also provide opportunities to reduce inequities. However, the study also demonstrates that both HPV vaccinated and unvaccinated women can develop high-grade cervical disease and this underlines the ongoing need for cervical screening in both vaccinated and unvaccinated women.

Career outcomes of students of an intercalated MBChB/PhD: experience from New Zealand

Yassar Alamri, Tim J Wilkinson

We reported the career choices and academic accomplishments of MBChB/PhD students at Otago University 17 years after the programme's introduction. A total of 25 students (of whom eight were current students) had enrolled in the combined programme between 2001 and 2018. Ten students (40%) were women. The rate of enrolment remained relatively steady through the years at 1.4±1.0 students/year. The rate of completion was high at 88.2% (15/17). The programme is considered worthwhile by our students most of whom continue (at various capacities) in academic work and produce a significant research output, although potentially in a field that is different to their PhD research.

Media representation of chronic pain in Aotearoa New Zealand—a content analysis of news media

Hemakumar Devan, Jessica Young, Ceonne Avery, Liv Elder, Yulia Khasyanova, Dominic Manning, Morghan Scrimgeour, Rebecca Grainger

Media reporting of health conditions can change people's beliefs and deliver key health messages. We evaluated how chronic pain was reported in the New Zealand news media since 2015. Chronic pain was reported to cause suffering and distress with no hope for the person living with pain. There was more focus on drug-based treatments using opioids and medicinal cannabis. There were few reports on non drug-based strategies like exercise and positive thinking, which were proven to be effective with minimal side-effects. The health system challenges of accessing pain services, inequities with access for Māori and Pasifika, and lack of trained clinicians were accurately represented. There is a need for developing media guidelines for chronic pain reporting and clinicians and researchers could work with media to provide evidence-based health information.

New Zealand should introduce nationwide pulse oximetry screening for the detection of critical congenital heart disease and other hypoxaemic conditions in the newborn

Elza Cloete, Thomas L Gentles, Frank H Bloomfield, for the Pulse Oximetry Screening Steering Committee

The early detection of congenital heart defects can improve outcomes for those affected. A pulse oximeter is a device that detects oxygen levels in the blood and can be utilised to screen for heart defects in newborns. The test has been adopted widely around the world as a screening tool. The feasibility of introducing the test in New Zealand's midwifery-led maternity setting has been demonstrated. Sector-led initiatives are, however, unlikely to result in equitable outcomes. New Zealand should therefore introduce a nationwide screening programme with adequate human and material resources that is governed by the National Screening Unit.

Teeth or no teeth: exploring punitive measures for adults smoking in cars containing children in Aotearoa/New Zealand

Frank Houghton, Diane O'Doherty, Ben Houghton

The recent announcement by the Government of New Zealand to ban smoking in cars with children is welcome. However, the thorny issue of enforcement and punishment remains. Internationally there is a deficit on research on this issue. The experiences of the UK and Ireland show little or no enforcement of such laws, unlike the State of Victoria in Australia, where the law was more robustly enforced. This viewpoint argues that enforcement is an important element in safeguarding the health and wellbeing of children.

Disasters, policies and micronutrients: the intersect among ethics, evidence and effective action

Neville M Blampied, Roger T Mulder, M Usman Afzali, Oindrila Bhattacharya, Meredith Blampied, Julia J Rucklidge

We will address health system policy issues relating to the ethical approval process for health research and dissemination as well as the willingness of the health system to incorporate information from published health research into clinical practice. This submission is based on recent direct experiences with the health system response to disasters and the ethical approval process. It is an expression of our responsibility, as university academics, to be 'critic and conscience of society' imposed by the Education Act (1989). Our experience demonstrated a disconnect between research and practice and between the needs of researchers to do prompt research and the laborious processes of ethics committee review.

Some history: in September 2010 one of us was conducting an ethically approved, randomised placebo-controlled trial (RCT) of a micronutrient treatment for adults with a diagnosis of attention-deficit/hyperactivity disorder (ADHD). At the time of the 7.1 Darfield (NZ) earthquake, 33 participants had been comprehensively assessed but only some were receiving active treatment when the earthquake struck. This established a natural experiment examining the way in which consumption of the nutritional supplement might impact the participants' response to the stress of a natural disaster. Consistent with prior research demonstrating efficacy of nutritional supplements on the stress response,[1–4] those taking the micronutrients were found to have statistically and clinically significantly reduced levels of depression, anxiety and stress one and two weeks post-earthquake, relative to the untreated group.[5] Approval for this extension to the research protocol was given immediately post-earthquake by the University of Canterbury Human Ethics Committee (UCHEC).

After the 22 February 22 2011 aftershock which killed 185 people and wrecked much of Christchurch City (NZ), the research team performed an RCT comparing several kinds and dose levels of nutritional supplementation (including micronutrients) to treatment-as-usual (TAU) with adult members of the Christchurch community as participants. The results of this study and its subsequent follow-up[6,7] confirmed the substantial benefits for psychological stress and distress resulting from taking micronutrients compared with TAU. In addition, rates of probable post-traumatic stress disorder (PTSD) dropped from 65 to 19% with a one-month micronutrient intervention compared with no change in the TAU group (whose PTSD risk remained ~48%). A further study demonstrated substantial benefits of micronutrient consumption for children with earthquake-exacerbated anxiety.[8] The benefits of micronutrients for survivors of a natural disaster were also subsequently replicated in an RCT that compared micronutrients with vitamin D following disastrous floods in Southern Alberta, Canada, in 2013.[9]

All the cited research was ethically approved, trial registered and conducted using rigorous research designs. The data were comprehensively analysed by appropriate analytic methods and published in peer-reviewed, international journals. Therefore, we argue that there is considerable scientific evidence that micronutrient treatment is an empirically supported therapy for survivors of highly stressful

events, including disasters, according to the Chambless and Hollon criteria,[10] specifically via support from at least two independently conducted, methodologically sound trials, and that the intervention reduces the risk of developing long-term PTSD symptoms.

On 15 March 2019, a gunman entered two Mosques in Christchurch, killed 51 people and injured 49. This catastrophe exposed a large number of people (both those directly surviving the attack and those in the wider community) to severe distress and increased their likelihood of PTSD, with PTSD incidence likely to range from 30–60% of those exposed and to potentially persist for up to two years post-event for up to one-third of those affected.[11]

In the immediate aftermath of the shootings, the authors felt individually and collectively that we faced a scientific and ethical dilemma. How best to use the knowledge we had gained from previous research in Christchurch and elsewhere to help the survivors of this latest catastrophe? Some of us contacted various responsible authorities to draw their attention to the benefits of supplying micronutrients to those affected. Those contacted included the Minister of Health, members of the Canterbury District Health Board (CDHB), general practice (GP) advisors at Pegasus Health (representing medical practitioners in general practice), local politicians and Members of Parliament, the Prime Minister's Chief Science Advisor, plus others. However, none of those contacted saw the use of a nutritional intervention as a priority, or they considered it too difficult to implement at the time.

Thus, the first of our 'critic and conscience' observations concerns the difficulty of getting a health system, even one with extensive, recent experience of disaster, to incorporate into post-disaster clinical practice new scientific evidence about treatments that are potentially beneficial to survivors and their wider community. A change in practice seems to be particularly difficult when it involves community rather than hospital-based treatment and when it involves psychological rather than physical injuries.

Thus, in light of the lack of official response to our evidence, we faced a continuing dilemma: What then should we do—another research study, or should we actively translate our scientific knowledge into clinical action? We chose the latter course, raised some money from donors to purchase supplies of micronutrients, and made these available to any self-identified members of the Christchurch Muslim community who sought treatment. We were fortunate that one member of our team is a member of this community and able to act as liaison and consultant in this clinical work. We monitored the psychological wellbeing and response to treatment of recipients, as is usual practice, via an online questionnaire.

In contrast to the research studies, but consistent with clinical practice, those receiving treatment were not randomised to treatment conditions, there was no control condition, there were no selection or exclusion criteria imposed (we advised participants concurrently taking other treatments, including medication, to discuss their micronutrient consumption with their therapist/prescriber) and we did not prescribe either the dose taken nor the duration of treatment. The manufacturer's recommended dose is three capsules twice a day, but some people took more, some less. We did, however, ensure that all participants gave full informed consent to treatment (and subsequent use of the data to assist with securing more funding), including information about possible side-effects of micronutrients, and other treatment options.

We did, after initiating this clinical work, consider if it might be extended into a research study. Preliminary approaches to both the UCHEC and to the Health and Disability Ethics Committee (HDEC) suggested to us that (a) these committees might well decline any application, and (b) that it was very likely to take many months to get a decision. Complicating ethical decision-making is that the micronutrient formulation is sometimes regarded as a medicine due to a possible therapeutic benefit for mental health symptoms. This therefore might require additional approval from other official Ministry of Health committees (such as the Standing Committee of Therapeutic Trials). Also, more ethical review steps have been instigated over the last few years, including external peer review, the development of a protocol, and more extensive community consultation, that make for a lengthier review process. Consequently, in our view, by the time that

any ethical approval for a research project was obtained (if it was), the opportunity to maximally help the community would have reduced substantially.

This leads to our second 'critic and conscience' observation: if intervention research is to be done into the aftermath of disasters, ethics committees need to establish some process for rapid approval of research protocols. We were fortunate that we were able to obtain rapid approval for our initial post-earthquake study. We can only speculate as to why the indications were that this would not happen in the current circumstances given the similarity in measures and intervention across the research studies over time: this was not a new treatment that the ethics committees had not been presented with before. We believe that this matter—clear policies about and the capacity to make rapid decisions about research in the immediate aftermath of a disaster—needs urgent attention.

The ethical debate then shifted to address the question "Could we publish our clinical observations?" A prolonged and arduous exchange with HDEC established (by 4 September 2019) that the committee considered that the clinical work we had done was within the scope of HDEC review and *should have received HDEC approval prior to commencement* because it was not considered to be part of standard care (whatever that might be). Nevertheless, HDEC advised that *this decision does not prohibit publication*. After another three months of further exchanges with UCHEC, they ruled similarly (25 November 2019). As a final 'critic and conscience' observation, we note that this is both a good outcome (in that it does not suppress potentially useful information freely provided by affected people in the expectation that it could be used to help others) and a potentially useful precedent. We further note that we do not for a moment suggest that the various individuals involved in making these two decisions were not doing anything other than striving to reach a correct, ethical decision. Nevertheless, the months it took for decisions to be reached and communicated meant that the clinical information we gathered could not be effectively shared in a more timely way with those who might have been able to implement the knowledge we had gained, to the benefit of the affected community. It also highlights that there is no obvious route for dissemination of information gathered through clinical practice in circumstances such as these.

Overall, our experience as clinicians and researchers was that our health and ethics systems are not set up to deal with the implementation nor the evaluation of nonstandard but evidence-based treatments given within both a clinical and research context under post-disaster conditions. The (informal) message we heard repeatedly was that there was no problem with providing any treatment, as long as we didn't want to evaluate its efficacy! We suspect, however, that the public would be keen for processes to be in place so that any interventions are routinely evaluated for efficacy such that adjustments can be made based on evidence and not politics or industry influence. We urge the leaders of our health system to listen to and be prepared to translate scientific evidence from disaster research into practice, and ethics committees to facilitate rather than obstruct future post-disaster research.

Competing interests:
Nil.

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Medical cannabis: knowledge and expectations in a cohort of North Island New Zealand general practitioners

Karen Oldfield, Irene Braithwaite, Richard Beasley, Allie Eathorne, Giles Newton-Howes, Alex Semprini

ABSTRACT

AIM: To investigate GP knowledge of the use of cannabis as a medicine and its regulation in New Zealand.

METHOD: A convenience sample of GPs completed a questionnaire during continuing medical education sessions. Key domains investigated were: patient interactions around use of cannabis as a medicine; prescription facilitation and impediments; knowledge of evidence for and against the use of cannabis as a medicine; knowledge of the New Zealand regulatory processes and knowledge of pharmaceutical grade products. Questionnaires were administered between June and October 2018.

RESULTS: There were 42/76 (55%) GPs who stated at least one patient had asked for a cannabis prescription for medical use in the last 12 months and 43/76 (57%) were aware of pharmaceutical grade preparations, the majority Sativex. There were 59/75 (79%) who expressed concerns about future prescribing; however, 63/75 (84%) indicated they would be 'somewhat' or 'very' likely to prescribe a PHARMAC-funded product with good evidence in specific conditions.

CONCLUSION: Some GPs have concerns about prescribing medicinal cannabis. Due to regulatory restrictions, including no currently funded products, and uncertain scientific evidence of efficacy and safety, education programmes will be required to inform the medico-legal, evidential and practical elements of prescribing cannabis as a medicine.

There has been a global shift in both the public perception of the medicinal value of cannabis and regulation of medicinal cannabis products.[1] Cannabis sativa sp. has been used for over 10,000 years in various cultures for the management of health conditions,[2,3] despite a paucity in the medical literature about its efficacy and safety. Cannabis-derived therapeutics have been the focus of contemporary pre-clinical work, but clinical trial programmes have been impeded by the heterogeneity of plant-based products, the quality and consistency of products available and the legality of undertaking trials.[2] High-quality randomised control trials (RCT) of delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) have led to the development of pharmaceutical grade medications such as Sativex[4] and Epidiolex,[5] and there is growing interest in the therapeutic potential of the other cannabinoids and constituents such as terpenes.[6]

New Zealand is undergoing a period of legislative change, with the passing of the Misuse of Drugs (Medicinal Cannabis) Amendment Bill into law in December 2018[7] and the proposed referendum regarding legalisation of cannabis in 2020.[8] This has been driven by growing interest in the use of cannabis for the treatment of medical conditions.[2] The 2012/2013 New Zealand Health Survey reported that 42% of cannabis users

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considered their use as medicinal in the 12 months prior,[9] despite cannabis-based medicines only infrequently being prescribed. This disparity is likely to reflect a variance of opinion between the perceived medical value of cannabis by users and doctors who typically ground practice in evidence. Overseas studies have shown a high level of patient support for access to medical cannabis compared with a more moderate level of support from doctors, depending on their area of specialty.[10,11] It is unknown if this is similar in the New Zealand population but likely, as New Zealand has an internationally high use of cannabis within its population.[12]

In 2016 there were 3,950 doctors who identified themselves as general practitioners (GPs).[13] Currently GPs require both hospital specialist and Ministry of Health approval to prescribe cannabis-related products (excluding CBD and neurologist-endorsed prescriptions of Sativex for spasticity in multiple sclerosis).[14] As interest in the use of cannabis as a medicine grows, it follows that GPs are likely to be fielding questions from their patients about it and requests for its prescription for a wide range of conditions. Other than Sativex, an oro-mucosal formulation that contains 2.7mg Δ9-THC and 2.5mg CBD per spray that is approved as an adjunct treatment for spasticity in multiple sclerosis,[15] there is no MedSafe approved cannabinoid-based medicine in New Zealand. Sativex is not subsidised by the Pharmaceutical Management Agency (PHARMAC).

This study assessed current GP experience with cannabis as a medicine, including patient interactions and prescribing practices, indications for use, regulatory processes for obtaining cannabis to be used as a medicine, knowledge of Sativex and other cannabinoid products, current prescribing concerns and preferences with respect to future delivery of education around cannabis to be used as a medicine. We hypothesised that GPs in New Zealand would have limited knowledge around the use of cannabis as a medicine due to the current regulatory environment, including possible limited exposure to the management of patients with multiple sclerosis (the sole MedSafe approved indication for a cannabinoid-derived medication), the lack of funded products as well as potentially limited education about cannabis and the endocannabinoid system in both medical schools and vocational training schemes.

Method

Participants

GPs, GP registrars and trainee interns on GP attachments working in general practices throughout the North Island of New Zealand (Northland, Bay of Plenty, Wairarapa and Wellington) were recruited between June and October 2018 using a snowball technique,[16] useful in groups who rarely participate in research. Peer groups and continuing medical education (CME) sessions were the nidus for these snowballs with initial participants identified through the Medical Research Institute of New Zealand GP research network. CME sessions were not associated with cannabis or substance abuse teaching. Specific GP caseloads or special interests (eg, chronic pain) were not established prior or during the recruitment period.

Questionnaires

The full questionnaire is provided in the online supplement. For the purposes of the questionnaire, medical cannabis was defined as “any use of cannabis plants and/or medications derived from cannabis used by a patient to treat a medical condition”.

Participants were asked to complete a paper questionnaire which included the following domains (see Figure 1):

- GP—patient interactions around the use of cannabis as a medicine
- GP prescriptions of cannabinoid medications—facilitation and impediments
- Knowledge of conditions with evidence for or against the use of cannabis as a medicine
- Knowledge of the regulatory process for approvals, import and funding in relation cannabinoid medications
- Awareness of pharmaceutical cannabinoid medications worldwide

The questionnaire was piloted on two GPs. Survey domains did not go through a validation process.

Ideally participants were asked to complete the questionnaire in the presence of a study investigator.

Figure 1: Examples of questions from each domain of the questionnaire.

- "Have you been approached by patients seeking a prescription for medical cannabis products over the past 12 months?" Answers were categorised as none, 1–4, 5–10, 10+.
- "What impediments (if any) occurred when facilitating the request (for prescribed medical cannabis)?" Categories for answers included cost, insufficient evidence base, side effects, insufficient understanding of process, and aware of process but benefit versus cost was inappropriate.
- "What conditions are you aware of that DO have Grade A/Level I RCT evidence for use of medical cannabis products?" and "what conditions are you aware of in which there is substantive evidence of NO benefit to support the use of medical cannabis products but for which products may have been recommended?"
- Completion of a table identifying responsibilities for approval, funding and import of CBD, Sativex and other medical cannabis products
- Of Dronabinol, Sativex, Naboline and Epidiolex, participants were asked to indicate awareness of the product, select primary constituents (THC and/or CBD), indicate if licensed in New Zealand, indicate formulation and estimate the annual cost to the patient for the product.

Data entry and analysis

All data was entered into REDCap (Research Electronic Data Capture).[17] Free text answers were grouped into related categories and reported numerically. Partially completed questionnaires were included in the analysis to the point of completion. If questionnaires had single missing data points such as a blank space in a table where other information had been input and it was clear that by leaving a question blank the participant did not know the answer it was analysed as such, otherwise this was recorded in the database as "No answer given".

Statistics

All submitted questionnaires were included in the analysis. Proportions and 95% confidence intervals were calculated using Java Stat.[18] The proportion denominator was determined by the number of participants who answered that specific area of the questionnaire. Free text answers were grouped into common themes for the purposes of reporting. Ethnicity data was prioritised according to the Health Information Standards Organisation.[19] The sample size represents a convenience sample, while taking into account the central limit theorem that in a sample >30 the distribution of the sample population mean will reflect that of the normal population.[20]

This research was approved by the Victoria University of Wellington Human Ethics Committee (#25835).

Results

A total of 82 potential participants were approached, of which 76 agreed to take part. Fifty-six questionnaires were completed in the presence of a study investigator (73.7%), with the remainder performed without supervision. Participant characteristics are shown in Table 1.

Patient interactions, prescribing practices and impediments

Of the GPs, 42/76 (55.3%) had at least one patient ask them for a medicinal cannabis prescription in the last 12 months (Table 2) most commonly for pain, cancer and palliative care. On request, 14/42 (33.3%) GPs attempted to prescribe, with 13 reporting impediments to prescribing and 7/13 reporting that the patient ultimately received their prescription (Table 2). Eight participants (8/73, 11.0%) reported they had patients who had been prescribed a medical cannabis product, with five reporting that this was specialist prescribed; however, it was not established if this was prior to the GP request. There were 51/75 (68.0%) GPs with patients reporting using illicit cannabis in order to manage medical conditions, mainly for pain, anxiety/depression and cancer/palliative care. Smoking was the preferred form of use (Table 2).

Evidence for use of medicinal cannabis products

Out of 76 GPs, 33 (43.4%) considered there was at least one condition with Grade A/Level 1 RCT[21] for cannabis use in medical

Table 1: Participant characteristics (stratified by experience).

	GP consultant (n)	%	GP registrar (n)	%	Trainee intern (n)	%	Not stated (n)	%	Total (n)	%
Total participants	67	88.2	3	3.9	2	2.6	4	5.3	76	100.0
Gender										
Male	42	55.3	1	1.3	1	1.3	0	0.0	45	59.2
Female	25	32.9	2	2.6	1	1.3	1	1.3	28	36.8
Not stated	0	0.0	0	0.0	0	0.0	3	3.9	3	3.9
Age band										
20–29	0	0.0	2	2.6	1	1.3	0	0.0	3	3.9
30–39	10	13.2	1	1.3	1	1.3	0	0.0	11	14.5
40–49	17	22.4	0	0.0	0	0.0	0	0.0	18	23.7
50–49	18	23.7	0	0.0	0	0.0	0	0.0	18	23.7
60–69	18	23.7	0	0.0	0	0.0	3	3.9	21	27.6
70–79	3	3.9	0	0.0	0	0.0	0	0.0	3	3.9
Not stated	1	1.3	0	0.0	0	0.0	1	1.3	2	2.6
Ethnicity (prioritised to Level 2)										
NZ European	49	64.5	1	1.3	2	2.6	1	1.3	53	69.7
Māori	3	3.9	0	0.0	0	0.0	0	0.0	3	3.9
Chinese	3	3.9	1	1.3	0	0.0	0	0.0	4	5.3
Indian	2	2.6	0	0.0	0	0.0	0	0.0	2	2.6
Other	10	13.2	1	1.3	0	0.0	0	0.0	11	14.5
Not stated	0	0.0	0	0.0	0	0.0	3	3.9	3	3.9

conditions; with the most commonly identified conditions listed in Table 3. A similar proportion (29/76, 38.2%) considered there were specific conditions for which there was clearly no evidence of benefit to support the use of medicinal cannabis products but that they were aware that these products might have been recommended or suggested outside evidence-based medicine, as listed in Table 3.

When asked about medicinal cannabis side effects, 49/76 (64.5%) GPs indicated at least one, with the most commonly stated side effects being drowsiness/sedation, psychosis/schizophrenia, nausea, and weight gain/increased appetite (n=25, 13, 13 and 9 respectively). 2/76 (2.6%) GPs stated there were no side effects, 13/76 (17.1%) did not know and 12/76 (15.8%) did not answer.

Knowledge of pharmaceutical-grade medicinal cannabis products

Just over half of GPs were aware of currently available pharmaceutical-grade cannabinoid preparations (n=43/76, 56.6%). Of these, most were aware of Sativex (n=37/43, 86.1%); 10/37 (27.0%) accurately described it constituents and 12/37 (32.4%) its formulation (Table 4). Of those aware of Sativex, 31/43 (72.1%) indicated they would prescribe it for at least one condition including pain syndromes (n=17), multiple sclerosis (spasticity/pain) (n=16) and epilepsy/seizures (n=11).

Regulatory processes

Less than half of GPs responded to the regulatory section of the questionnaire, with 37/76 (48.7%) answering questions

Table 2: Patient interactions relating to medicinal cannabis products and use of recreational cannabis for medicinal purposes.

	n	%	95% CI
Number of participants receiving patient requests for medicinal cannabis prescriptions	42/76	55.3	43.4–66.7
1–4 patients	38/42	90.5	77.4–97.3
5–10 patients	2/42	4.8	0.6–16.2
10+ patients	2/42	4.8	0.6–16.2
Number of participants attempting to prescribe	14/42	33.3	19.6–49.6
Number of participants with impediments (more than one answer could be given)	13/14	92.9	66.1–99.8
Specialist/ministry approval needed	6/13	46.2	19.2–74.9
Cost prohibitive to patient	6/13	46.2	19.2–74.9
Lack of general knowledge/information	2/13	15.4	1.9–45.5
Put off by assuming responsibility of assuring CBD:THC ratio	1/13	7.7	0.2–36.0
Number of participants not prescribing at time of request	28/42	66.7	50.5–80.4
Reasons for not prescribing at time of request (more than one answer could be given)			
Insufficient evidence base	14/28	50.0	30.7–69.4
Cost	6/28	21.4	8.3–41.0
Insufficient understanding of process	4/28	14.3	4.0–32.7
Clinical benefit vs logistics/cost inappropriate	3/28	10.7	2.3–28.2
Anticipated side effects	0/28	0	0.0–12.3
No answer given	8/28	28.6	13.2–48.7
Number of participants with patients reporting recreational cannabis use for medicinal purposes	51/75	68.0	56.2–78.3
1–4 patients	35/51	68.6	54.1–80.9
5–10 patients	9/51	17.6	8.4–30.9
10+ patients	6/51	11.8	4.4–23.9
No answer given	1/51	2.0	0.0–10.4
Preferred forms of use elicited from patients by participants (more than one answer could be given)			
Smoking	44/51	86.3	73.7–94.3
Edibles	19/51	37.3	24.1–51.9
Other (cannabis drops, oils, vaping, unknown)	8/51	15.7	7.0–28.6

Table 3: GP knowledge of evidence for medical cannabis use and future prescribing concerns.

Response	**Conditions with Grade A/ Level 1 RCT evidence for use is available**			**Conditions with substantive evidence of no benefit for use but GP aware may have been suggested outside evidence-based medicine**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**
None	17/76	22.4	13.6–33.4	5/76	6.6	2.2–14.7
Didn't know	13/76	17.1	9.4–27.5	15/76	19.7	11.5–30.5
Didn't supply an answer	13/76	17.1	9.4–27.5	27/76	35.5	24.9–47.3
At least one condition	33/76	43.4	32.1–55.3	29/76	38.2	27.3–50.0
Conditions cited	**N**			**N**		
Pain (all types)	19			15		
Epilepsy/seizure	16			7		
Multiple sclerosis	15			0		
Nausea and vomiting	8			1		
Psychological/psychiatric illness	0			12[a]		
Cancer	0			3		
Other	10[b]			11[c]		
Concerns about future prescribing of medical cannabis products (more than one option could be given)				**n**	**%**	**95% CI**
				59/75	78.7	67.7–87.29
Insufficient evidence base				39/59	66.1	52.6–77.9
Cost				19/59	32.2	20.6–45.6
Insufficient understanding of process				31/59	52.5	39.1–65.7
Clinical benefit vs logistics/cost inappropriate				18/59	30.5	19.2–43.9
Side effects				12/59	20.3	11.0–32.8

a: Anxiety; n=5, post traumatic stress disorder (PTSD); n=3, depression; n=3, psychiatric illnesses; n=1.
b: Anxiety; n=2, Parkinson's disease; n=2, arthritis/rheumatological disorders; n=2, depression; n=1, dystonia; n=1, motor neurone disease; n=1, poor appetite; n=1.
c: Headache; n=2, dementia; n=2, cardiovascular disease; n=1, reduce adverse effects of antipsychotics; n=1, head injuries; n=1, autism spectrum disorder; n=1, HIV; n=1, rheumatological disorders; n=1, muscle spasms; n=1.

relating to Sativex funding and 36/76 (47.4%) about its approval. Of those who supplied answers (for which more than one answer could be given), there were an equal number of responses indicating that specialist or MOH approval was needed for a Sativex prescription (n=21/36, 58.3%), with 20/37 (54.1%) indicating that they thought PHARMAC funding was available (Table 5).

59/75 (78.7%) GPs reported concerns about prescribing medical cannabis products in the future (Table 3). 63/75 GPs (84.0%) indicated that if there was a PHARMAC funded, licensed product with good scientific evidence for specific conditions, they would be 'somewhat' or 'very' likely to prescribe this in their day to day practice.

Accessing information

When asked about education 75 GPs responded, with 43/75 (57.3%) stating they had accessed one or more sources of information regarding cannabis use as a medicine. The educational sources accessed were journals (n=19/43, 44.2%), CME sessions (n=13/43, 30.2%), the Ministry of Health Website (n=12/43, 27.9%) and

Table 4: GP knowledge of pharmaceutical-grade medicinal cannabis products.

	N	%	95% CI
Any pharmaceutical grade medicinal cannabis medication	43/76	56.6	44.7–67.9
Nabiximols (Sativex)	37/43	86.1	72.1–94.7
Dronabinol (Marinol)	5/43	11.6	3.9–25.1
Nabilone (Cesamet)	2/43	4.7	0.6–15.8
Epidiolex	1/43	2.3	0.1–12.3
Knowledge of Sativex			
Primary constituents			
THC only	6/37	16.2	6.2–32.0
THC/CBD	10/37	27.0	13.8–44.1
CBD only	15/37	40.5	24.8–57.9
No answer given	6/37	16.2	6.2–32.0
Aware licensed in New Zealand	29/37	78.4	61.8–90.2
Formulation			
Capsule/tablet	1/37	2.7	0.1–14.2
Buccal/sublingual	12/37	32.4	18.0–49.8
Both	7/37	18.9	8.0–35.2
No answer given	17/37	46.0	29.5–63.1
Estimated cost per year to patient (NZ$)			
Less than $10,000	11/37	29.7	15.9–47.0
Greater or equal to $10,000	7/37	18.9	8.0–35.2
No answer given	19/37	51.4	34.4–68.1

other sources (n=15/43, 34.9%). Preferred educational methods were CME sessions (n=54/75,72.0%), followed by CME online modules and information sheets (n=32/75, 42.7% and n=25/75, 33.3% respectively).

Discussion

This study has identified that just over half of 76 GPs surveyed reported having patients ask about medicinal cannabis prescriptions in the past 12 months and two-thirds had patients discuss their use of illicit cannabis for medical reasons. Less than a third of GPs asked attempted to facilitate prescription requests citing cost and the need for specialist/ministerial approval as the largest impediments encountered. Just over half of the GPs were aware of pharmaceutical-grade cannabinoid products, with the majority of them referencing Sativex. Responses to the regulatory questions were limited and suggest uncertainty around the regulatory processes currently in place. Three quarters of participants expressed some concerns about prescribing medicinal cannabis in the future; however, most (four in five) reported that they would be willing to prescribe a PHARMAC-funded prescription medication with Grade A/Level 1 RCT evidence in specific medical conditions. Half of the participants had accessed some educational material about medicinal cannabis, with the majority preferring CME sessions as their future way of having information disseminated.

Table 5: GP knowledge of responsibility for the regulatory process relating to medical cannabis in New Zealand.

Entity responsible for approval of medicinal cannabis products									
	Sativex (n=36)			**CBD (n=21)**			**Other cannabis products (n=9)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 76)	36	47.4	35.8–59.2	21	27.6	18.0–39.1	9	11.8	5.6–21.3
PHO	0	0.0	0.0–9.7	1	4.8	0.1–23.8	0	0.0	0.0–33.6
DHB	1	2.8	0.1–14.5	1	4.8	0.1–23.8	1	11.1	0.3–48.3
Specialist	21	58.3	40.8–74.5	8	38.1	18.1–61.6	2	22.2	2.8–60.0
MoH	21	58.3	40.8–74.5	12	57.1	34.0–78.2	6	66.7	29.9–92.5
PHARMAC	12	33.3	18.6–51.0	10	47.6	25.7–70.2	6	66.7	29.9–92.5
Entity responsible for funding of medicinal cannabis products									
	Sativex (n=37)			**CBD (n=25)**			**Other cannabis products (n=13)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 76)	37	48.7	37.0–60.4	25	32.9	22.5–44.6	13	17.1	9.4–27.5
PHO	0	0.0	0.0–9.5	0	0.0	0.0–13.7	0	0.0	0.0–24.7
DHB	3	8.1	1.7–21.9	3	12.0	2.6–31.2	0	0.0	0.0–24.7
Patient	16	43.2	27.1–60.5	12	48.0	27.8–68.7	7	53.9	25.1–80.8
MoH	6	16.2	6.2–32.0	1	4.0	0.1–20.4	0	0.0	0.0–24.7
PHARMAC	20	54.1	36.9–70.5	12	48.0	27.8–68.7	7	53.9	25.1–80.8
Entity responsible for the import of medical cannabis products									
	Sativex (n=32)			**CBD (n=25)**			**Other cannabis products (n=11)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 76)	32	42.1	30.9–54.0	25	32.9	22.5–44.6	11	14.5	7.5–24.4
Prescribing doctor	5	15.6	5.3–32.8	6	24.0	9.4–45.1	3	27.3	6.0–61.0
Pharmacy	10	31.3	16.1–50.0	9	36.0	18.0–57.5	3	27.3	6.0–61.0
Specialist	4	12.5	3.5–29.0	5	20.0	6.8–40.7	1	9.1	0.2–41.3
MoH	6	18.8	7.2–36.4	3	12.0	2.6–31.2	1	9.1	0.2–41.3
PHARMAC	11	34.4	18.6–53.2	9	36.0	18.0–57.5	5	45.5	16.8–76.6

*PHO: Primary Health Organisation, DHB: District Health Board, MOH: Ministry of Health, PHARMAC: Pharmaceutical Management Agency.

The Misuse of Drugs (Medicinal Cannabis) Amendment Act December 2018 allows for patients with any illness that requires palliation, as determined by a medical doctor or nurse practitioner, a defence against the charge of possession of a cannabis plant or preparation, pipe or utensil.[7] In addition, CBD products were removed from the Misuse of Drugs Regulations 1977, and it was required that the regulations for a Medical Cannabis Scheme to improve access to quality medicinal cannabis products be in place within one year of the law being implemented.[22]

While this legal and regulatory environment for the use of cannabis as a medicine is changing, it does not necessarily follow that the medical profession are prepared for or support these changes. There is no conclusive definition as to what "medicinal cannabis" comprises; be it a pharmaceutical-grade medicine that has undergone the scrutiny of drug development phases or a locally grown cannabis plant that is smoked or from which a preparation is made, with or without the presence of THC. From a prescriber perspective, any cannabis product that has not been developed to a pharmaceutical grade and approved by MedSafe is considered an unapproved medicine, and as such can only be prescribed under Section 25 of the Medicines Act 1981.[23] This means the prescriber assumes responsibility in regards to independently investigating and conveying risks, benefits and contraindications related to the unapproved medication while providing appropriate follow-up if they choose to prescribe it.[24,25]

Currently GPs who feel there is evidence for use of cannabis -based products for their patients and who attempt to facilitate a request find they are impeded by a confusing regulatory process and a high cost to the patient. They report some patients choose to self-manage using an unregulated illicit product, often delivered by smoking. This reported use of illicit cannabis to manage medical conditions is in agreement with the New Zealand Health Survey 2012/2013,[9] suggesting that use of cannabis as a medicine has some currency in the eyes of the public.

There are varying levels of GP knowledge of the evidence for the use of cannabis as a medicine, with the same conditions being described in both the 'Grade A/Level 1 RCT evidence' and 'substantive evidence of no benefit of use' categories. While there is a large amount of peer-reviewed literature available,[2] there is a current lack of high-quality randomised controlled trials. The National Academies of Science, Engineering and Medicine report into the Health Effects of Cannabis and Cannabinoids in 2017 found conclusive/substantial evidence for the use of cannabis-derived therapeutics in three areas: chemotherapy-induced nausea and vomiting, patient-reported multiple sclerosis-related spasticity and the treatment of chronic pain in adults. However, they also specifically stated the need for further research.[2] There are ongoing randomised controlled trials of cannabis products in other medical conditions such as trials of Epidiolex in refractory childhood epilepsy syndromes.[5,26]

Almost half of GPs who participated in this study were aware of Sativex; however, the majority of those could not recall its constituents or its formulation. The majority of GPs were informed as to the potential side effects of using cannabis-based medications, likely reflecting knowledge of the adverse effects of recreational/illicit cannabis use. A minority were aware of the annual cost to patients (approximately $14,500) for the PHARMAC-approved indication for prescribing. This is not unsurprising, as the prevalence of multiple sclerosis in New Zealand was most recently recorded as 73.1/100,000,[27] meaning many GPs may not have experience with patients who have multiple sclerosis and do not have experience prescribing Sativex.

The majority of GPs expressed reservations about prescribing cannabis products in the future but indicated they would likely prescribe an approved medication that was PHARMAC funded and had Grade A/Level 1 RCT evidence for a specific medical condition.

The lack of substantial evidence for the use of cannabis as a medicine in many medical conditions and the relatively recent discovery of the endocannabinoid system is likely to have impacted the potential

education that GPs have received. Overseas studies report that despite the legalisation of medical cannabis products in certain states of the US, the training given at medical schools is limited, with 85% of residents and fellows reporting receiving no training about medical cannabis in medical school or residency and only 9% of medical schools having medical cannabis training in their curriculum.[28] This may reflect that although advocacy for use and legalisation of the products has occurred, the limited strength of evidence for the use of cannabis as a medicine precludes it from being included within the therapeutics section of medical school curricula. Current Australasian curricula concentrates on basic cannabinoid pharmacology; including receptors and signalling pathways, as well as cannabis -related drug tolerance and harms, with discussions around therapeutics if and when substantial evidence for use is available.

There are a range of Australian resources available from the Therapeutics Goods Administration[29] and the Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE)[30] for practitioners to access about the use of cannabis as a medicine. However, with changing regulatory requirements, the addition of New Zealand-focused education modules including regulatory processes involved, cannabinoid products available in New Zealand and supporting evidence for or against their use that is made available for post-graduate doctors, would add to the tools that healthcare professionals can use to have informed conversations with their patients.

This study has limitations in its size, with 76 participants; however, it has strengths in the fact that the majority of questionnaires (73.9%) were undertaken in the presence of a study investigator rather than through an online portal, ensuring answers were based on immediate recall and therefore current knowledge. There is a likelihood that unanswered questions reflect areas that GPs have little or no knowledge, so the positive responses likely indicate the maximal current understanding in the GP community. There is a possibility of selection bias in that all participants were recruited through CME and peer group sessions, so only those doctors that attend these sessions would be approached; however, it is a requirement of the Medical Council of New Zealand that all doctors undertake a CME programme. It is acknowledged specific GPs may have areas of special interest that mean they would receive a higher amount of interest in the use if medical cannabis as a medicine and that this was not established at the time of the questionnaire being undertaken. The sample was small and skewed towards male GPs which may limit the generalisability of the results. There were also a greater number of GPs from urban practices compared with rural practices involved in the study, which also has potential to limit the generalisability.

In conclusion, the Misuse of Drugs (Medicinal Cannabis) Amendment Act 2018 has increased the likelihood that GPs will have patients wanting to discuss the use of cannabis as a medicine. Due to the issue of regulatory restrictions, limited pharmaceutical-grade preparations available in New Zealand and the poor evidence base of efficacy in many conditions, individual GPs may feel the need to take on the responsibility of prescribing an unapproved medication under the Medicines Act. To counter this, it is essential that evidence based, New Zealand-focused education modules are developed to allow GPs and their patients to have informed discussions around the legislative, evidential and practical elements of prescribing cannabis as a medicine.

Appendix

Medicinal cannabis in primary care questionnaire

General knowledge

1. Are you aware of any pharmaceutical-grade cannabis medications available worldwide?

   Yes ○ No ○

   a. If yes, please indicate which medications you are aware of, the primary constituents, whether they are licensed in New Zealand, the delivery route and rough cost to the patient. If no, please continue to page 2.

	Aware of product? (Y/N)	**Primary constituents (tick all that apply)**		**Licensed in NZ? (Y/N)**	**Capsule/ tablet (tick all that apply)**	**Buccal/ sublingual (tick all that apply)**	**Estimated cost per year (NZ $ amt)**
		THC*	**CBD***				
Dronabinol (Marinol)							
Nabiximols (Sativex)							
Nabilone (Cesamet)							
Epidiolex							

*THC= delta-9-tetrahydrocannabinol, CBD= Cannabidiol.

   b. What medical conditions, if any, would you prescribe each medication for?

	Condition 1	**Condition 2**	**Condition 3**	**Don't know**
Dronabinol (Marinol)				
Nabiximols (Sativex)				
Nabilone (Cesamet)				
Epidiolex				

Medical conditions

Cannabis has been suggested as a treatment for numerous medical conditions:

1. What conditions are you aware of that DO have Grade A/Level I RCT evidence for use of medicinal cannabis products? Please list up to 5.

   i) _____

   ii) _____

   iii) _____

   iv) _____

   v) _____

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2. What conditions are you aware of in which there is substantive evidence of NO benefit to support the use of medicinal cannabis products, but for which such products may have been recommended? Please list up to 5.
   i) _____
   ii) _____
   iii) _____
   iv) _____
   v) _____
3. Please list up to 5 side effects that are associated with use of medicinal cannabis products
   i) _____
   ii) _____
   iii) _____
   iv) _____
   v) _____

Regulatory requirements

There are three Ministry of Health categories of cannabis-based products in New Zealand presently. Please mark where the responsibilities of approval, funding and import lie with each (you may tick more than one option):

	Approval				
	PHO	**DHB**	**Specialist**	**MOH**	**PHARMAC**
CBD					
Sativex					
Other					
	Funding				
	PHO	**DHB**	**Patient**	**MOH**	**PHARMAC**
CBD					
Sativex					
Other					
	Import				
	Prescribing doctor	**Pharmacy**	**Patient**	**MOH**	**PHARMAC**
CBD					
Sativex					
Other					

PHO = Primary Health Organisation; DHB = District Health Board; MOH = Ministry of Health; PHARMAC = Pharmaceutical Management Agency.

Professional experience

1. Have you been approached by patients seeking a prescription for medical cannabis products over the past 12 months?

   Yes ○ No ○

   a. If yes, how many patients have approached you?

   1–4 ○ 5–10 ○ 10+ ○

   i) For what condition/s? _____

   _____

   b. Did you facilitate any of the requests?

   Yes ○ No ○

   i) If Yes:

      i. What impediments (if any) occurred when facilitating the request?

      _____

      _____

      ii. Did the patient receive their product?

   Yes ○ No ○

   ii) If No, why not:

   ○ Cost

   ○ Insufficient evidence base

   ○ Side effects

   ○ Insufficient understanding of process

   ○ Aware of process but considered potential clinical benefit vs logistics/cost inappropriate

2. Have any patients for whom you are the named GP been prescribed a medical cannabis product?

   Yes ○ No ○

   a) If yes, who prescribed this?

   Me ○ Another GP ○ Specialist ○

3. Have any of your patients informed you that they are using cannabis for medical conditions in the last 12 months?

   Yes ○ No ○

   a) If yes, how many patients?

   1–4 ○ 5–10 ○ 10+ ○

   i) For what condition/s? _____

   _____

   b) What are they using (tick more than one if required)?

   ○ Cannabis (smoked)

   ○ Cannabis (edible)

   ○ Other (please specify) _____

4. Have you accessed information about medical cannabis from any of the following sources?

   ○ CME session

   ○ Journals

   ○ MOH website

   ○ Other (please detail)

   _____

5. Do you have reservations or concerns in relation to prescribing medical cannabis products, either currently or in the future?

   Yes ◯ No ◯

   a) If yes, please give a reason:

   ◯ Cost

   ◯ Insufficient evidence base

   ◯ Side effects

   ◯ Insufficient understanding of process

   ◯ Aware of process but considered potential clinical benefit vs logistics/cost inappropriate

6. How would you prefer to receive educational content about medical cannabis?

   ◯ CME session

   ◯ CME online module

   ◯ Information sheet

   ◯ Podcast

   ◯ Other (please detail)

   _____

7. If there was a PHARMAC funded, licensed product with good RCT evidence for specific conditions how likely would you be to prescribe this in your day to day practice?

   ◯ Very Likely

   ◯ Somewhat Likely

   ◯ Neutral

   ◯ Somewhat Unlikely

   ◯ Very Unlikely

8. Demographic Information:

   Age (Years):

   ◯ Under 20

   ◯ 20–29

   ◯ 30–39

   ◯ 40–49

   ◯ 50–59

   ◯ 60–69

   ◯ 70–79

   ◯ 80+

   Gender:

   ◯ Male

   ◯ Female

   ◯ Other (please specify)

   _____

   ◯ Prefer not to disclose

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Ethnicity: Which ethnic group do you belong to? (Tick all that apply)

◯ NZ European
◯ Māori
◯ Samoan
◯ Cook Island Māori
◯ Tongan
◯ Niuean
◯ Chinese
◯ Indian
◯ Other (such as Dutch, Japanese, Tokelauan). Please state:

_____

Source: SNZ, 2001 Census

Specialty: _____

◯ Consultant/GP
◯ Senior Registrar
◯ Junior Registrar
◯ Senior House Officer
◯ House Officer
◯ Other (please specify)

_____

Years in practice: _____

Competing interests:
Karen Oldfield, Irene Braithwaite, Giles Newton-Howes and Alex Semprini are members of the Medical Cannabis Research Collaborative (NZ), an impartial collaboration of academics and regulatory experts with an interest in research into the use of cannabis as a medicine. The Medical Research Institute of New Zealand has undertaken research activity that is unrelated to this article for Helius and Whakaora Pharma, both of which are New Zealand-based medicinal cannabis companies. There are no other conflicts of interest to declare.

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Trends in length of stay following acute coronary syndrome hospitalisation in New Zealand 2006–2016: ANZACS-QI 32 study

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ABSTRACT

AIMS: Length of hospital stay (LOS) for acute coronary syndrome (ACS) has important clinical and cost implications. We report recent trends and predictors of ACS hospitalisation LOS in New Zealand.

METHODS: Using routine national hospitalisation datasets, we calculated mean LOS for ACS admissions annually from 2006 to 2016, by demographics, ACS subtype and ACS procedures (coronary angiography, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)). We also identified predictors of longer LOS.

RESULTS: Among 185,962 ACS hospitalisations, mean LOS decreased from 7.8 to 6.7 days between 2006 and 2016 (adjusted decrease = -0.18 days/year). Decline in LOS was observed for all demographic subgroups by age, sex, ethnicity and deprivation quintile. While coronary angiography and PCI rates increased during this time, LOS declined for all management strategies. However, the adjusted rate of decline was greater for patients receiving coronary angiography without revascularisation (-0.24 days/year), PCI (-0.22 days/year) and CABG (0.33 days/year)—than those not receiving angiography (-0.14 days/year), P<0.001. A greater decline occurred for NSTEMI and STEMI (9.4 to 7.5 days and 7.8 to 6.2 days, respectively) than UA (5.4 to 4.9 days). Predictors of longer LOS in 2016 were older age, female, Māori or Pacific ethnicity, not receiving coronary angiography, initial presentation to a non-interventional hospital and CABG.

CONCLUSIONS: Mean LOS for ACS hospitalisations declined between 2006 and 2016. The decline was greatest in the increasing proportion of patients who received a coronary angiogram. Further reductions in LOS may be achieved by implementation of nationally agreed pathways for adequate and timely access to coronary angiography.

Length of hospital stay (LOS) following an acute coronary syndrome (ACS) hospitalisation has significant clinical, prognostic and cost implications for the patients and healthcare systems.[1–3] Gradual decline in ACS hospitalisation LOS has been observed in many countries[3–5] and a range of factors can prolong LOS, resulting in wide heterogeneity in LOS.[2,6] Several studies have also shown that early discharge is safe and feasible after revascularisation and not associated with adverse prognosis.[5,8–12] This is reflected in guidelines which now recommend early discharge for low risk and uncomplicated patients, particularly for ST-elevation myocardial infarction (STEMI).[2,7] In New Zealand, all ACS hospital admissions are captured in routinely collected national hospitalisation datasets using ICD-10 AM codes and available to the All New Zealand

ACS Quality Improvement (ANZACS-QI) investigators. We have previously validated the accuracy of these codes for identifying ACS. We have also developed and validated a method for 'bundling' hospital admission associated with a single ACS episode to allow LOS to be accurately determined.[13–15] The aim of this study is to report the trends and predictors of LOS following ACS hospitalisations in New Zealand from 2006 to 2016.

Methods

The methodology of the ANZACS-QI Programme, which serves as the platform for this study, has been previously reported.[13] All ACS admissions to New Zealand public hospitals between 2006 and 2016 were identified from the national hospitalisations dataset using standard ICD-10 codes I20.0, I21-I22. These codes include STEMI, non-ST elevation MI (NSTEMI), unstable angina (UA) and a small sub-group as MI unspecified. ACS admissions were 'bundled' to take into account transfers to other hospitals within the same hospitalisation. This bundling process identified discrete episodes of care, associated hospital admission and discharge dates. LOS was defined as the time in days from first hospital admission to final hospital discharge for each discrete episode of care.[13] A small number of patients with LOS >8 weeks (1.2% of total admissions) were excluded from this analysis because the prolonged LOS is likely due to other non-ACS comorbidity and their inclusion would carry undue weight in the analysis.

Mean LOS for the combined cohort and subgroups each year were calculated. The subgroups of interest included demographic variables: age groups (20–44, 45–59, 60–69, 70–79 and 80–89 years old), sex (male and female), ethnicity (Māori, Pacific, Indian, Other Asian and European/other) and New Zealand Deprivation Index (NZDep2013) quintiles (Q1-Q5);[16] whether the initial admission was to a hospital with or without a coronary intervention-capable catheterisation laboratory; ACS subtypes (STEMI, NSTEMI and UA); investigation/management strategy (no angiography, angiography without revascularisation, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)).

SAS version 9.4 (SAS Institute Inc. Cary NC) was used for statistical analysis. Data were presented as mean+/-standard deviation or frequency (percentage) for continuous and categorical variables respectively. P-value less than 0.05 was deemed statistically significant. Multivariable linear regression was performed for the whole cohort to calculate the overall rate of change of LOS per year adjusting for covariates, including all the aforementioned demographic, catheterisation laboratory, ACS subtype and management strategy variables. This was repeated for the different invasive strategies subgroup to see if their LOS decreased adjusting for covariates. Finally, this was also performed for the 2016 ACS hospitalisations cohort only to identify independent predictors of longer LOS. Model estimates represented the number of days the LOS is increased or decreased by.

Ethics approval was obtained from the Northern Region Ethics Committee (AKY/03/12/314) and Multi-Region Ethics Committee (MEC/01/19/EXP and MEC/11/EXP/078) as part of the VIEW research programme.

Results

There were 185,962 ACS hospitalisations during 2006–2016. Baseline characteristics from 2006 and 2016 are shown in Table 1. Mean LOS by year of all ACS hospitalisations are shown in Figure 1. From 2006–2008 LOS remained stable (7.8–8.1 days), followed by a steady decline to 6.7 days in 2016. The overall adjusted rate of decrease was 0.18 (95% confidence interval 0.17–0.20) days per year. LOS by regions and by centres with and without interventional catheterisation lab is illustrated in Figure 1B.

A relatively similar decline in LOS occurred across all demographic groups—age, sex, ethnicity and deprivation quintile. The mean LOS increased with age, but the age group-related declined steepest for those over 80 years. Females had slightly longer mean LOS than males, although the gap reduced with time. While LOS declined overall for all ethnic groups, there was variability within each group. The decline in LOS was similar in all NZDep quintiles over the period.

Table 1: Baseline characteristics.

Characteristic	2006	2016
N	**20,166**	**14,464**
Age (years)		
20–44	670 (3.3%)	428 (3.0%)
45–59	3,454 (17.1%)	2,622 (18.1%)
60–69	3,370 (16.7%)	3,367 (23.2%)
70–79	5,426 (26.9%)	3,726 (25.8%)
80–89	6,886 (34.1%)	4,321 (30.0%)
Sex		
Male	11,580 (57.4%)	8,832 (61.1%)
Female	8,586 (42.6%)	5,632 (38.9%)
Ethnicity		
Māori	1,844 (9.1%)	1,572 (10.9%)
Pacific	643 (3.2%)	677 (4.7%)
Indian	405 (2.0%)	517 (3.6%)
Asian	273 (1.4%)	326 (2.3%)
European/Other	17,001 (84.3%)	11,372 (78.6%)
Presented to interventional hospital		
Yes	11,559 (57.3%)	10,094 (69.8%)
No	8,607 (42.7%)	4,370 (30.2%)
NZDep 2013 Quintiles		
Q1	2,421 (12.0%)	2,160 (14.9%)
Q2	3,031 (15.0%)	2,305 (15.9%)
Q3	3,972 (19.7%)	2,902 (20.1%)
Q4	5,324 (26.4%)	3,416 (23.6%)
Q5	5,347 (26.5%)	3,651 (25.2%)
ACS subtype		
STEMI	2,852 (14.1%)	2,678 (18.2%)
NSTEMI	10,413 (51.6%)	7,817 (54.0%)
UA	5,978 (29.6%)	3,291(22.8%)
MI unspecified	923 (4.6%)	678 (4.7%)
Investigation/management		
No angiography	13,375 (66.3%)	6,394 (44.2%)
Angiography	6,791 (33.7%)	8,070 (55.8%)
Coronary revascularisation	4,173 (20.7%)	5,402 (37.3%)
PCI	3,251 (16.1%)	4,482 (31.0%)
CABG	922 (4.6%)	920 (6.4%)

Figure 1: Length of stay of ACS admission 2006–2016 overall.

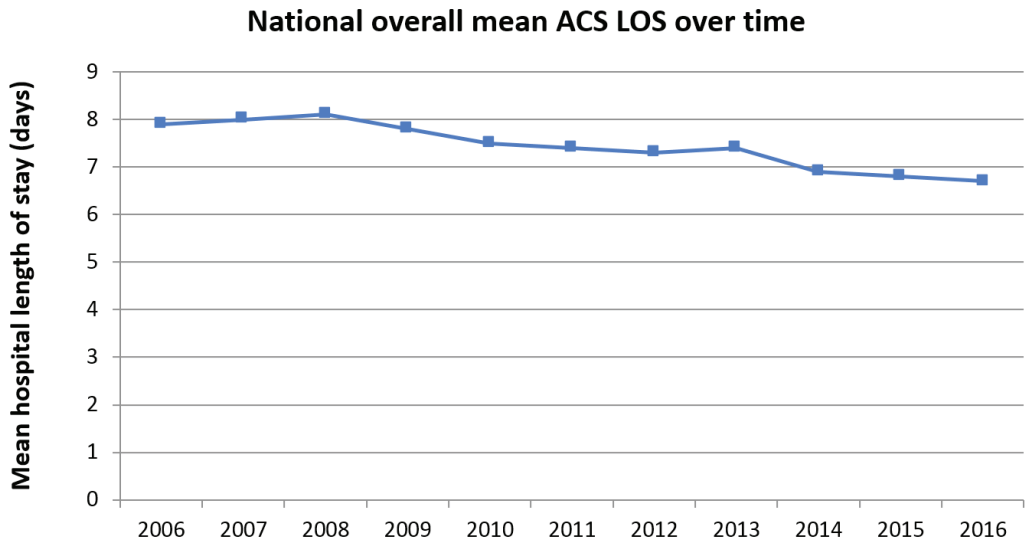


Figure 2: Length of stay of ACS admission 2006–2016 by (a) age group, (b) sex and (c) ethnicity (d) New Zealand Deprivation Index 2013.

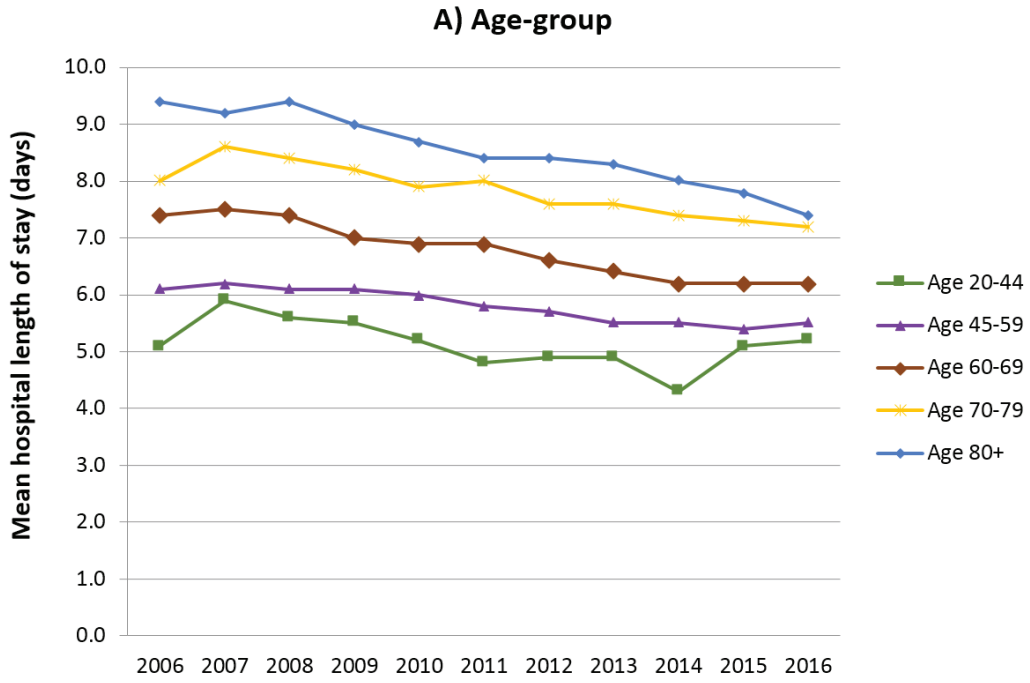
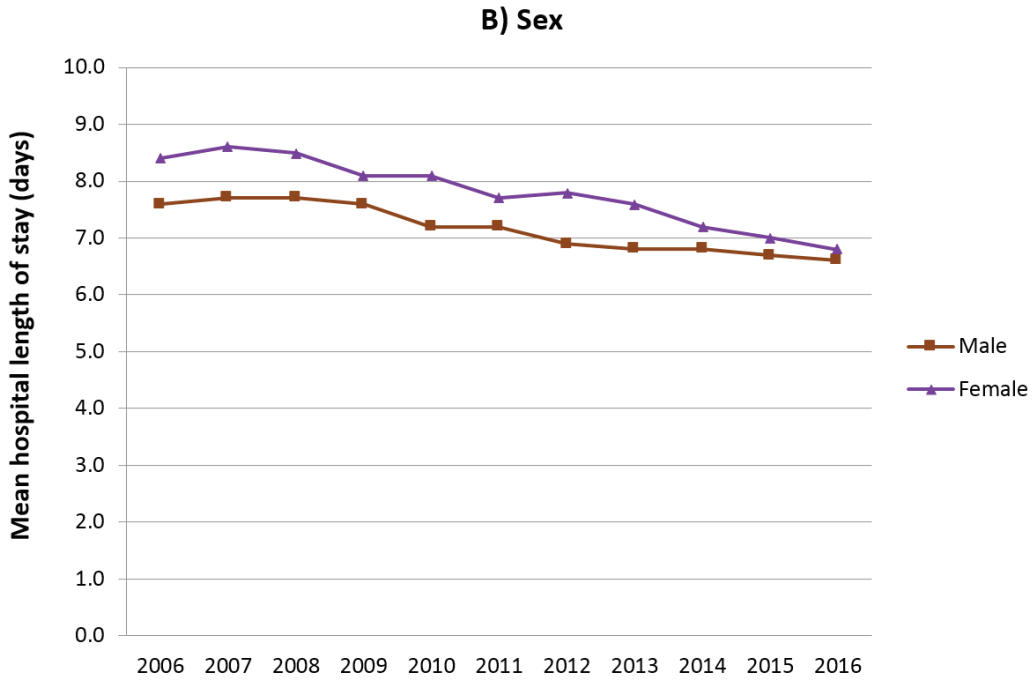


Figure 2: Length of stay of ACS admission 2006–2016 by (a) age group, (b) sex and (c) ethnicity (d) New Zealand Deprivation Index 2013 (continued).



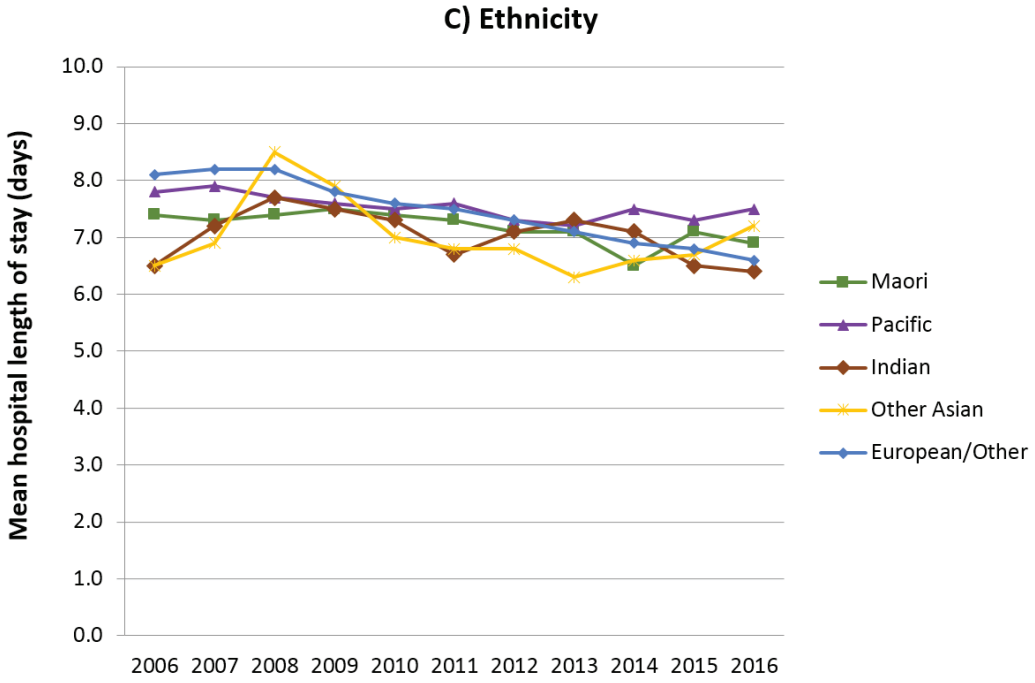


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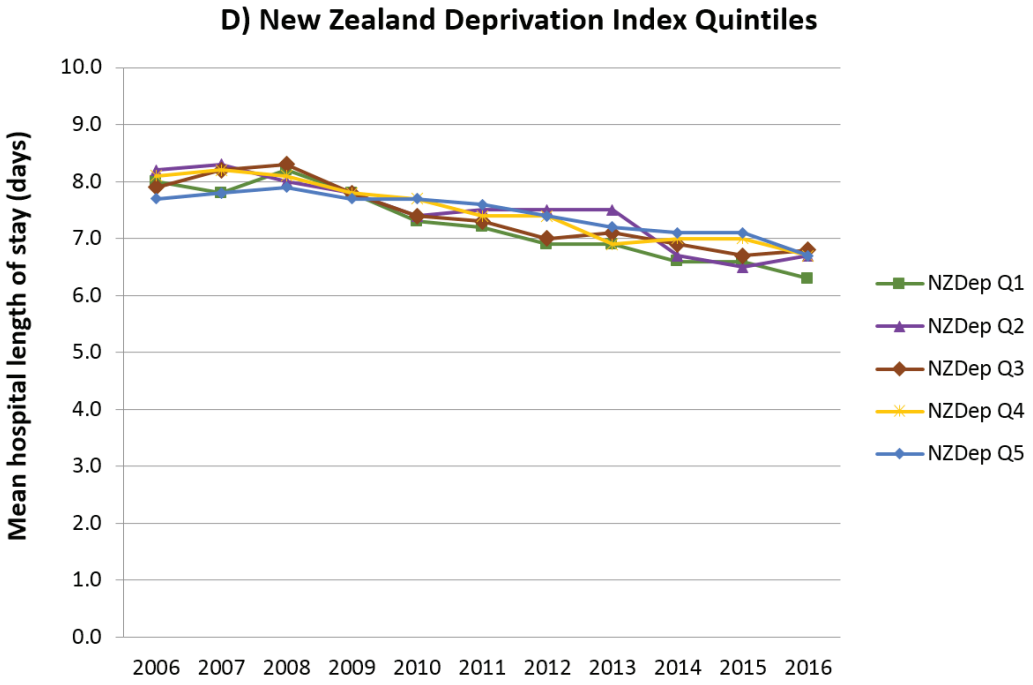
Figure 2: Length of stay of ACS admission 2006–2016 by (a) age group, (b) sex and (c) ethnicity (d) New Zealand Deprivation Index 2013 (continued).



Between 2006 and 2016 the percentage of ACS patients having coronary angiography increased from 34 to 56% and PCI increased from 16 to 31%, while CABG rates were largely unchanged. Those receiving CABG had a much longer mean LOS then non-CABG admissions across the time period (Figure 3). There was reduction in LOS for all management strategies from 2006 to 2016. The adjusted rate of decline was greater for patients receiving coronary angiography—angiography without revascularisation (-0.24 days/year), PCI (-0.22 days/year) and CABG (0.33 days/year)—than for those not receiving angiography (-0.14 days/year), P<0.001.

A greater decline between 2006 and 2016 occurred for NSTEMI and STEMI patients (9.4 to 7.5 days and 7.8 to 6.2 days, respectively) than for UA patients (5.4 to 4.9 days) (Figure 4). In the small group of MI unspecified patients, there was no clear change in LOS. NSTEMI had the longest mean LOS, followed by STEMI and UA.

Centres with interventional catheterisation lab had longer mean LOS by 0.8 days in 2005 but declined faster than centres without interventional catheterisation lab and in recent years have had similar LOS (Figure 5).

Results of the multivariable linear regression analysis are shown in Table 2. In 2016, older age, female sex, Māori or Pacific ethnicity and initial presentation to a non-interventional hospital were associated with longer LOS. ACS subtypes had similar LOS, except for UA, which was associated with shorter LOS. Among management strategies, PCI had the shortest LOS and CABG had the longest.

Figure 3: Length of stay of ACS admission 2006–2016 by ACS management strategy A) all strategies, B) all strategies excluding CABG.

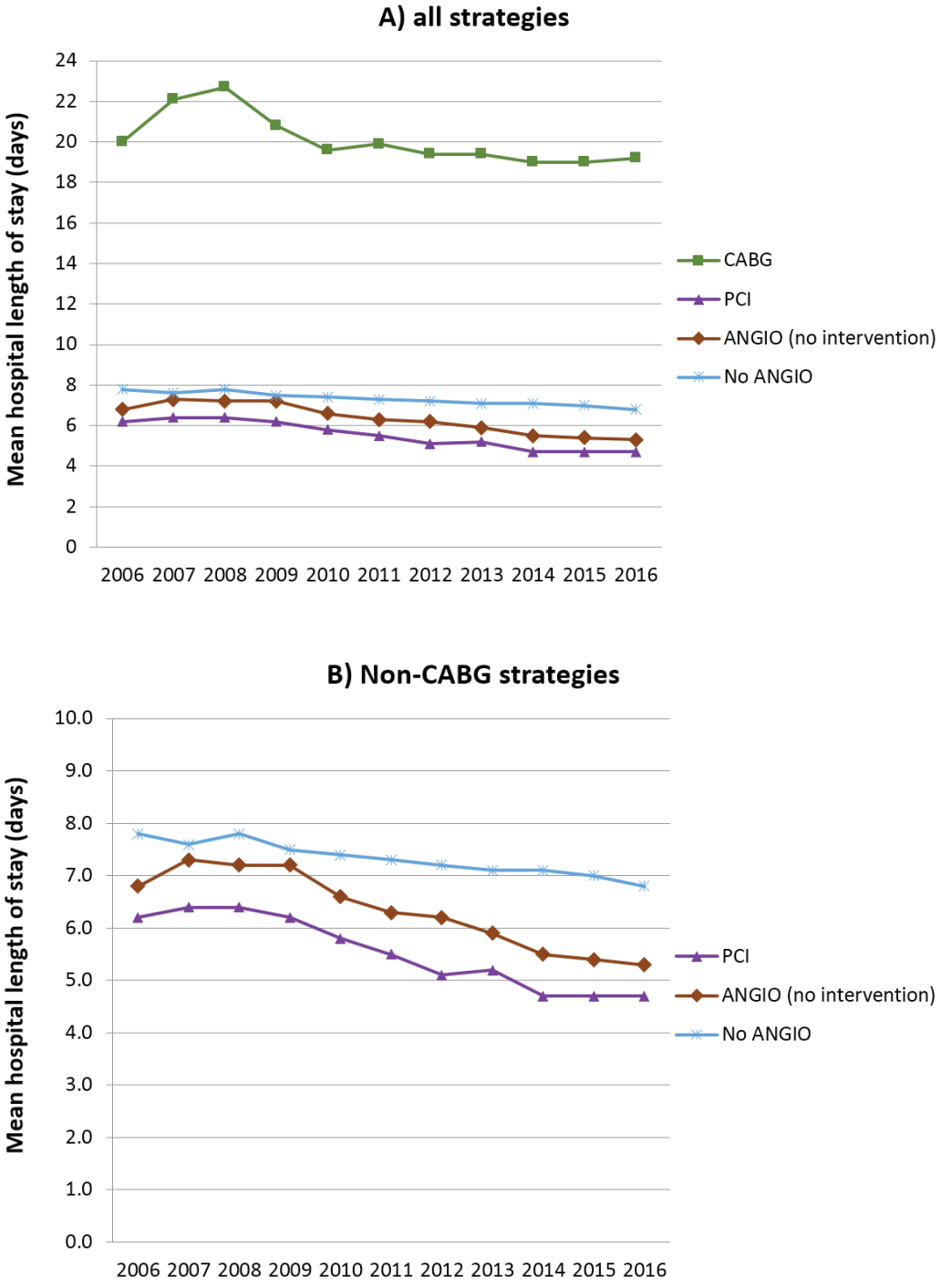


Figure 4: Length of stay of ACS admission 2006–2016 by ACS subtypes.

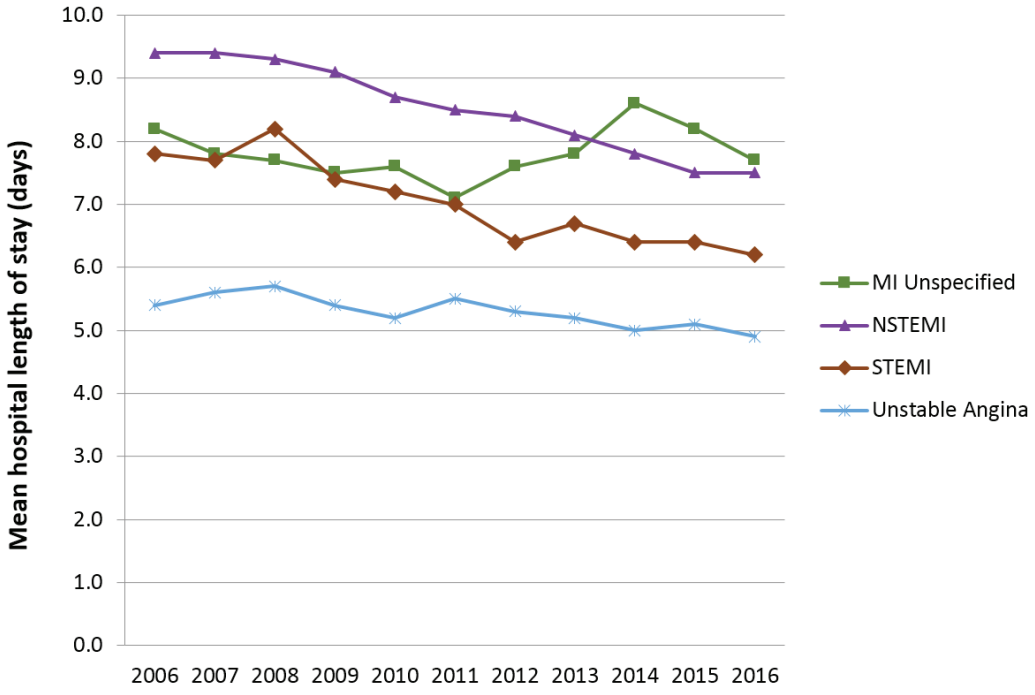


Figure 5: Length of stay of ACS admission 2006–2016 by presence of interventional laboratory at initial admitting hospital.

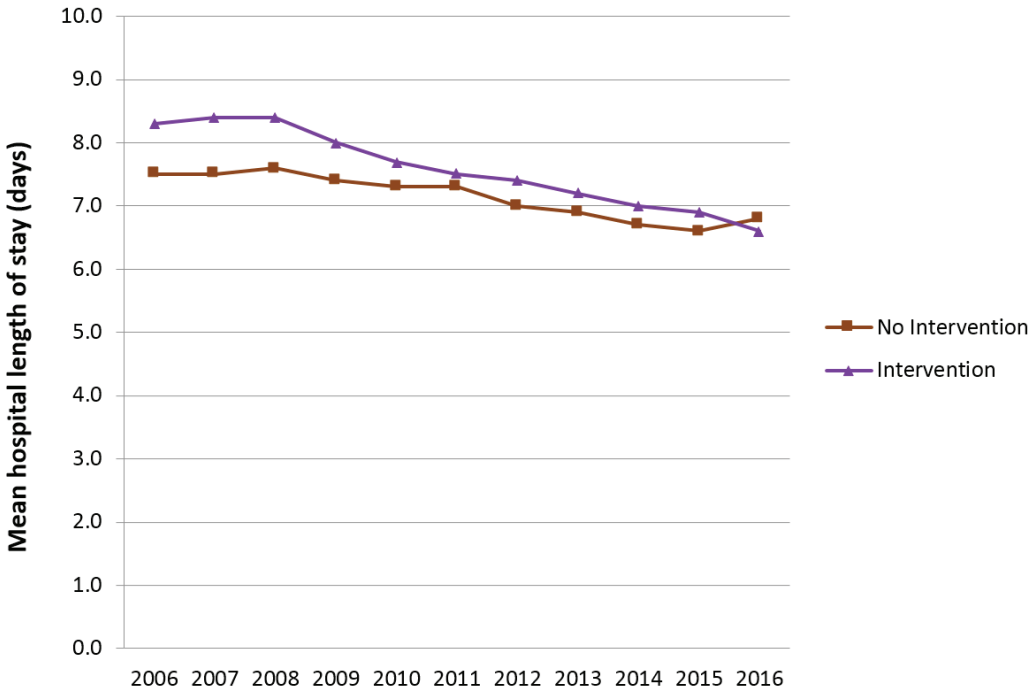


Table 2: Adjusted differences in LOS (days) by demographics, ACS subtype and management, after ACS hospitalisations in 2016.

Parameter	Difference in LOS (days)	95% confidence interval	P value
Age (years)			
20–44 (reference)	0.00		
45–59	0.23	-0.5. 1.0	0.543
60–69	0.63	-0.1, 1.4	0.090
70–79	1.9	1.1, 2.6	<0.001
80–89	2.5	1.7, 3.2	<0.001
Sex			
Male	0.0		
Female	0.4	0.1, 0.6	0.006
Ethnicity			
European/Other	0.0		
Māori	0.9	0.5, 1.3	<0.001
Pacific	0.7	0.1, 1.3	0.020
Indian	-0.1	-0.8, 0.5	0.700
Asian	0.4	-0.4, 1.2	0.362
NZDep 2013 Quintiles			
Q1	0.0		
Q2	0.2	-0.2, 0.7	0.220
Q3	0.4	0.0, 0.8	0.057
Q4	0.5	0.1, 0.9	0.011
Q5	0.4	0.0, 0.8	0.073
Catheterisation laboratory available acutely			
Yes	0.0		
No	0.4	0.1, 0.6	0.012
ACS subtype			
NSTEMI	0.0		
STEMI	-0.3	-0.6, 0.0	0.171
MI unspecified	0.1	-0.5, 0.7	0.296
UA	-2.8	-3.1, -2.4	<0.001
Management strategy			
PCI	0.0		
No angiography	1.5	1.2, 1.9	<0.001
Angiography without revascularisation	0.7	0.3, 1.0	<0.001
CABG	14.9	14.4, 15.5	<0.001

Model estimates for each parameter correspond to the mean difference in LOS in days compared to the reference level after adjustment for covariates. Reference groups appear first for each parameter. For example, after adjustment, 80–85-year-olds have a mean LOS 2.5 days longer than 20–44-year-olds.

Discussion

The mean LOS after hospitalisation in New Zealand for an ACS event has declined over 10 years by more than a day. This decline occurred for almost all demographic subgroups, and also for those receiving different management strategies. Furthermore, while only a third of ACS patients received angiography in 2006, this had increased to over half by 2016. The decline in LOS was greater in these patients than in those not receiving coronary angiography. The decline in LOS was also greater for NSTEMI and STEMI compared to UA. In the most recent year of this study (2016), the independent predictors of longer LOS were older age, female sex, Māori or Pacific ethnicity and receipt of CABG, while initial admission to a hospital with catheterisation laboratory access, UA and receipt of angiography with or without PCI was associated with shorter LOS.

Trends in LOS

An overall decline in mean LOS has also been reported in other countries.[3–5] This decline is a consequence of several factors, including more frequent and earlier use of coronary procedures and other evidence-based treatments, reduced in-hospital complications for ACS patients, as well as recent guidelines recommending earlier discharge from hospital with appropriate therapy and follow-up.[2,7] In our study the most striking decline in LOS was in NSTEMI and STEMI patients. In this analysis we cannot determine the reasons for this reduction. However, reductions in time to angiography and PCI are likely to be an important factor, as other New Zealand studies have reported both a strong correlation between time from admission to angiography and overall LOS,[17] and 1–2 day reductions in this door to angiography time, and percutaneous revascularisation during the same procedure.[18,19] As angiography rates have increased more in patients with MI than for those with UA, this would explain the observed LOS decline trends by ACS subtype.

Other changes in interventional management that may be important include a greater use of primary PCI for STEMI over this period and increasing utilisation of same-visit angiography and PCI, rather than these procedures occurring as two separate visits to the catheterisation laboratory.[19] Alongside these changes in coronary interventional management, there is increasing confidence from other studies suggesting that uncomplicated patients who have been successfully revascularised can be safely discharged earlier.[5,8–12] This was reflected in our cohort with greater adjusted rates of decline for those undergoing angiography or revascularisation than those who did not have angiography. While it is reassuring that in the same cohort of patients, other ANZACS-QI analyses have reported a decrease in both one-year mortality and non-fatal reinfarction, further analyses are planned to assess the impact of earlier discharge on outcomes.

Predictors of LOS

Age and sex: This study found a strong association between LOS and age. This is likely to be largely due to age-related comorbidity, which puts older patients at higher risk of ACS and non-ACS related complications.[20–22] Length of stay was particularly prolonged in those aged over 80 years, who may take longer to become fit enough for discharge due to the burden of cardiovascular disease, deconditioning and frailty. The reasons for the observation that females, even after adjustment, have 0.4 day longer LOS than males, requires further study. A recent ANZACS-QI study reported that rates of angiography after ACS in women were lower than for men, but that similar rates of angiography were observed after taking into account relative contraindications to having angiography, suggesting that differences in comorbidity burden and type of disease may be important factors.[23]

Ethnicity

Māori patients were more frequently admitted to hospitals without a catheterisation laboratory, which will have contributed to their longer LOS.[24] However, even after adjustment for this, Māori and Pacific patients had 0.9 and 0.7 days longer LOS than European/Other patients. Prior studies have shown that Māori and Pacific patients with coronary heart disease, although on average younger, have a greater prevalence of cardiovascular risk factors, and more complex clinical presentations including more heart failure and comorbidities. These factors may result in clinically appropriate delays in angiography and

reduce overall angiography rates relative to other ethnic groups.[17,24–25] One study also reported higher rates of adverse outcomes for Māori after CABG, although LOS was not longer than for Europeans.[26]

ACS sub-types: The main reason why patients with NSTEMI have longer LOS than those with STEMI is because they typically wait until the next available day time list for coronary angiography and revascularisation, whereas in New Zealand the standard of care for STEMI is urgent revascularisation, by primary PCI or fibrinolysis, and increasingly, transfer for early coronary angiography for those receiving fibrinolysis.[2,7] Another contributing factor is that CABG, with the associated implications for LOS, is more frequent after NSTEMI than STEMI. UA has a better prognosis than either MI subtypes due to the absence of myocardial necrosis and damage, and these patients can often be safely discharged earlier. There was no decline for the 5% of patients classified as MI unspecified.

Management strategy: Length of stay was shortest among those who had PCI. These patients receive a definitive treatment and the cause of ACS is clear, so clinicians have more confidence in discharging them early. The slightly longer LOS for those having angiography without revascularisation may be due to a need for further investigations to identify the cause, as well as keeping patients in hospital until their cardiac biomarkers fall. In contrast, the persisting greater LOS in patients who do not undergo coronary angiography is often due to critical clinical presentations and multiple comorbidities, which can lead to worse prognosis and prolonged recovery time. Patients requiring CABG continue to have the longest mean LOS by almost two weeks, compared to other treatment modalities, and indeed all subgroups. The Society of Thoracic Surgeon's Database reports that half of the patients after isolated CABG are discharged less than six days after operation and only 6% more than 14 days after operation.[27] Although comparable data are not currently available for ACS patients in New Zealand, it is likely that the largest component of modifiable LOS in CABG patients is in reducing the waiting time for surgery. Over the 10-year period of this study there has been a lot of work in New Zealand put in to improving out-patient waiting times for cardiac surgery but less emphasis on in-patient waiting times.[28] Mean LOS after CABG, which is necessary for post-operative care, was approximately 8–9 days in one New Zealand study.[29]

Interventional facility: It was reassuring that for patients residing in regions without catheterisation, who therefore needed transfer for coronary procedures, LOS was on average less than half a day longer only, reflecting efficiency of the cardiac transfer and collaborative services throughout the country.

Study implications

Extrapolating the observed reduction in mean LOS of 1.4 days from its peak in 2008 to the nadir in 2016 to the 14,464 ACS admissions in 2016, indicates that approximately 20,000 bed days were saved in New Zealand in 2016. This represents a major financial benefit in an increasingly costly health funding environment. There are also benefits for patients who are receiving appropriate treatment more rapidly and are spending less time in hospital.

However, there is still room for further reductions in LOS. Much of the improvement in LOS over the study decade has likely been related to more rapid and frequent use of angiography. Recent data suggests that the current rate of angiography in metropolitan centres is probably clinically appropriate,[23] although increases may still be needed particularly in centres without on-site interventional access.[18] ANZACS-QI registry data also shows persisting modifiable delays in those who do receive angiography, particularly for patients presenting to regional hospitals without catheterisation laboratories. Earlier in-hospital CABG should be possible. There is some regional variability in how long patients stay in hospital after PCI and angiography and by identifying and propagating best practice using national guidelines/pathways it may be possible to safely reduce LOS further.

Limitations

There are some limitations to this study. ACS diagnosis, subtypes, characteristics, procedures and LOS rely on ICD-coding, which may be imprecise. Local validation studies have however demonstrated very good accuracy relative to an independent clinical registry.[14] Other variables that

may influence LOS that were not available included co-morbidities, cardiac investigation results and frailty measures. We were unable to collect data on specific clinical reasons that could have influenced LOS. Patients who die during hospitalisation may have very short or long hospital stays depending on their clinical course, so a short LOS does not always imply an uncomplicated hospitalisation. Overall resource utilisation and cost-effectiveness (both in-hospital and ambulatory) were not able to be assessed in this study.

Conclusion

In summary, there was an overall decline in mean LOS for ACS hospitalisation between 2006 and 2016 in New Zealand. The fall in LOS has been greatest in the increasing proportion of patients who receive a coronary angiogram. Further improvements to ensure adequate and timely access to coronary angiography, and the implementation of nationally agreed pathways can reduce LOS further.

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Stage at diagnosis for Māori cancer patients: disparities, similarities and data limitations

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ABSTRACT

Māori are more likely than non-Māori to get cancer, and once they have cancer they are less likely to survive it. One frequently proposed explanation for this survival disparity is differences between these groups in terms of stage at diagnosis—whereby Māori may be less likely to be diagnosed at an earlier stage, when treatment is more feasible and outcomes are better for the patient. However, this simple explanation ignores the true complexity of the issue of stage at diagnosis as a driver of survival disparities, and makes critical assumptions about the quality of available staging data. In this manuscript we draw on New Zealand Cancer Registry and available clinical audit data to explore this issue in detail. We found that Māori are less likely than European/Other patients to have localised disease and more likely to have advanced disease for several commonly diagnosed cancers; however, we also found that this was not the case for several key cancers, including lung and liver cancer. There is evidence that Māori have more advanced disease at diagnosis for each of the cancers for which we currently have a national screening programme, reinforcing the importance of achieving equity in access to these programmes. Missing stage information on our national registry undermines our ability to both a) monitor progress towards achieving early diagnosis, and b) examine and monitor the role of stage at diagnosis as a driver of survival disparities for several important cancers for Māori, including lung, liver and stomach cancers.

Māori are more likely than non-Māori to get cancer,[1] and once they have cancer they are less likely to survive it.[1,2] One frequently proposed explanation for the observed survival differences between Māori and non-Māori New Zealanders is differential stage at diagnosis—whereby Māori may be less likely to be diagnosed at an earlier stage, when treatment is more feasible and outcomes are better for the patient.[1,3,4]

The New Zealand Cancer Registry (NZCR) is the primary source of population-level stage information for all new cases of malignant cancer diagnosed in New Zealand. The typical protocol followed by the NZCR when attributing cancer stage involves registrars manually attributing stage primarily on the basis of pathology reports following tumour excision, but also using additional information from hospitalisation records, death certificates and autopsy reports—all of which must be available in the four-month period after the cancer was first diagnosed.[5,6] For this reason, cancer staging is most complete for cancers where the primary and first treatment is surgical. To complicate matters, if neo-adjuvant therapy (such as chemotherapy or radiotherapy) is given prior to surgery, this will undermine the accuracy of the pathological staging of this cancer (since these therapies will often alter the stage). Furthermore, since the NZCR has minimal access to quality clinical staging information, they are often unable to attribute stage in cases where only a biopsy is provided or if a cancer is only diagnosed clinically without any pathology report (eg, via imaging).

Because of these limitations, the quality of data used to investigate this important prognostic indicator is sometimes not robust. For

some cancers, there are a high proportion of cases in the NZCR which are missing stage data, and for some of these cancers Māori patients are more likely than other patients to be recorded as 'unstaged'.[7] We also know that those in the 'unstaged' group are generally more likely to have more advanced disease (and associated poor outcomes), but this is not always the case.[7] This differential ascertainment of stage has (at least) two important implications: first, for at least some cancers, there is a disparity between Māori and non-Māori in the completeness of stage data on our national cancer registry. Second, the unstaged cancer issue means that it is difficult to definitively compare the distribution of cancer stage between Māori and non-Māori for a cancer where the proportion of missing stage is high, or where the level of missingness is differential by ethnicity.

Drawing on both administrative health data and more granular clinical notes data, this manuscript considers the extent to which any apparent disparity in stage between Māori and non-Māori is due to differences in data collection and/or recording by ethnicity, including whether completeness varies by cancer type. We also aim to combine these data sources to specifically explore the extent to which Māori are more likely than non-Māori to have more advanced disease at diagnosis, and to explore the characteristics of these cancers—for example, whether these cancers have a tendency to be amenable to early diagnosis, or have a more complex diagnostic pathway.

Methods

Data for this study were extracted from two sources: the NZCR and from previously published clinical note audits, for which study methods have been published elsewhere.[4,8–11] In terms of NZCR data, the current study included those diagnosed with a new malignancy between 2007–2016, as reported to the NZCR (n=196,967). Individuals were excluded if they had haematological malignancies, for which stage is never recorded in the NZCR.[6] Prioritised ethnicity was taken from the NZCR,[12] and was categorised as Māori, Pacific, Asian or non-Māori/Pacific/Asian (European/Other); however, primary analyses were restricted to comparing Māori with the European/Other population. The European/Other population were used as the reference group, since they represent the majority population in New Zealand. While all cancer types were included (excluding haematological cancers), we have focused on reporting the 10 highest-incidence cancers for Māori over the study period. All other cancers are presented in the Appendix (Appendix Tables 1–4).

For the NZCR data, cancer stage at diagnosis was based on the SEER Summary Stage method for recording stage, which largely reflects the anatomical spread of disease,[13] with this stage classified as 'A' to 'F' on the NZCR.[6] We categorised stage into Local ('B'), Regional ('C' and 'D'), Advanced ('E') and Unknown ('F').[14]

We reviewed several previously published clinical note audits. Breast cancer data were extracted from published data from the Auckland and Waikato Breast Cancer Registers, which included 12,390 female patients diagnosed with breast cancer between 2000–2013.[4,15] Colon and rectal cancer data were extracted from published data from the PIPER study, which included 3,660 patients diagnosed with colon cancer and 1,334 patients diagnosed with rectal cancer between 2007–2008.[9] Lung cancer data were extracted from published data from the Midland Lung Cancer Registry, which included 2,057 patients diagnosed with lung cancer between 2011–2015.[15] Stomach cancer data were extracted from published data from the C3 study, which included 335 patients diagnosed with stomach cancer between 2006–2008. In each of these studies, hospital notes reviews were carried out by the respective research teams and clinical staging was attributed according to the TNM clinical staging system for each cancer. Since the SEER and TNM staging systems differ in terms of how non-metastatic disease is attributed, these stages were not compared between the NZCR and notes review data sources (only distant/Stage IV and unstaged disease were included in this comparison).

Statistical analysis

For this study, two main comparisons were made: first, we compared stage at diagnosis on the NZCR between Māori and European/Other patients across all stages of diseases. Secondly, we compared data from the NZCR

to available clinical audit data on advanced and unstaged disease, for both Māori and European/Other patients.

For the NZCR data, crude descriptive analysis was used to describe the number of patients diagnosed with each cancer type by ethnicity, with stage of disease at diagnosis stratified within cancer type. To adjust for differences in population age structure between ethnic groups we directly age standardised the data to the total New Zealand cancer population from 2007–2016, giving age-standardised proportions by ethnic group. This population includes everyone diagnosed with any cancer over this time period, and was used because of the likely similarities between the age structure of this standard population and the cancer-specific populations under investigation.[11,16,17]

We compared the odds of having a given stage of disease at diagnosis between ethnic groups using unconditional logistic regression, adjusted for differences in age between groups. Results are presented as odds ratios with 95% confidence intervals. An informal descriptive comparison between NZCR and clinical notes review data was made. Further formal statistical testing was not conducted, since the existing data sources were only available in a summarised form.

Data management and analysis were performed in SAS v9.3 and Microsoft Excel. Ethical approval for the study was received from the University of Otago Human Ethics Committee (Health), reference #HD18/056.

Results

The age-standardised proportion of cancers diagnosed by stage as recorded in the NZCR is presented in Figure 1 for Māori and European/Other populations, restricted to the 10 most common cancers for Māori. Age-adjusted odds ratios comparing the likelihood of local, regional, distant and unknown stage of disease at diagnosis between Māori and European/Other patients are presented in Figure 2. The patterning of differing stage by ethnicity varied substantially by cancer type; the most substantial differences were observed for prostate cancer, wherein Māori patients were much less likely to have localised disease and much more likely to have metastatic disease than European/Other patients. On the other hand, Māori lung cancer patients appeared less likely to be diagnosed with distant metastases than European/Other patients. There was no difference by ethnicity in stage distribution for liver cancer. Complete data for all cancers and all ethnicities are presented in the Appendix (Appendix Tables 2–4).

A comparison of NZCR staging data with that derived from audits of clinical notes review data is shown in Table 1, with the key observations of this comparison further detailed in the Discussion. In brief, there was substantial difference between the NZCR and clinical notes review data in terms of the proportion of unstaged cancers, wherein stage tends to be more complete for notes review data. The most extreme example of this was observed for liver cancer, wherein only a third (~35%) had a stage on the NZCR compared to 100% in clinical notes review data. However, in this case there was no clear difference between ethnic groups in terms of stage completeness between the NZCR and clinical notes review data.

In terms of metastases, the NZCR tended to underestimate the proportion of patients with advanced disease relative to notes review data. However, both data sources tended to show the same trend in terms of ethnic differences in the proportion of metastatic disease. In other words, while the selection of data source altered the absolute proportion of Māori and European/Other patients observed to have advanced disease, it did not meaningfully alter the size of the difference between the two ethnic groups (Table 1).

Figure 1: Stacked bar chart showing the age-standardised distribution of NZCR stage of disease at diagnosis for the 10 most common cancers among Māori between 2007–2016, stratified by cancer type and ethnicity.

Figure 2: Forest plot (odds ratio with 95% confidence interval) comparing age-adjusted odds of NZCR local, regional, distant and unknown stage for Māori compared with European/Other patients, for the 10 most common cancers among Māori.

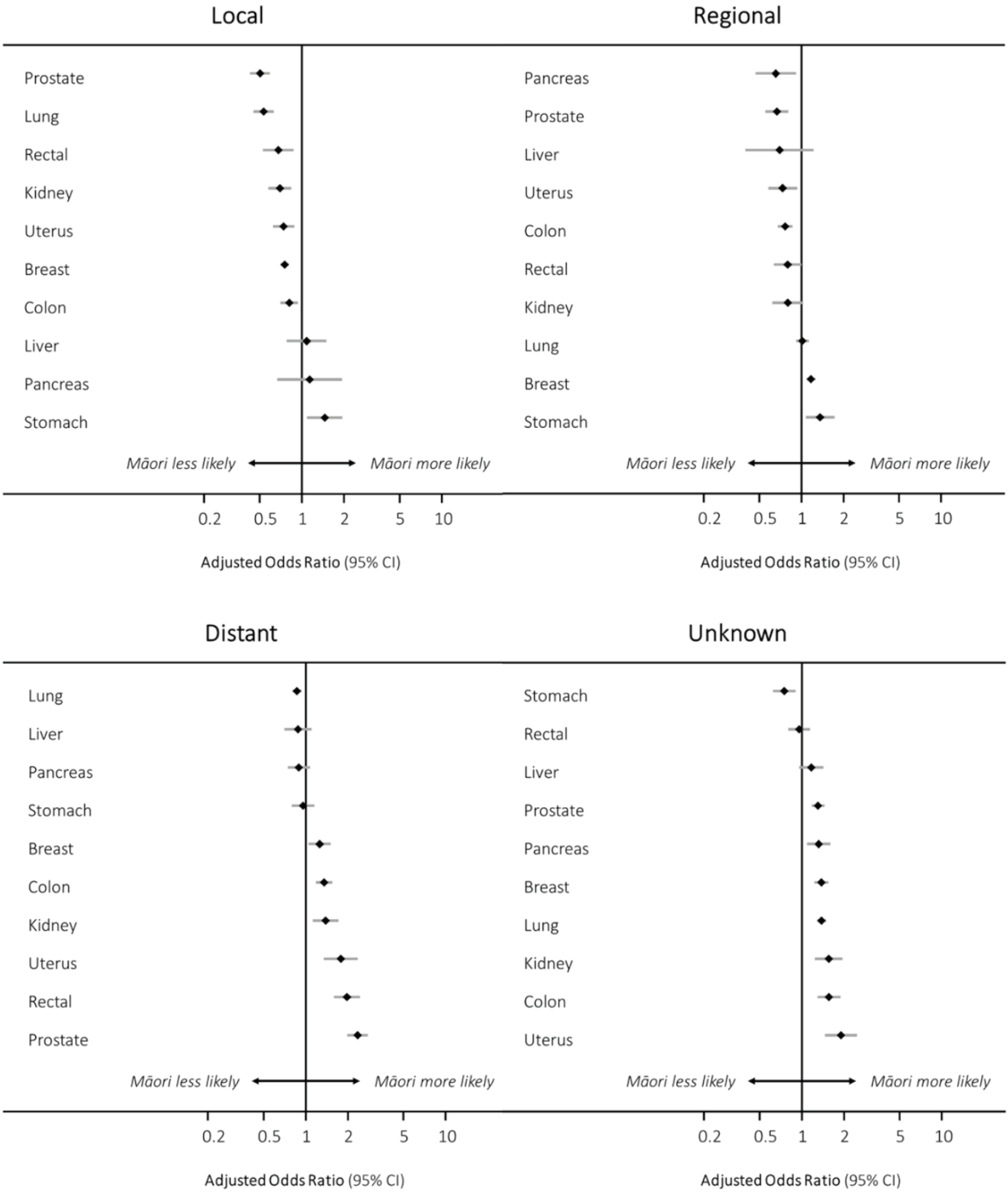

Table 1: Comparison of New Zealand Cancer Registry staging data with clinical notes review staging data, for distant/metastatic and unstaged disease. Ethnicity groupings for NZCR cohort have been altered to match the groupings used in each clinical stage study, to support comparability. All percentages are crude (unadjusted). Percentages refer to the proportion of patients with that given stage of disease within the given data source.

	SEER Stage	**n**	**%**	**n**	**%**	**Clinical stage**	**n**	**%**	**n**	**%**
Breast[a]	**NZCR, 2007–2016**					**Auckland and Waikato BCR, 2000–2013**				
		Māori		NZ European			Māori		NZ European	
	Distant	147	4%	645	3%	Metastatic (IV)	88	8%	351	4%
	Unknown	407	11%	2,034	10%	Unknown	0	0%	0	0%
Colon[b]	**NZCR, 2007–2016**					**PIPER study, 2007–2008**				
		Māori		Non-Māori/Pacific			Māori		Non-Māori/Pacific	
	Distant	341	30%	4,471	22%	Metastatic	42	29%	775	22%
	Unknown	137	12%	2,335	11%	Unknown	13	9%	267	8%
Rectal[b]	**NZCR, 2007–2016**					**PIPER study, 2007–2008**				
		Māori		Non-Māori			Māori		Non-Māori	
	Distant	129	24%	961	13%	Metastatic	40	29%	217	18%
	Unknown	224	42%	3,077	43%	Unknown	5	4%	55	5%
Lung[c]	**NZCR, 2007–2016**					**Midlands LCR, 2011–2015**				
		Māori		Non-Māori			Māori		Non-Māori	
	Distant	1,763	44%	7,577	46%	Metastatic (IV)	375	57%	830	59%
	Unknown	1,509	38%	5,929	36%	Unknown	23	4%	64	5%
Liver[d]	**NZCR, 2007–2016**					**C3 Study, 2006–2008**				
		Māori		Non-Māori			Māori		Non-Māori	
	Distant	140	23%	550	23%	Metastatic (IV)	33	34%	35	38%
	Unknown	392	64%	1,549	65%	Unknown	0	0%	0	0%
Stomach[e]	**NZCR, 2007–2016**					**C3 study, 2006–2008**				
		Māori		Non-Māori			Māori		Non-Māori	
	Distant	267	37%	1,033	33%	Metastatic (IV)	85	49%	73	45%
	Unknown	238	33%	1,437	46%	Unknown	0	0%	5	3%

[a]Clinical stage data from Tin Tin et al.[4] Stage data were missing for n=5 of 12,390 breast cancer patients (0.04% of total cohort), but this was not presented by ethnicity. [b]Clinical stage data from Jackson et al.[9] [c]Clinical stage data from Lawrenson et al.[15] [d]Clinical stage data from Chamberlain et al.[16] [e]Clinical stage data from Signal et al.[11]

Discussion

We have brought together available data on ethnic differences in stage of cancer at diagnosis from both the NZCR and previously published clinical audits. Each of these sources has its strengths and weaknesses: NZCR data has breadth (because it is mandated to capture all diagnosed malignancies), while the clinical audit data has depth (because it draws on more granular clinical notes data). Because of the complexities associated with staging many cancers, the depth that clinical audit data provides is preferable when comparing stage distribution between groups; however, the time and resource required to conduct such reviews means that such data are only available for a few cancers, and in some instances these reviews are specific to one

region. Clinical audit data is also updated with varying regularity or not at all, so has limited use for ongoing monitoring.

Where data from both sources are available (Table 1), we can make several observations. The first is that a very high proportion of several common cancers are unstaged on the NZCR (this is further discussed below). Secondly, if we assume that the clinical audit data are the gold-standard, then there appears to be a tendency for the proportion of metastatic disease to be underestimated on the NZCR (for both Māori and European/Other patients)—with these patients misclassified into other stage categories. Since both data sources are comparable in terms of how they define distant metastases (any metastases beyond the regional lymph nodes triggers the attribution of distant disease on the SEER staging system,[18] and of Stage IV disease on the clinical [TNM] staging system), this tendency for underestimation is likely linked to the issue of unstaged cancers on the NZCR. Thirdly, and perhaps most crucially, when comparing the data sources we observe that the *relative* differences between Māori and European/Other patients in the likelihood of metastatic disease remains broadly the same, regardless of whether we are using NZCR or clinical audit data (even though these differences vary across cancer types). In other words, both data sources tend to paint the same picture regarding whether Māori patients are more, less or as likely to have distant metastases at diagnosis compared to European/Other patients.

Bearing in mind these factors regarding the data sources, we have addressed a number of key questions below.

Are there real differences between Māori and non-Māori in terms of stage of disease at diagnosis?

For those cancers most commonly diagnosed among Māori, there is a tendency for Māori to be less likely to be diagnosed with localised disease than European/Other patients. The strongest examples were observed for prostate (age-adjusted OR 0.50, 95% CI 0.43–0.59) and lung cancers (age-adjusted OR 0.53, 95% CI 0.45–0.63), but this was seen to a lesser extent for rectal, kidney, uterine, breast and colon cancers (age-adjusted ORs ranging from 0.68–0.81). Māori also appear more likely to be diagnosed with distant (metastatic) disease for the same cancers (age-adjusted ORs ranging from 1.25–2.35), with the exception of lung cancer (age-adjusted OR 0.87, 95% CI 0.80–0.93). These observations regarding metastatic disease are echoed by the clinical audit data: while acknowledging substantial unstaged disease on the NZCR, the clinical notes review and NZCR data largely agree that Māori with breast, colon and rectal cancers are more likely to be diagnosed with metastatic disease (Table 1). In summary, it is clear that there remains substantial unmet need in terms of timely diagnosis for Māori for several cancers.

However, these observations are not true for all cancer types. For example, in both the NZCR and clinical audit data Māori appear to be marginally less likely to be diagnosed with metastatic lung and liver cancers than European/Other patients, and differences for pancreatic and stomach cancers are negligible. It is also important to note that we cannot fairly compare the distribution of local, regional and advanced stage cancer between Māori and European/Other groups without knowing how this distribution might be altered had all cancers been staged on the NZCR (the issue of unstaged data is further discussed later). For this reason, the comparison of stage distribution in Figures 1 and 2 should be interpreted with caution.

Is there a pattern underlying cancers for which Māori are diagnosed with more advanced disease?

What is clear from both the NZCR and clinical audit data (where available) is that Māori are more likely than European/Other patients to be diagnosed with metastatic disease for those cancers for which national screening programmes are now in place (breast, colon, rectal, and cervical; see Appendix Tables 3 and 4 for cervical cancer data). Although many of these cancers are diagnosed outside of these programmes, this observation reinforces the importance of our national screening programmes as levers by which ethnic disparities in cancer stage at diagnosis can be either reduced or exacerbated.[19]

Both NZCR and clinical audit data point to a disparity between Māori and European/Other patients in the stage of disease at

diagnosis for both colon and rectal cancers. These observations highlight the need for careful monitoring of Māori access to our new national bowel screening programme, as well as renewed investment in the care pathway to ensure equitable access to early symptom recognition and referral, followed by best-practice diagnosis and treatment for Māori patients.[20,21]

Māori also appear more likely than European/Other patients to be diagnosed with metastatic prostate cancer (and less likely to be diagnosed with localised disease), which may reflect disparities in the uptake of prostate-specific antigen (PSA) testing. A recent general population study found that asymptomatic Māori men were half as likely to be screened with a PSA test than asymptomatic non-Māori men (age-adjusted risk ratio 0.52, 95% CI 0.48-0.56).[22] Greater rates of opportunistic screening in asymptomatic European/Other men means that proportionally more of these men are being diagnosed with localised (often indolent) disease compared to Māori men—which effectively increases the denominator of European/Other men with localised disease, thereby altering stage comparisons between ethnic groups.[23] However, it remains unknown whether Māori men with early symptoms of prostate cancer are less likely to undergo a PSA test, digital rectal examination (DRE) and/or other follow-up care than symptomatic non-Māori men; any disparity in the context of examining symptomatic men is more likely to confer an important impact on patient survival than disparities in the uptake of opportunistic screening. The issue of whether or not PSA-based opportunistic screening leads to a reduction in mortality from prostate cancer remains controversial, and the benefit-to-harm ratio problematic.[24]

Outside of cancers with established (or expanding) screening programmes, we also observed that Māori appear more likely to have advanced disease for cancers with relatively complete data on the NZCR (eg, testicular, melanoma, uterine and kidney cancers[7]). This observation would support the need for heightened vigilance in primary care to support symptom recognition and early detection of these cancers for Māori patients—as well as additional attention on ensuring Māori have equal timely access to such care.

How important is stage of disease as a driver of the survival disparities between Māori and non-Māori New Zealanders?

Stage at diagnosis is an important indicator of prognosis. Given the enduring and substantial disparities in cancer survival for Māori New Zealanders, it is tempting to attribute the bulk of this disparity to later diagnosis for Māori compared to non-Māori patients. As highlighted above, there are examples where Māori are more likely to have advanced disease at diagnosis—and in some contexts such as breast cancer, this disparity directly contributes to poorer survival outcomes.[4,25]

However, there are counter-examples: for example, Māori patients with stomach, liver and lung cancer are 25% more likely to die from their cancer compared to non-Māori patients,[1] but both the NZCR and clinical notes review data (Table 1) show no evidence of a strong difference between Māori and non-Māori in the likelihood of advanced disease at diagnosis for these cancers. In other words, the survival disparities observed for these cancers cannot be explained by differential stage of disease.

Because of this variability between cancers, and because of the limitations of the available data (discussed later in this section), it is important to consider factors beyond stage at diagnosis in understanding differences in cancer survival between Māori and non-Māori, particularly in the absence of strong evidence from comprehensive reviews of clinical records. It is important to note that substantial cancer survival disparities persist between Māori and non-Māori even after adjusting for stage at diagnosis,[26] and that many other factors besides stage contribute to survival inequities for a given cancer. These include disparities in access to high-quality cancer services,[8,26,27] under-treatment of cancer patients who have comorbidity,[28] and many other service- and patient-level factors. In summary, stage is an important prognostic factor, but it is not the only important prognostic factor.

How much of the differences in stage at diagnosis are driven by limitations in the way that data are collected and reported by our national registry?

For several key cancers, NZCR staging data is inadequate for ascertaining the stage at diagnosis (particularly for Māori), and a review of clinical notes is required to gauge what is actually happening. A key example is lung cancer, where 38% of Māori (and 36% of European/Other) patients remained unstaged on the NZCR, compared to only 4% in the clinical review performed by Lawrenson et al (Table 1).[15]

This problem is largely driven by two key factors: 1) the manner in which cancer stage is attributed on the NZCR, which is dictated by a need to adhere to international best-practice in managing a high-quality cancer registry in terms of comparability, validity, timeliness and completeness;[29,30] and 2) the clinical reality of cancer staging, which is a dynamic process for many cancers (especially when surgical resection is not necessarily the first or primary treatment). This is a topic of considerable ongoing discussion: on the one hand, there is a move towards more comprehensive clinical staging information being made available on the NZCR, and on the other a move towards cancer-specific clinical registries that sit parallel to the NZCR (prime examples being breast cancer and prostate cancer). Both of these strategies are in varying stages of progress across the cancer spectrum in New Zealand.[5,15]

In terms of cancer survival disparities for Māori, the issue of unstaged cancer on the NZCR (or more broadly the absence of clinical staging data) is of crucial importance for two key reasons: firstly, it undermines our ability to use our national registry to monitor national or regional progress towards achieving early diagnosis for key cancers such as stomach (44% unstaged overall) and liver (65%). Secondly, the way that stage of disease is systematically attributed (or not attributed) on the NZCR undermines our ability to use our national registry to understand how cancer stage might drive our observed survival disparities. A key example of this is haematological cancers: all blood cancers (including leukaemia, lymphoma and myeloma) are automatically attributed a stage 'G' ('Non-Applicable') when entered onto the NZCR—driven by the NZCR adherence to the SEER staging system, which attributes cancer stage based on the extent to which it has spread from the organ of origin. Because of this caveat, we are entirely prevented from using NZCR data to understand the role of early diagnosis as a driver of the 60% survival disparity between Māori and non-Māori patients with non-Hodgkin's lymphoma (age- and sex-adjusted HR: 1.60, 95% CI 1.36–1.88).[1] Current approaches to the staging of blood cancers vary between cancer types, and tend to be include a combination of clinical imaging and blood pathology.[31,32]

Conclusions

There is strong evidence that Māori cancer patients are more likely to die of their cancer than non-Māori cancer patients, and one of the possible drivers of this inequity is differential access to timely diagnosis both through symptomatic detection and access to screening. In this manuscript we have brought together national registry and clinical notes review data, and shown that Māori are less likely to have early stage at diagnosis for several commonly diagnosed cancers; however, we have also shown that this is not the case for all cancers—which indicates that this is an area of unmet need that may be amenable to intervention. Missing stage information in our national registry undermines our ability to both a) monitor progress towards achieving early diagnosis, and b) examine and monitor the role of stage at diagnosis as a driver of survival disparities for multiple important causes of cancer death for Māori, including lung, liver and stomach cancer. Higher-quality staging information on the NZCR is likely to more accurately highlight where potential equity gaps are occurring and enable more focused policy and care interventions, in order to reduce the survival inequity between Māori and non-Māori.

Appendix

Appendix Table 1: Cancer types and associated ICD-10 codes.

Cancer type	ICD-10 Codes
Head and neck	C00-C14; C30-C32, C73
Oesophagus	C15
Stomach	C16
Small intestine	C17
Colon	C18-C19
Rectal	C20
Anus	C21
Liver	C22
Gallbladder and other biliary tract	C23-C24
Pancreas	C25
Other digestive organs	C26
Lung	C33–C34
Other respiratory and intrathoracic organs	C37-C39
Bone and articular cartilage	C40–C41
Melanoma	C43
Non-melanoma skin	C44
Mesothelial and soft tissue	C45-C49
Breast	C50
Other female genital organs	C51-C52; C57; C58
Cervix	C53
Uterus	C54–C55
Ovary	C56
Other male genital organs	C60; C63
Prostate	C61
Testis	C62
Kidney	C64
Other urinary organs	C65-C66; C68
Bladder	C67
Eye, brain and other CNS	C69-C72
Thyroid and other endocrine glands	C73-C75
Ill-defined, secondary and unspecified sites	C76-C80
Hodgkin lymphoma	C81
Non-Hodgkin lymphoma	C82–C86
Other Immunoproliferative, lymphoid and related cancers	C88; C96
Myeloma	C90
Leukaemia	C91–C95

Appendix Table 2: Māori, Pacific, Asian and European/Other New Zealanders diagnosed with cancer between 2007–2016 (NZCR), stratified by cancer type.

	Total		Māori		Pacific		Asian		Euro/Other	
Cancer type	**n**	**%[1]**	**n**	**%[1]**	**n**	**%[1]**	**n**	**%[1]**	**n**	**%[1]**
Anus	627	0.3%	66	0.3%	14	0.2%	8	0.1%	539	0.3%
Bladder	3,800	1.9%	223	1.2%	67	0.9%	72	1%	3,438	2.1%
Bone and articular cartilage	400	0.2%	70	0.4%	38	0.5%	22	0.3%	270	0.2%
Breast	29,897	15.2%	3,744	19.4%	1,399	19.1%	1,528	21.9%	23,226	14.2%
Cervix	1,611	0.8%	359	1.9%	122	1.7%	129	1.9%	1,001	0.6%
Colon	22,011	11.2%	1,153	6%	381	5.2%	650	9.3%	19,827	12.1%
Eye, brain and other CNS	3,736	1.9%	328	1.7%	146	2%	120	1.7%	3,142	1.9%
Gallbladder and other biliary tract	1,326	0.7%	180	0.9%	98	1.3%	80	1.1%	968	0.6%
Head and Neck	5,280	2.7%	497	2.6%	250	3.4%	265	3.8%	4,268	2.6%
Ill-defined, secondary and unspecified sites	4,446	2.3%	483	2.5%	200	2.7%	95	1.4%	3,668	2.2%
Kidney	5,250	2.7%	546	2.8%	164	2.2%	175	2.5%	4,365	2.7%
Liver	3,004	1.5%	611	3.2%	285	3.9%	286	4.1%	1,822	1.1%
Lung	20,651	10.5%	4,009	20.8%	889	12.1%	802	11.5%	14,951	9.1%
Melanoma	23,200	11.8%	339	1.8%	66	0.9%	39	0.6%	22,756	13.9%
Mesothelial and soft tissue	2,577	1.3%	278	1.4%	125	1.7%	75	1.1%	2,099	1.3%
Oesophagus	2,863	1.5%	257	1.3%	71	1%	55	0.8%	2,480	1.5%
Other digestive organs	1,179	0.6%	118	0.6%	38	0.5%	44	0.6%	979	0.6%
Other female genital organs	1,208	0.6%	136	0.7%	65	0.9%	49	0.7%	958	0.6%
Other male genital organs	191	0.1%	8	0%	3	0%	11	0.2%	169	0.1%
Other respiratory and intrathoracic organs	274	0.1%	58	0.3%	23	0.3%	30	0.4%	163	0.1%
Other urinary organs	707	0.4%	20	0.1%	17	0.2%	40	0.6%	630	0.4%
Ovary	2,811	1.4%	297	1.5%	164	2.2%	139	2%	2,211	1.4%
Pancreas	5,122	2.6%	574	3%	176	2.4%	196	2.8%	4,176	2.6%
Prostate	31,460	16%	1,903	9.9%	869	11.8%	719	10.3%	27,969	17.1%
Rectal	7,683	3.9%	530	2.8%	246	3.4%	308	4.4%	6,599	4%
Skin (not melanoma)	1,384	0.7%	65	0.3%	23	0.3%	14	0.2%	1,282	0.8%
Small intestine	972	0.5%	135	0.7%	61	0.8%	27	0.4%	749	0.5%
Stomach	3,831	1.9%	725	3.8%	344	4.7%	295	4.2%	2,467	1.5%
Testis	1,525	0.8%	336	1.7%	55	0.7%	40	0.6%	1,094	0.7%
Thyroid and other endocrine glands	2,990	1.5%	507	2.6%	267	3.6%	369	5.3%	1,847	1.1%
Uterus	4,951	2.5%	705	3.7%	674	9.2%	284	4.1%	3,288	2%

[1]Crude column percentage.

Appendix Table 3: Māori, Pacific, Asian and European/Other New Zealanders diagnosed with cancer between 2007–2016 (NZCR), stratified by cancer type and stage of disease.

	Total		Māori		Pacific		Asian		Euro/Other	
Cancer type and stage	n	%	n	% (95% CI)	n	%	n	%	n	%
Anus										
Local	49	8%	10	16% (6%,26%)	1	5% (-4%,13%)	1	2% (-2%,7%)	37	7% (5%,9%)
Regional	104	17%	6	9% (1%,17%)	4	20% (5%,35%)	1	28% (28%,28%)	93	17% (14%,20%)
Advanced	50	8%	10	14% (5%,23%)	4	21% (4%,38%)	3	20% (-1%,41%)	33	6% (4%,8%)
Unknown	424	68%	40	59% (46%,73%)	5	54% (38%,69%)	3	20% (-1%,41%)	376	70% (66%,74%)
Bladder										
Local	262	7%	19	8% (5%,12%)	4	6% (0%,11%)	7	9% (3%,15%)	232	8% (7%,10%)
Regional	436	11%	34	15% (10%,19%)	10	16% (7%,25%)	8	12% (6%,19%)	384	13% (12%,15%)
Advanced	440	12%	25	11% (7%,15%)	16	25% (14%,35%)	7	10% (3%,17%)	392	12% (11%,13%)
Unknown	2,662	70%	145	65% (59%,71%)	37	53% (41%,65%)	50	68% (58%,78%)	2,430	66% (64%,68%)
Bone and articular cartilage										
Local	36	9%	3	2% (0%,4%)	1	15% (-6%,35%)	1	0% (0%,0%)	31	15% (9%,20%)
Regional	104	26%	12	2% (0%,3%)	6	16% (-5%,36%)	4	15% (-4%,35%)	82	30% (23%,37%)
Advanced	76	19%	18	21% (4%,37%)	9	30% (27%,32%)	6	17% (-3%,36%)	43	16% (10%,22%)
Unknown	184	46%	37	46% (30%,62%)	22	40% (37%,43%)	11	9% (5%,12%)	114	40% (32%,48%)
Breast										
Local	15,561	52%	1,790	45% (43%,47%)	562	38% (35%,41%)	805	52% (48%,56%)	12,404	52% (51%,53%)
Regional	9,888	33%	1,400	34% (32%,36%)	526	33% (30%,37%)	521	31% (28%,35%)	7,441	31% (30%,32%)
Advanced	1,128	4%	147	5% (4%,6%)	103	9% (7%,12%)	38	3% (1%,4%)	840	4% (4%,4%)
Unknown	3,320	11%	407	16% (14%,18%)	208	19% (16%,23%)	164	14% (11%,17%)	2,541	13% (12%,13%)
Cervix										
Local	624	39%	143	23% (16%,30%)	19	8% (4%,12%)	59	25% (17%,33%)	403	22% (19%,25%)
Regional	277	17%	51	21% (12%,31%)	25	19% (8%,31%)	23	23% (10%,37%)	178	22% (19%,26%)
Advanced	183	11%	44	20% (11%,29%)	24	25% (12%,38%)	8	16% (3%,30%)	107	17% (14%,20%)
Unknown	527	33%	121	36% (26%,45%)	54	47% (32%,61%)	39	36% (20%,51%)	313	39% (34%,43%)
Colon										
Local	5,256	24%	248	21% (19%,24%)	59	15% (11%,18%)	158	24% (21%,27%)	4,791	24% (24%,25%)
Regional	9,295	42%	427	37% (35%,40%)	146	37% (32%,42%)	280	44% (40%,47%)	8,442	43% (42%,43%)
Advanced	4,932	22%	341	29% (26%,31%)	120	31% (26%,36%)	140	21% (18%,25%)	4,331	23% (23%,24%)
Unknown	2,528	11%	137	13% (11%,15%)	56	17% (13%,21%)	72	11% (9%,14%)	2,263	10% (9%,10%)
Eye, brain and other CNS										
Local	3,218	86%	272	94% (91%,98%)	119	95% (91%,98%)	106	90% (79%,101%)	2,721	87% (86%,89%)
Regional	48	1%	7	1% (0%,2%)	2	0% (0%,1%)	2	1% (-1%,4%)	37	1% (1%,1%)
Advanced	50	1%	11	0% (0%,1%)	6	1% (-1%,3%)	2	1% (-1%,2%)	31	1% (0%,1%)
Unknown	420	11%	38	5% (2%,8%)	19	4% (1%,7%)	10	8% (-3%,18%)	353	11% (10%,12%)
Gallbladder and other biliary tract										
Local	100	8%	23	13% (8%,17%)	4	4% (0%,7%)	6	8% (2%,14%)	67	8% (6%,10%)
Regional	312	24%	50	27% (20%,33%)	18	16% (10%,22%)	18	23% (13%,32%)	226	27% (23%,30%)
Advanced	457	34%	63	34% (27%,41%)	45	45% (35%,55%)	27	32% (22%,42%)	322	33% (30%,36%)
Unknown	457	34%	44	26% (19%,32%)	31	35% (26%,44%)	29	37% (27%,47%)	353	31% (28%,34%)
Head and neck										
Local	1,292	24%	76	14% (10%,17%)	38	15% (10%,21%)	50	21% (15%,28%)	1,128	27% (25%,28%)
Regional	1,690	32%	185	35% (30%,40%)	84	31% (25%,38%)	84	29% (22%,36%)	1,337	31% (29%,32%)
Advanced	369	7%	43	9% (6%,13%)	35	13% (8%,18%)	18	9% (4%,14%)	273	6% (6%,7%)
Unknown	1,929	37%	193	42% (36%,47%)	93	40% (33%,47%)	113	40% (33%,47%)	1,530	36% (35%,38%)

Appendix Table 3: Māori, Pacific, Asian and European/Other New Zealanders diagnosed with cancer between 2007–2016 (NZCR), stratified by cancer type and stage of disease (continued).

Ill-defined, secondary and unspecified sites										
Local	-	0%	-	-	-	-	-	-	-	-
Regional	15	0%	2	0% (0%,1%)	-	-	-	-	13	1% (0%,1%)
Advanced	4,142	93%	454	94% (92%,96%)	190	95% (93%,98%)	89	93% (88%,98%)	3,409	94% (94%,95%)
Unknown	289	7%	27	6% (4%,8%)	10	5% (2%,7%)	6	6% (1%,11%)	246	5% (4%,6%)
Kidney										
Local	2,237	43%	220	34% (30%,39%)	69	33% (25%,42%)	88	45% (37%,52%)	1,860	42% (41%,44%)
Regional	862	16%	79	13% (10%,16%)	24	11% (5%,17%)	29	18% (12%,24%)	730	17% (15%,18%)
Advanced	1,143	22%	134	25% (21%,30%)	25	24% (14%,34%)	26	17% (11%,23%)	958	22% (21%,23%)
Unknown	1,008	19%	113	28% (23%,32%)	46	32% (22%,42%)	32	20% (14%,27%)	817	19% (18%,20%)
Liver										
Local	282	9%	62	8% (6%,10%)	31	9% (6%,12%)	57	18% (14%,22%)	132	8% (7%,10%)
Regional	91	3%	17	2% (1%,3%)	7	2% (0%,4%)	7	2% (1%,4%)	60	4% (3%,5%)
Advanced	690	23%	140	25% (21%,28%)	61	21% (16%,26%)	46	17% (12%,21%)	443	25% (23%,27%)
Unknown	1,941	65%	392	65% (61%,70%)	186	67% (62%,73%)	176	63% (57%,69%)	1,187	63% (61%,65%)
Lung										
Local	1,279	6%	179	4% (4%,5%)	44	5% (3%,6%)	83	10% (8%,12%)	973	8% (8%,9%)
Regional	2,594	13%	558	13% (12%,14%)	107	12% (10%,14%)	125	15% (13%,18%)	1,804	13% (12%,13%)
Advanced	9,340	45%	1,763	44% (42%,46%)	488	56% (52%,59%)	388	48% (45%,51%)	6,701	46% (46%,47%)
Unknown	7,438	36%	1,509	39% (37%,40%)	250	28% (25%,31%)	206	26% (23%,29%)	5,473	33% (32%,33%)
Melanoma										
Local	19,146	83%	251	70% (64%,75%)	35	53% (41%,65%)	24	59% (42%,75%)	18,836	82% (82%,83%)
Regional	1,752	8%	33	10% (6%,13%)	9	14% (6%,22%)	9	24% (10%,38%)	1,701	8% (7%,8%)
Advanced	1,186	5%	36	13% (8%,17%)	15	22% (13%,32%)	5	15% (2%,28%)	1,130	5% (5%,5%)
Unknown	1,116	5%	19	8% (4%,11%)	7	10% (3%,18%)	1	2% (-2%,6%)	1,089	5% (5%,5%)
Mesothelial and soft tissue										
Local	386	15%	48	17% (11%,22%)	29	28% (18%,38%)	18	19% (9%,28%)	291	14% (13%,16%)
Regional	168	7%	14	4% (2%,7%)	16	7% (3%,12%)	5	3% (-1%,8%)	133	7% (6%,8%)
Advanced	594	23%	74	23% (17%,29%)	28	19% (12%,25%)	14	24% (11%,36%)	478	22% (20%,24%)
Unknown	1,429	55%	142	56% (48%,63%)	52	46% (35%,57%)	38	54% (40%,69%)	1,197	57% (55%,59%)
Oesophagus										
Local	61	2%	4	1% (0%,3%)	1	1% (-1%,3%)	1	2% (-1%,5%)	55	3% (2%,4%)
Regional	225	8%	21	7% (4%,10%)	5	7% (1%,13%)	5	8% (1%,15%)	194	9% (8%,10%)
Advanced	747	26%	83	32% (26%,37%)	23	30% (20%,40%)	14	28% (15%,41%)	627	28% (26%,30%)
Unknown	1,830	64%	149	59% (53%,65%)	42	61% (51%,72%)	35	61% (47%,75%)	1,604	59% (57%,62%)
Other digestive organs										
Local	1	0%	-	-	-	-	-	-	1	0% (0%,1%)
Regional	12	1%	1	1% (-1%,3%)	1	2% (-2%,7%)	1	2% (-2%,6%)	9	1% (0%,2%)
Advanced	655	56%	91	75% (69%,82%)	27	72% (60%,84%)	37	85% (76%,94%)	500	72% (69%,74%)
Unknown	511	43%	26	24% (17%,30%)	10	24% (12%,36%)	6	12% (4%,20%)	469	27% (24%,30%)
Other female genital organs										
Local	375	31%	32	19% (12%,25%)	9	17% (6%,27%)	9	13% (5%,20%)	325	34% (31%,37%)
Regional	176	15%	15	9% (4%,13%)	6	7% (2%,12%)	6	10% (2%,17%)	149	16% (13%,18%)
Advanced	390	32%	46	36% (27%,45%)	33	45% (32%,58%)	22	45% (30%,61%)	289	30% (27%,33%)
Unknown	267	22%	43	35% (27%,44%)	17	32% (19%,44%)	12	33% (19%,46%)	195	20% (18%,23%)

Appendix Table 3: Māori, Pacific, Asian and European/Other New Zealanders diagnosed with cancer between 2007–2016 (NZCR), stratified by cancer type and stage of disease (continued).

Other male genital organs										
Local	111	58%	4	50% (37%,63%)	1	15% (-6%,35%)	4	36% (15%,57%)	102	60% (53%,68%)
Regional	42	22%	3	34% (10%,58%)	1	12% (12%,12%)	4	40% (24%,55%)	34	20% (14%,26%)
Advanced	4	2%	1	15% (-6%,35%)	-	-	-	-	3	2% (0%,3%)
Unknown	34	18%	-	-	1	15% (-6%,35%)	3	24% (3%,44%)	30	18% (12%,24%)
Other respiratory and intrathoracic organs										
Local	20	7%	3	4% (0%,8%)	-	-	3	8% (-2%,17%)	14	9% (5%,14%)
Regional	57	21%	9	16% (4%,29%)	10	39% (18%,60%)	9	34% (10%,58%)	29	17% (12%,23%)
Advanced	80	29%	18	34% (18%,49%)	4	3% (0%,6%)	7	21% (7%,34%)	51	29% (22%,36%)
Unknown	117	43%	28	46% (30%,62%)	9	28% (7%,49%)	11	38% (13%,63%)	69	44% (36%,52%)
Other urinary organs										
Local	147	21%	3	13% (-1%,28%)	3	35% (28%,42%)	9	26% (12%,41%)	132	24% (19%,28%)
Regional	213	30%	6	26% (8%,44%)	5	16% (3%,29%)	15	31% (19%,44%)	187	29% (25%,33%)
Advanced	139	20%	5	26% (8%,45%)	5	16% (3%,29%)	8	22% (8%,35%)	121	19% (16%,23%)
Unknown	208	29%	6	21% (7%,34%)	4	19% (6%,32%)	8	20% (7%,33%)	190	27% (23%,31%)
Ovary										
Local	417	15%	71	14% (10%,18%)	34	14% (8%,21%)	27	10% (6%,14%)	285	13% (12%,14%)
Regional	496	18%	56	15% (11%,20%)	40	20% (13%,27%)	36	24% (15%,33%)	364	17% (15%,18%)
Advanced	1,692	60%	144	58% (51%,65%)	77	56% (46%,65%)	71	63% (54%,72%)	1,400	63% (61%,65%)
Unknown	206	7%	26	12% (7%,17%)	13	10% (3%,17%)	5	3% (0%,7%)	162	7% (6%,8%)
Pancreas										
Local	108	2%	19	3% (2%,4%)	5	3% (1%,5%)	11	6% (3%,9%)	73	2% (2%,3%)
Regional	421	8%	45	7% (5%,9%)	11	6% (3%,10%)	23	12% (7%,16%)	342	10% (9%,11%)
Advanced	2,761	54%	310	53% (49%,58%)	99	57% (49%,64%)	103	53% (46%,60%)	2,249	56% (54%,57%)
Unknown	1,832	36%	200	36% (32%,40%)	61	34% (28%,41%)	59	30% (23%,36%)	1,512	32% (31%,34%)
Prostate										
Local	4,484	14%	176	9% (7%,10%)	46	7% (4%,9%)	84	12% (9%,15%)	4,178	16% (16%,17%)
Regional	2,650	8%	120	5% (4%,6%)	46	6% (4%,8%)	60	7% (5%,8%)	2,424	8% (8%,8%)
Advanced	1,874	6%	179	11% (10%,13%)	95	12% (10%,15%)	34	5% (4%,7%)	1,566	6% (6%,7%)
Unknown	22,452	71%	1,428	74% (71%,76%)	682	74% (70%,78%)	541	75% (71%,79%)	19,801	69% (69%,70%)
Rectal										
Local	1,520	20%	76	14% (10%,17%)	26	11% (7%,15%)	65	21% (16%,25%)	1,353	20% (19%,21%)
Regional	1,772	23%	101	19% (16%,23%)	61	25% (19%,31%)	70	23% (18%,28%)	1,540	23% (22%,24%)
Advanced	1,090	14%	129	22% (18%,26%)	44	18% (13%,24%)	36	12% (8%,16%)	881	14% (13%,15%)
Unknown	3,301	43%	224	44% (39%,49%)	115	45% (38%,51%)	137	44% (39%,50%)	2,825	43% (42%,44%)
Skin (not melanoma)										
Local	726	52%	37	59% (47%,70%)	12	59% (42%,76%)	9	51% (31%,70%)	668	54% (51%,57%)
Regional	159	11%	7	10% (3%,16%)	3	11% (-2%,24%)	-	-	149	12% (10%,14%)
Advanced	98	7%	4	9% (0%,17%)	2	10% (-3%,23%)	1	14% (-5%,33%)	91	7% (5%,8%)
Unknown	401	29%	17	23% (14%,32%)	6	18% (4%,33%)	4	6% (1%,10%)	374	27% (24%,30%)
Small intestine										
Local	125	13%	23	17% (10%,24%)	7	10% (2%,18%)	3	12% (0%,25%)	92	12% (10%,15%)
Regional	384	40%	57	45% (36%,55%)	21	37% (24%,50%)	11	41% (23%,60%)	295	40% (36%,43%)
Advanced	285	29%	38	25% (18%,33%)	20	30% (19%,41%)	4	14% (1%,27%)	223	30% (26%,33%)
Unknown	178	18%	17	12% (6%,19%)	13	22% (11%,33%)	9	31% (15%,48%)	139	18% (16%,21%)

Appendix Table 3: Māori, Pacific, Asian and European/Other New Zealanders diagnosed with cancer between 2007–2016 (NZCR), stratified by cancer type and stage of disease (continued).

Stomach										
Local	311	8%	89	9% (7%,11%)	27	8% (5%,11%)	27	9% (6%,13%)	168	7% (6%,8%)
Regional	545	14%	131	19% (16%,22%)	45	13% (9%,17%)	51	17% (13%,21%)	318	14% (12%,15%)
Advanced	1,300	34%	267	36% (32%,40%)	125	33% (28%,38%)	107	35% (30%,41%)	801	35% (33%,37%)
Unknown	1,675	44%	238	36% (32%,40%)	147	46% (41%,51%)	110	38% (33%,44%)	1,180	45% (43%,47%)
Testis										
Local	1,178	77%	247	60% (54%,65%)	35	24% (3%,44%)	33	40% (39%,42%)	863	64% (55%,73%)
Regional	158	10%	30	5% (1%,10%)	7	16% (-4%,37%)	3	1% (0%,2%)	118	19% (9%,28%)
Advanced	158	10%	52	35% (31%,38%)	10	2% (1%,3%)	3	1% (0%,2%)	93	9% (3%,15%)
Unknown	31	2%	7	0% (0%,1%)	3	1% (0%,2%)	1	0% (0%,1%)	20	9% (1%,17%)
Thyroid and other endocrine glands										
Local	1,642	55%	270	41% (34%,48%)	135	40% (31%,50%)	203	49% (40%,58%)	1,034	51% (49%,54%)
Regional	726	24%	108	25% (18%,33%)	61	22% (14%,30%)	116	31% (22%,40%)	441	24% (21%,26%)
Advanced	249	8%	54	16% (10%,23%)	34	16% (8%,23%)	17	11% (4%,18%)	144	10% (8%,12%)
Unknown	373	12%	75	17% (11%,24%)	37	22% (13%,31%)	33	9% (4%,14%)	228	15% (13%,17%)
Uterus										
Local	3,146	64%	447	56% (52%,61%)	385	48% (43%,54%)	190	64% (55%,73%)	2,124	63% (61%,65%)
Regional	838	17%	94	12% (9%,15%)	84	14% (10%,18%)	47	16% (10%,23%)	613	19% (17%,20%)
Advanced	417	8%	76	14% (10%,18%)	77	13% (10%,17%)	16	6% (2%,11%)	248	8% (7%,9%)
Unknown	550	11%	88	18% (14%,21%)	128	24% (19%,29%)	31	13% (6%,20%)	303	10% (9%,12%)

[1]Age-standardised proportion.

Appendix Table 4: Age-adjusted odds of stage of disease between European/Other (reference) and Māori, Pacific and Asian New Zealanders, by cancer type (NZCR).

	Māori	**Pacific**	**Asian**	**Euro/Other**
Cancer type and stage	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Anus				
Local	2.65 (1.23, 5.7)	1.09 (0.14, 8.57)	2.55 (0.29, 22.34)	Reference
Regional	0.85 (0.7, 1.04)	0.76 (0.59, 0.99)	0.91 (0.72, 1.14)	Reference
Advanced	1.36 (1.07, 1.72)	0.94 (0.67, 1.33)	1.34 (0.96, 1.85)	Reference
Unknown	0.96 (0.34, 2.72)	1.45 (0.33, 6.39)	1.46 (0.18, 11.99)	Reference
Bladder				
Local	0.91 (0.55, 1.5)	0.67 (0.24, 1.89)	1.19 (0.53, 2.64)	Reference
Regional	0.74 (0.62, 0.88)	0.5 (0.41, 0.59)	0.8 (0.61, 1.04)	Reference
Advanced	0.86 (0.56, 1.32)	1.31 (0.58, 2.98)	0.73 (0.22, 2.41)	Reference
Unknown	0.86 (0.57, 1.31)	1.09 (0.62, 1.91)	0.41 (0.14, 1.18)	Reference
Bone and articular cartilage				
Local	0.41 (0.12, 1.42)	0.24 (0.03, 1.86)	0.43 (0.06, 3.34)	Reference
Regional	0.51 (0.21, 1.21)	1.97 (0.6, 6.42)	0.81 (0.1, 6.85)	Reference
Advanced	0.87 (0.68, 1.1)	0.95 (0.7, 1.29)	1.47 (1.15, 1.88)	Reference
Unknown	0.96 (0.8, 1.15)	0.98 (0.77, 1.24)	1.02 (0.79, 1.32)	Reference

Appendix Table 4: Age-adjusted odds of stage of disease between European/Other (reference) and Māori, Pacific and Asian New Zealanders, by cancer type (NZCR) (continued).

Breast				
Local	0.75 (0.7, 0.81)	0.55 (0.49, 0.61)	0.89 (0.81, 0.99)	Reference
Regional	1.17 (1.09, 1.26)	1.17 (1.04, 1.31)	0.98 (0.88, 1.1)	Reference
Advanced	1.26 (1.05, 1.51)	2.5 (2.02, 3.1)	0.83 (0.59, 1.15)	Reference
Unknown	1.38 (1.23, 1.55)	2.08 (1.77, 2.44)	1.52 (1.28, 1.8)	Reference
Cervix				
Local	0.8 (0.61, 1.04)	0.3 (0.18, 0.5)	1.29 (0.87, 1.91)	Reference
Regional	0.84 (0.6, 1.19)	1.18 (0.73, 1.88)	1.05 (0.65, 1.7)	Reference
Advanced	1.47 (1, 2.17)	2.14 (1.3, 3.52)	0.62 (0.29, 1.32)	Reference
Unknown	1.56 (1.29, 1.89)	2.12 (1.57, 2.85)	1.33 (1.03, 1.72)	Reference
Colon				
Local	0.81 (0.7, 0.94)	0.54 (0.41, 0.72)	0.97 (0.8, 1.16)	Reference
Regional	0.77 (0.68, 0.87)	0.81 (0.65, 0.99)	0.99 (0.85, 1.16)	Reference
Advanced	1.35 (1.18, 1.55)	1.46 (1.17, 1.83)	0.9 (0.75, 1.09)	Reference
Unknown	1.56 (1.29, 1.89)	2.12 (1.57, 2.85)	1.33 (1.03, 1.72)	Reference
Eye, brain and other CNS				
Local	1.09 (0.79, 1.51)	1.05 (0.67, 1.65)	1.54 (0.86, 2.73)	Reference
Regional	1.18 (0.5, 2.8)	0.7 (0.16, 3.05)	1.05 (0.25, 4.49)	Reference
Advanced	1.62 (0.77, 3.43)	1.82 (0.71, 4.67)	1.03 (0.24, 4.42)	Reference
Unknown	0.78 (0.54, 1.13)	0.85 (0.51, 1.42)	0.59 (0.3, 1.14)	Reference
Gallbladder and other biliary tract				
Local	1.59 (0.95, 2.68)	0.43 (0.15, 1.23)	0.94 (0.39, 2.25)	Reference
Regional	0.92 (0.63, 1.35)	0.48 (0.28, 0.85)	0.76 (0.43, 1.34)	Reference
Advanced	1.03 (0.73, 1.45)	1.61 (1.05, 2.48)	0.99 (0.61, 1.61)	Reference
Unknown	0.82 (0.56, 1.2)	1.28 (0.8, 2.06)	1.3 (0.79, 2.14)	Reference
Head and neck				
Local	0.48 (0.37, 0.62)	0.47 (0.33, 0.68)	0.61 (0.44, 0.84)	Reference
Regional	1.17 (0.96, 1.42)	0.99 (0.75, 1.3)	0.88 (0.67, 1.15)	Reference
Advanced	1.44 (1.02, 2.03)	2.48 (1.69, 3.65)	1.12 (0.68, 1.85)	Reference
Unknown	1.3 (1.07, 1.58)	1.23 (0.94, 1.6)	1.59 (1.23, 2.06)	Reference
Ill-defined, secondary and unspecified sites				
Local	-	-	-	Reference
Regional	-	-	-	Reference
Advanced	0.62 (0.41, 0.94)	0.8 (0.41, 1.55)	0.77 (0.33, 1.81)	Reference
Unknown	1.73 (1.12, 2.67)	1.44 (0.74, 2.81)	1.43 (0.61, 3.38)	Reference

Appendix Table 4: Age-adjusted odds of stage of disease between European/Other (reference) and Māori, Pacific and Asian New Zealanders, by cancer type (NZCR) (continued).

Kidney				
Local	0.7 (0.58, 0.84)	0.67 (0.48, 0.93)	1.07 (0.78, 1.47)	Reference
Regional	0.8 (0.62, 1.03)	0.79 (0.51, 1.23)	0.94 (0.62, 1.41)	Reference
Advanced	1.39 (1.12, 1.72)	0.81 (0.53, 1.26)	0.73 (0.48, 1.12)	Reference
Unknown	1.56 (1.24, 1.96)	2.66 (1.84, 3.83)	1.28 (0.86, 1.92)	Reference
Liver				
Local	1.08 (0.78, 1.5)	1.25 (0.82, 1.91)	2.7 (1.91, 3.82)	Reference
Regional	0.7 (0.4, 1.22)	0.64 (0.29, 1.42)	0.65 (0.29, 1.44)	Reference
Advanced	0.88 (0.7, 1.1)	0.82 (0.6, 1.11)	0.58 (0.41, 0.81)	Reference
Unknown	1.17 (0.96, 1.43)	1.17 (0.89, 1.53)	0.97 (0.75, 1.26)	Reference
Lung				
Local	0.53 (0.45, 0.63)	0.61 (0.45, 0.83)	1.37 (1.08, 1.74)	Reference
Regional	1.02 (0.92, 1.13)	0.88 (0.71, 1.08)	1.19 (0.98, 1.46)	Reference
Advanced	0.87 (0.8, 0.93)	1.37 (1.2, 1.57)	1.06 (0.92, 1.23)	Reference
Unknown	1.38 (1.28, 1.49)	0.83 (0.71, 0.97)	0.71 (0.61, 0.84)	Reference
Melanoma				
Local	0.52 (0.41, 0.67)	0.22 (0.14, 0.36)	0.3 (0.16, 0.58)	Reference
Regional	1.52 (1.06, 2.19)	2.04 (1, 4.14)	4.13 (1.94, 8.77)	Reference
Advanced	2.49 (1.75, 3.55)	5.82 (3.25, 10.4)	3.01 (1.17, 7.73)	Reference
Unknown	1.3 (0.81, 2.07)	2.43 (1.11, 5.35)	0.56 (0.08, 4.08)	Reference
Mesothelial and soft tissue				
Local	1.14 (0.81, 1.61)	1.64 (1.05, 2.55)	1.71 (0.98, 2.96)	Reference
Regional	0.66 (0.37, 1.17)	1.81 (1.03, 3.18)	0.87 (0.34, 2.22)	Reference
Advanced	1.19 (0.89, 1.6)	0.95 (0.61, 1.47)	0.75 (0.42, 1.36)	Reference
Unknown	0.91 (0.7, 1.17)	0.62 (0.43, 0.9)	0.9 (0.57, 1.44)	Reference
Oesophagus				
Local	0.45 (0.16, 1.27)	0.42 (0.06, 3.11)	0.69 (0.09, 5.12)	Reference
Regional	0.8 (0.5, 1.3)	0.7 (0.28, 1.78)	1.07 (0.42, 2.73)	Reference
Advanced	1.14 (0.85, 1.51)	1.17 (0.7, 1.96)	0.93 (0.5, 1.73)	Reference
Unknown	1.03 (0.78, 1.35)	1.04 (0.63, 1.71)	1.08 (0.61, 1.9)	Reference
Other digestive organs				
Local	-	-	-	Reference
Regional	0.85 (0.1, 7.31)	2.71 (0.31, 23.4)	2.34 (0.27, 20.06)	Reference
Advanced	1.05 (0.61, 1.79)	0.77 (0.33, 1.79)	2.6 (0.99, 6.81)	Reference
Unknown	0.98 (0.57, 1.7)	1.19 (0.5, 2.83)	0.32 (0.12, 0.89)	Reference

Appendix Table 4: Age-adjusted odds of stage of disease between European/Other (reference) and Māori, Pacific and Asian New Zealanders, by cancer type (NZCR) (continued).

Other female genital organs				
Local	0.52 (0.34, 0.8)	0.27 (0.13, 0.55)	0.38 (0.18, 0.79)	Reference
Regional	0.62 (0.35, 1.1)	0.5 (0.21, 1.2)	0.69 (0.29, 1.67)	Reference
Advanced	1.24 (0.84, 1.83)	2.52 (1.51, 4.2)	1.99 (1.11, 3.58)	Reference
Unknown	2.14 (1.43, 3.22)	1.66 (0.92, 2.98)	1.53 (0.77, 3.02)	Reference
Other male genital organs				
Local	0.65 (0.16, 2.71)	0.4 (0.03, 4.69)	0.37 (0.1, 1.31)	Reference
Regional	2.38 (0.54, 10.48)	1.9 (0.16, 22.72)	2.28 (0.63, 8.25)	Reference
Advanced	-	-	-	Reference
Unknown	-	-	-	Reference
Other respiratory and intrathoracic organs				
Local	-	-	-	Reference
Regional	0.86 (0.38, 1.94)	3.91 (1.48, 10.32)	2.09 (0.85, 5.11)	Reference
Advanced	0.97 (0.51, 1.86)	0.38 (0.12, 1.22)	0.6 (0.24, 1.51)	Reference
Unknown	1.28 (0.7, 2.34)	0.96 (0.38, 2.42)	0.83 (0.37, 1.87)	Reference
Other urinary organs				
Local	0.62 (0.18, 2.17)	0.58 (0.16, 2.06)	0.89 (0.41, 1.95)	Reference
Regional	1 (0.38, 2.63)	0.89 (0.31, 2.59)	1.34 (0.69, 2.62)	Reference
Advanced	1.4 (0.5, 3.94)	1.77 (0.6, 5.18)	1.06 (0.47, 2.36)	Reference
Unknown	1.1 (0.41, 2.95)	1.14 (0.36, 3.62)	0.71 (0.32, 1.61)	Reference
Ovary				
Local	1.16 (0.84, 1.59)	0.82 (0.53, 1.27)	0.77 (0.48, 1.24)	Reference
Regional	1 (0.72, 1.37)	1.35 (0.92, 1.99)	1.46 (0.97, 2.19)	Reference
Advanced	0.78 (0.6, 1.01)	0.77 (0.55, 1.08)	0.93 (0.65, 1.33)	Reference
Unknown	1.8 (1.14, 2.83)	1.67 (0.91, 3.06)	0.74 (0.3, 1.87)	Reference
Pancreas				
Local	1.14 (0.67, 1.94)	0.88 (0.34, 2.3)	2.27 (1.16, 4.43)	Reference
Regional	0.65 (0.47, 0.92)	0.5 (0.26, 0.94)	1.13 (0.71, 1.78)	Reference
Advanced	0.89 (0.75, 1.07)	0.99 (0.73, 1.35)	0.87 (0.65, 1.16)	Reference
Unknown	1.32 (1.09, 1.6)	1.24 (0.89, 1.72)	0.96 (0.69, 1.32)	Reference
Prostate				
Local	0.5 (0.43, 0.59)	0.29 (0.22, 0.39)	0.74 (0.59, 0.94)	Reference
Regional	0.67 (0.55, 0.81)	0.57 (0.42, 0.77)	0.96 (0.73, 1.25)	Reference
Advanced	2.35 (1.98, 2.78)	2.67 (2.12, 3.36)	0.9 (0.63, 1.29)	Reference
Unknown	1.31 (1.17, 1.46)	1.55 (1.31, 1.83)	1.26 (1.06, 1.5)	Reference

Appendix Table 4: Age-adjusted odds of stage of disease between European/Other (reference) and Māori, Pacific and Asian New Zealanders, by cancer type (NZCR) (continued).

Rectal				
Local	0.68 (0.53, 0.87)	0.48 (0.32, 0.73)	1.08 (0.81, 1.43)	Reference
Regional	0.8 (0.64, 1)	1.12 (0.83, 1.51)	0.99 (0.75, 1.3)	Reference
Advanced	1.97 (1.59, 2.45)	1.32 (0.95, 1.85)	0.82 (0.57, 1.17)	Reference
Unknown	0.96 (0.8, 1.15)	1.15 (0.89, 1.48)	1.05 (0.84, 1.33)	Reference
Skin (not melanoma)				
Local	1.1 (0.66, 1.84)	0.88 (0.38, 2.02)	1.2 (0.39, 3.71)	Reference
Regional	-	-	-	Reference
Advanced	0.96 (0.34, 2.72)	1.45 (0.33, 6.39)	1.46 (0.18, 11.99)	Reference
Unknown	0.94 (0.53, 1.67)	0.97 (0.38, 2.51)	1.32 (0.4, 4.38)	Reference
Small intestine				
Local	1.31 (0.78, 2.19)	0.84 (0.37, 1.91)	0.87 (0.26, 2.97)	Reference
Regional	1.02 (0.69, 1.49)	0.74 (0.43, 1.29)	1.04 (0.48, 2.28)	Reference
Advanced	0.86 (0.57, 1.31)	1.09 (0.62, 1.91)	0.41 (0.14, 1.18)	Reference
Unknown	0.93 (0.53, 1.63)	1.7 (0.87, 3.3)	2.47 (1.06, 5.77)	Reference
Stomach				
Local	1.46 (1.09, 1.95)	0.93 (0.6, 1.44)	1.17 (0.76, 1.8)	Reference
Regional	1.36 (1.07, 1.72)	0.94 (0.67, 1.33)	1.34 (0.96, 1.85)	Reference
Advanced	0.96 (0.8, 1.15)	0.98 (0.77, 1.24)	1.02 (0.79, 1.32)	Reference
Unknown	0.75 (0.62, 0.9)	1.11 (0.87, 1.41)	0.8 (0.62, 1.04)	Reference
Testis				
Local	0.73 (0.55, 0.98)	0.46 (0.26, 0.82)	1.24 (0.54, 2.85)	Reference
Regional	0.86 (0.56, 1.32)	1.31 (0.58, 2.98)	0.73 (0.22, 2.41)	Reference
Advanced	1.84 (1.27, 2.66)	2.17 (1.05, 4.47)	0.79 (0.24, 2.63)	Reference
Unknown	1.33 (0.55, 3.25)	3.77 (1.06, 13.43)	1.69 (0.22, 13.12)	Reference
Thyroid and other endocrine glands				
Local	0.85 (0.7, 1.04)	0.76 (0.59, 0.99)	0.91 (0.72, 1.14)	Reference
Regional	0.87 (0.68, 1.1)	0.95 (0.7, 1.29)	1.47 (1.15, 1.88)	Reference
Advanced	1.52 (1.09, 2.12)	1.86 (1.24, 2.78)	0.62 (0.37, 1.04)	Reference
Unknown	1.32 (0.99, 1.75)	1.22 (0.84, 1.78)	0.75 (0.51, 1.1)	Reference
Uterus				
Local	0.74 (0.62, 0.88)	0.5 (0.41, 0.59)	0.8 (0.61, 1.04)	Reference
Regional	0.73 (0.58, 0.93)	0.71 (0.55, 0.92)	0.98 (0.7, 1.36)	Reference
Advanced	1.78 (1.35, 2.36)	2.08 (1.56, 2.77)	0.94 (0.55, 1.59)	Reference
Unknown	1.91 (1.47, 2.48)	3.68 (2.88, 4.71)	1.83 (1.22, 2.73)	Reference

Competing interests:
Dr Jackson is medical director of the Cancer Society of New Zealand, and a member of the Advisory Council of the Cancer Control Agency.

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Sudden unexpected death in epilepsy (SUDEP) in New Zealand; a retrospective review

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ABSTRACT

AIM: Sudden unexpected death in epilepsy (SUDEP) is well recognised and widely reported but remains poorly understood. SUDEP in young adults is 27 times more common than sudden death in control populations. The incidence of SUDEP in New Zealand is not known but up to 40 people with epilepsy may die from SUDEP every year. A review of coroner's reports of SUDEP was undertaken to learn more about SUDEP in New Zealand.

METHOD: Coroner's reports of all cases of possible SUDEP in New Zealand from 2007–2016 (n=190) were obtained and post-mortem and toxicology results were reviewed. Cases were categorised using published criteria.

RESULTS: We obtained reports of 190 cases from the coroner's office. Of these 190 cases, we determined that 123 were definite SUDEP, 40 were definite SUDEP plus, three were probable SUDEP, seven were possible SUDEP and 17 were probably not SUDEP. The number of cases per year varied from 11–26 (2013). Cases were aged 1.5–67 years, with 63% aged 15–45 (mean 37 years). Sixty-one percent were male. Eighty-seven percent of the deaths occurred at home, with 74% found dead in their bed or bedroom. The majority were not employed, with only 33% working or retired at the time of death; 15% were children or students. Information regarding work status was not available for 11%. Toxicology results were available for 155 cases; antiepileptic drug (AED) use was detected in 67% of these cases, with a single AED detected in 44%, two AEDs in 21%, and three AEDs in 3% of samples taken at autopsy. Approximately half who took an AED were taking either sodium valproate or carbamazepine.

CONCLUSION: This study suggests that people with epilepsy who die from SUDEP in New Zealand are young and are often compliant with their medication. We plan to establish a nationwide SUDEP registry using the EpiNet database to determine the incidence of SUDEP in New Zealand, and to track changes in SUDEP rates. We are also planning to take part in an international case-control study of SUDEP in the hope that we might learn more about risk factors that predispose people with epilepsy to SUDEP, and factors that might reduce the risk.

Epilepsy is a common neurological condition. The prevalence of epilepsy in developed countries is estimated at between 5–10/1,000 people, with most Western countries reporting a prevalence of about 0.7%.[1] Several studies have established that people with epilepsy have a lower life expectancy than that of the general population.[2–4] This lower life expectancy is explained, in part, by high rates of comorbidity, the risk of injury during seizures and status epilepticus. However, there is also a significant risk of sudden unexpected death in epilepsy (SUDEP).[2–4]

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomic cause of death.[5]

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Table 1: Nashef sudden unexpected death in epilepsy classification.[5]

Definite SUDEP	Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death that occurs in benign circumstances in an individual with epilepsy, with or without evidence for a seizure, and excludes documented status epilpeticus, in which post-mortem examination does not reveal a cause of death.
Definite SUDEP plus	Death satisfying criteria for definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death might have been due to the combined effect of both conditions, and if autopsy or direct observations or recording of the terminal event did not prove the concomitant condition to be the cause of death.
Probable SUDEP or probable SUDEP plus	Same definition as definite SUDEP or SUDEP plus, but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.
Possible SUDEP	A competing cause for death is present.
Not SUDEP	A clear alternative cause of death is known.
Unclassified	Incomplete information available; not possible to classify.

The incidence of sudden death in young adults with epilepsy is reported to be 27 times higher than the incidence of sudden death in control populations.[6] The annual incidence of SUDEP in patients with epilepsy is estimated to be 1.2 per 1,000 people.[7] When epilepsy begins in early childhood, the average cumulative risk of SUDEP is as high as 8% by 70 years.[7]

When the age at which SUDEP occurs is taken into account, SUDEP ranks second only to stroke, in terms of potential years of life lost.[7]

The strongest SUDEP risk factor appears to be poor control of tonic-clonic seizures.[8,9] Other potential risk factors are male sex, epilepsy onset before 16 years of age, longer duration of epilepsy and intellectual disability.[9]

Despite an increase in research into SUDEP, the underlying mechanisms remain unclear. Currently, there are no proven strategies to prevent SUDEP.

Here we present the results of a retrospective review of coroners' reports of people who have died of SUDEP in New Zealand between 2007 and 2016. Our aim was to obtain a better understanding of SUDEP in New Zealand and identify future areas of research.

Method

The coroner's office provided documentation for all cases between July 2007 and July 2016 where the cause of death was thought to have been SUDEP. Documentation included the coroner's verdict on the cause of death and whether an enquiry was opened into the cause of death. We reviewed these cases and extracted demographic data and information regarding the circumstances of death (date of death, place of death etc).

After approval from the Chief Coroner and the Health and Disability Ethics committee (Northern B; 18/NTB/28), the coroner's office also provided post-mortem and toxicology reports. We were then able to record additional information about the circumstances of death. We determined if anti-epileptic drugs were identified post-mortem, and whether other medications, alcohol and/or recreational drugs were detected.

The epilepsy fellow at Auckland Hospital (SS) used the Nashef criteria for SUDEP to categorise each case into definite SUDEP, definite SUDEP plus, probable SUDEP, probable SUDEP plus, possible SUDEP, not SUDEP or unclassified (Table 1).[5] Where there was uncertainty about the appropriate category, the case was reviewed by a second member of the research team (PB), and consensus was reached.

Table 2: Breakdown of SUDEP categories.

Definite SUDEP	Definite SUDEP plus	Probable SUDEP	Possible SUDEP	Not SUDEP	Unclassified
123	40	3	7	14	3

Results

The coroner's office identified 190 cases where the cause of death may have been SUDEP between July 2007 and July 2016.

Following our review, we concluded that 166 cases fulfilled the Nashef criteria for either definite SUDEP, definite SUDEP plus or probable SUDEP.

The breakdown of the different SUDEP categories can be seen in Table 2.

Five of the possible SUDEP cases also had significant cardiac disease which may have caused their deaths. One had a high level of methadone detected at post mortem, and one died following a fall and did not have a post mortem. Of the 14 patients that were considered not to have had SUDEP, we concluded that five patients had drowned, three probably died from a cardiac cause, two had died from probable status epilepticus, one died as a result of septicaemia, one was having palliative care and had stopped AEDs, and one died from suicide. The final patient had a probable symptomatic seizure, but he had not had previous seizures and did not have a diagnosis of epilepsy.

Demographics of 166 definite, definite + or probable SUDEP patients

The patients with definite SUDEP, definite SUDEP plus or probable SUDEP were aged between 1.5 years and 67 years (Figure 1). The mean age for this group was 37 years.

Sixty-one percent of all the SUDEP cases were male. Figure 2 shows the cases of SUDEP by year and gender.

The ethnicity was not recorded for 56 patients. Twenty-one patients were Māori and 77 were recorded as Caucasian.

The type of epilepsy was stated in less than one-third of cases. Information about seizure frequency was not available and duration of epilepsy was rarely stated.

Circumstances of death

One hundred and forty-six patients' (88%) deaths occurred at home; 74% were found in their bedroom and 7% of patients were found dead in the bathroom. One hundred and forty-four patients (87%) were alone when they died.

We also looked at what position the body was found in; in particular, whether the

Figure 1: Age at time of death.

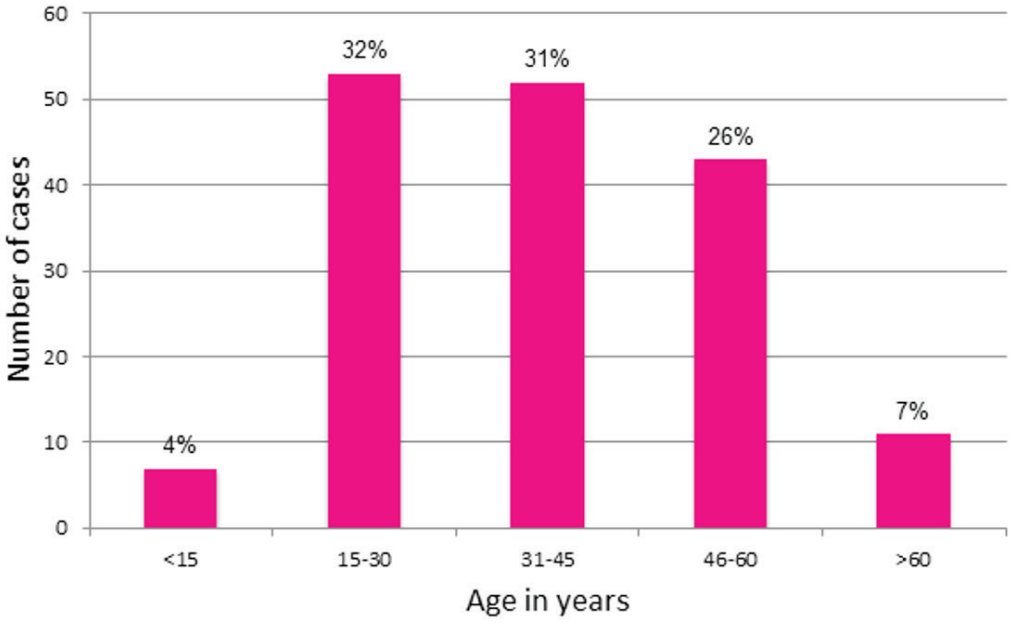

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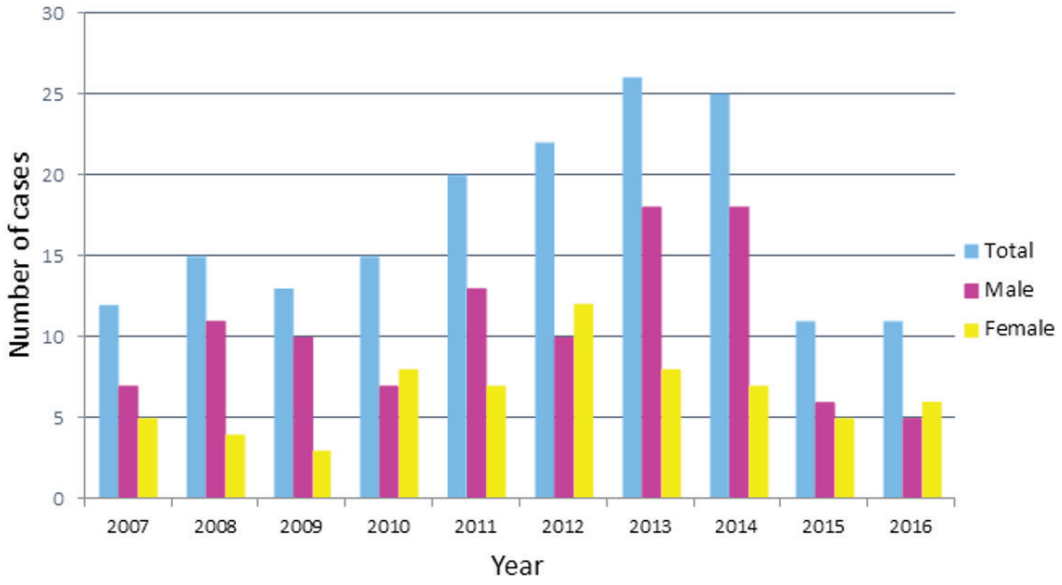
Figure 2: SUDEP cases by year and gender.



deceased was in bed, and if lying, whether supine or prone (Figure 3).

Toxicology

We obtained toxicology reports on 155 of the 166 definite and probable SUDEP cases. Anti-epileptic drugs (AED) were detected in 67% of the cases in which toxicology was performed; a single AED was detected in 68 people (44%), two AEDs were detected in 32 patients (21%), and three AEDs were detected in four people (3%) (Figure 4). Approximately half of those who took an AED were either taking sodium valproate or carbamazepine.

High alcohol levels were not identified in any patient. Recent cannabis use was detected in 20 people (12%) and other recreational drugs in six people (4%). Anti-depressants and antipsychotic medications were identified in small numbers of patients.

Figure 3: Position of body when found.

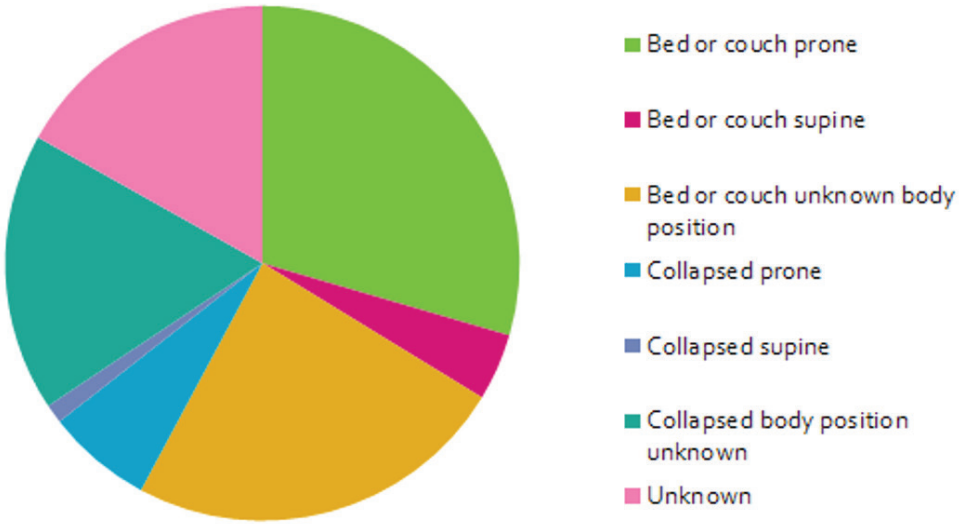
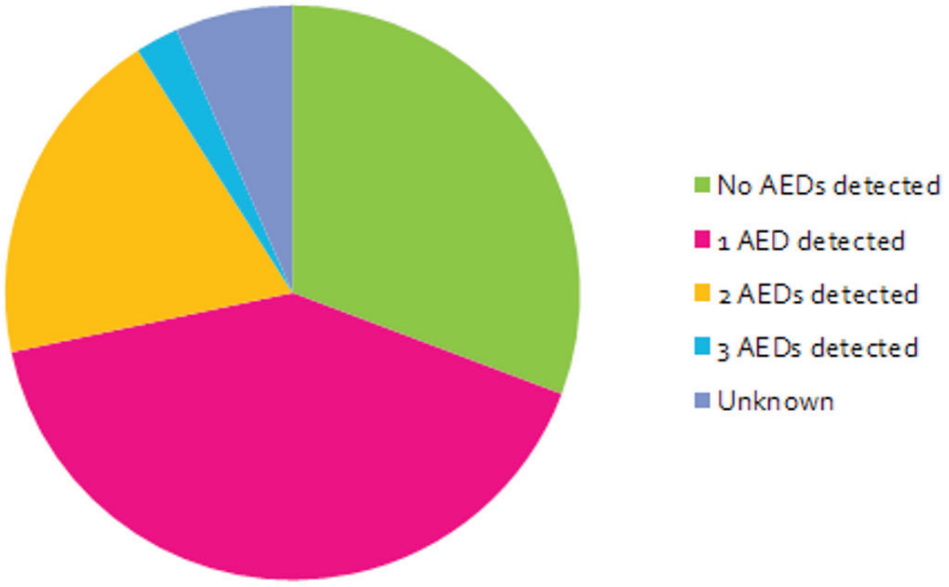


Figure 4: Number of AEDs at the time of death detected by toxicology.



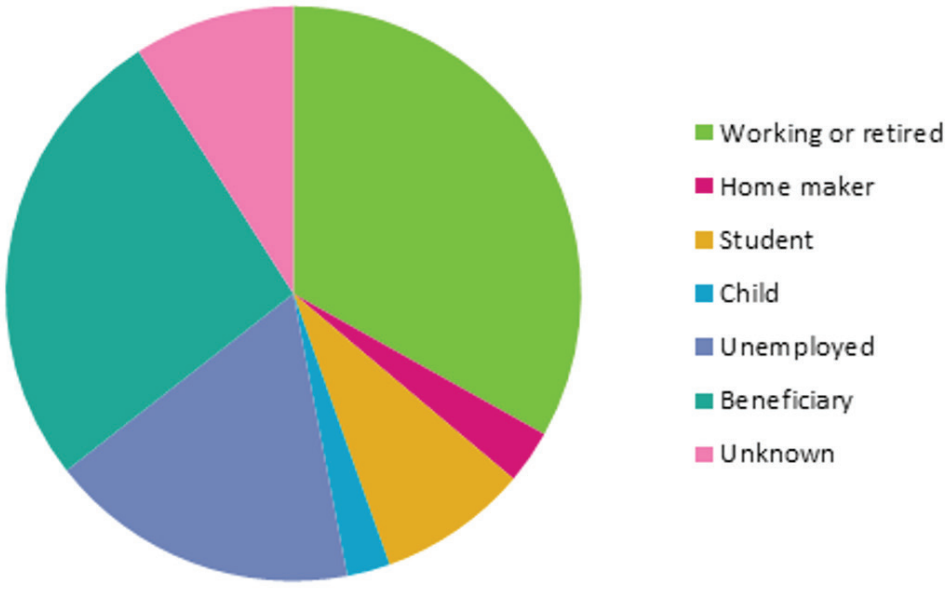
Employment status

A large proportion of patients were not employed at the time of death (73 patients, 44%); 55 patients (33%) were working or retired; 44 patients (27%) were beneficiaries; 18 patients (11%) were children or students, five patients (3%) were home makers and work status was not available for 15 patients (9%) (Figure 5).

Discussion

By definition, SUDEP is always sudden and unexpected, and it causes enormous grief to families. It is a tragic cause of early loss of life. In this study 67% of patients were under the age of 46 years at the time of their death, and 36% were younger than 31 years.

Figure 5: Employment status.



As with previous studies, we found a higher proportion of male deaths than female deaths.

Our findings are similar to those reported recently from the North American SUDEP registry (NASR).[10] The authors identified 237 definite and probable cases of SUDEP. The median age at death was 26 (range 1–70), and 62% were male. Most (93%) SUDEPs were unwitnessed; 70% occurred during apparent sleep; and 69% of patients were prone when discovered.

AED non-compliance has previously been considered a contributing factor for SUDEP. In the NASR study, only 37% of cases of SUDEP took their last dose of anti-seizure medications (ASMs).[10] We could not determine whether patients had taken their most recent dose of ASM, but the majority of patients in our study had at least one anti-epileptic detected by toxicology.

Unemployment rates in our cohort (73 patients, 44%) are far higher than in the general population. This may indicate that these patients had particularly severe epilepsy, but it also indicates serious social disadvantage in this group.

This retrospective study, based on coroners' reports, and post-mortem and toxicology reports, has confirmed that SUDEP is a major cause of premature mortality in people with epilepsy in New Zealand. However, there is much that we still do not know. For example, the type of epilepsy and the aetiology was only documented in one-third of cases in this series, and information about seizure frequency and duration of epilepsy was not consistently reported. It is likely that this study underestimated the number of patients who died due to SUDEP. A recent meta-analysis of SUDEP, noted that previous studies were likely to underestimate the true incidence of SUDEP.[6] The incidence of epilepsy in New Zealand is uncertain, but most Western countries report a prevalence of approximately 0.7%.[11] If this is true for New Zealand, we would expect approximately 33,500 people to have epilepsy. If the incidence of SUDEP in New Zealand is 1.2 per 1,000 people with epilepsy per year,[6] we would expect that approximately 40 people with epilepsy will die annually from SUDEP. However, in this study, the number of deaths per year ranged from 11 to 26. It is possible that the incidence of SUDEP is declining, but we suspect that not all cases were identified.

We are now planning to conduct a prospective study to determine the true incidence of SUDEP in New Zealand. This study is being performed in conjunction with the chief coroner, Judge Marshall, and the Neurological Association of New Zealand. The study is being funded by the Neurological Foundation of New Zealand and the Auckland Medical Research Foundation. During this study we will also gather information about possible risk factors for SUDEP. All coroners will be made aware of the study, as will forensic and coronial pathologists. We would like to hear about cases from multiple sources, and we would therefore request that all neurologists, paediatric neurologists, general physicians, paediatricians and general practitioners notify the research group of all deaths in patients with epilepsy, so that we can be sure that we identify all SUDEP cases.

We hope that this future study will provide valuable information about this tragic condition.

Competing interests:
Nil.
Acknowledgements:
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Impact of human papillomavirus vaccination on rates of abnormal cervical cytology and histology in young New Zealand women

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ABSTRACT

AIM: Determine the impact of quadrivalent human papillomavirus (HPV) vaccination on abnormal cervical cytology and histology rates in young New Zealand women.

METHODS: Retrospective population-based cohort study of women born 1990–1994, with a cervical cytology or histology recorded when aged 20–24 between 1 January 2010 and 31 December 2015. Data was obtained through linking the National Immunisation Register and National Cervical Screening Programme Register.

RESULTS: N=104,313 women (376,402 person years of follow up) were included. The incidence of high-grade cytology was lower in vaccinated women (at least one dose prior to 18 years) than in unvaccinated women (8.5 vs 11.3 per 1,000 person years [p1000py], incidence rate ratio [IRR 0.75], 95% CI 0.70, 0.80, p<.001). The incidence of high-grade histology was lower in vaccinated women than in unvaccinated women (6.0 vs 8.7 p1000py, IRR 0.69, 95% CI 0.64, 0.75, p<.001). There was no evidence of a difference in the incidence of high-grade histology between European and Māori women overall or after taking vaccination status into account.

CONCLUSIONS: Receiving at least one dose of quadrivalent HPV vaccine prior to 18 years was associated with a 25% lower incidence of high-grade cytology and 31% lower incidence of high-grade histology in women aged 20–24 years.

Cervical cancer is a largely preventable disease. In New Zealand, the commencement of the National Cervical Screening Programme (NCSP) in 1990 initially led to markedly reduced cervical cancer incidence and mortality rates; however, since 2005, rates of cervical cancer have been relatively stable (~6 per 100,000 women).[1] Higher rates of cervical cancer incidence and death among Māori remain a major concern (eg, in 2015 there was an incidence of 9.1 vs 5.4 per 100,000 women and mortality rate of 3.0 vs 1.4 per 100,000 women in Māori compared with European women).[1]

The human papillomavirus (HPV) is the main cause of cervical cell abnormalities and cervical cancer.[2–4] Cervical cancer can be caused by a number of high-risk HPV types but approximately 70% are caused by HPV 16 and 18.[5] The development of cervical cancer is preceded by high-grade intraepithelial cervical abnormalities which are the target of cervical screening programmes. Approximately 50–60% of high-grade cervical abnormalities are caused by HPV 16 and 18.[5,6] A three-dose quadrivalent HPV vaccine (containing HPV virus-like particles of types 6, 11, 16 and 18) was first licensed

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in 2006 and the efficacy of the vaccine for preventing high-grade cervical abnormalities has been demonstrated through large randomised controlled trials.[7]

In order to further reduce the incidence and mortality of cervical cancer and other HPV-related disease, a National HPV vaccination programme was commenced in New Zealand in 2008. When introduced, the quadrivalent HPV vaccine was offered (fully subsidised) to young women born in 1990 and 1991 (ie, women who were 17–18 years old). In 2009, the HPV vaccination programme was extended to girls and young women born from 1992 onwards.

As might be expected following the introduction of HPV vaccination programmes, studies performed in other jurisdictions have demonstrated reductions in HPV 16/18 infection[8–13] and cervical precancer rates.[14–16] The impact of vaccination will depend on a number of factors that vary between different populations; these include the vaccination coverage, the age of vaccination, the age specific prevalence of HPV infection, vaccination type and screening participation. It is therefore important to document and quantify the impact of HPV vaccination in different populations.

Although recent reports from the NCSP have shown a reduction in the rates of cervical abnormalities in young women, there has also been an approximate 5% reduction in screening rates in this age group.[17] The screening register does not have access to vaccination information so limited conclusions can be made regarding the impact of HPV vaccination on disease rates.

The New Zealand National Immunisation register (NIR) holds information from the HPV Immunisation Programme on dispensed doses of vaccine per person. HPV vaccination coverage in New Zealand has increased from 39% (for all three HPV doses) for the cohort born in 1990 to 67% (for all three HPV doses) for the cohort born in 2003.[18]

All cervical cytology, histology and HPV test results for New Zealand women are held in the NCSP Register unless a woman opts off. Opt off rates are very low (eg, 1–4 in 100,000 women withdrew from the NCSP register 2010–2015).[17] In 2010, the rate of high-grade histologies (cervical intraepithelial neoplasia [CIN] grade 2 or 3) in the overall population was 21.2 per 1,000 women screened (ages 20–24 years).[19] The primary objective of this audit was to determine the incidence of high-grade cytology and high-grade histology diagnoses reported in young women (aged 20–24 years) vaccinated with the quadrivalent HPV vaccine compared with HPV-unvaccinated young women. In addition, we investigated the impact of other factors such as ethnicity and number of vaccine doses on incidence of high-grade cytology and histology. Secondary objectives were to determine the incidence of low-grade cytology and low-grade histology diagnoses reported in young HPV-vaccinated women (aged 20–24 years) compared with HPV-unvaccinated young women.

Methods

The data included all women who (a) were born in 1990–1994 and (b) had had a cervical cytology or histology and associated data recorded in the NCSP Register (when aged 20–24 years) between 1 January 2010 and 31 December 2015 ('audit period').

Data from the NCSP Register during the audit period for women aged 20–24 years and HPV vaccination data from the NIR were linked using a unique national health identifier and de-identified data were provided to the research team. Prioritised ethnicity was obtained from the NCSP register and was coded using Health Information Standards Organisation (HISO) standards for output of ethnicity data.[20]

The women were split into three groups:

- Vaccinated prior to 18 years (ie, at least one dose of the HPV vaccine prior to 18 years)
- Late vaccinated (ie, all doses of the HPV vaccine at 18 years or older)
- Unvaccinated (ie, no HPV vaccination at any age)

Low-grade cytology was defined as atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL). High-grade cytology was defined as atypical squamous cells—cannot exclude high-grade (ASC-H) or worse.

Low-grade histology was defined as HPV effect, atypia, CIN not otherwise specified or CIN1. High-grade histology was defined as CIN2 or worse or glandular lesion.

Incidence of high- and low-grade cytology or histology per 1,000 person years was calculated for each group. The time that women were considered at risk of an event is from age 20 years until the earliest of the following:

- First occurrence of the outcome being assessed (eg, CIN2 histology), or
- age 25 years,
- end of audit period (31 December 2015).

Power analyses

Previous research has reported a wide range for HPV vaccine effectiveness depending on the study population with studies reporting a decrease in high-grade cervical abnormalities of between 26–80% in women who have had at least one dose of the HPV vaccine.[14,21]

In 2011, 150 per 1,000 cervical cytology samples showed low-grade abnormalities and 27 per 1,000 showed high-grade abnormalities in women aged 20–24 years.[19] Taking the lowest estimated rate reduction of 26%, sample sizes of 10,063 in each group would provide 90% power for observing a change in the rate of high-grade cervical cell abnormalities of at least 26% (p=.05).

In 2011, 38.3 per 1,000 women screened were diagnosed with histologically-confirmed CIN in women ages 20–24 years (14.7 per 1,000 for CIN1 and 23.6 per 1,000 for CIN2 or worse).[19] Sample sizes of 6,962 in each group would provide 90% power for observing a change in the rate of CIN of at least 26% (p=.05). If considering only high-grade CIN (CIN2 or worse), sample sizes of 11,547 in each group would provide 90% power for observing a change in the rate of CIN2 or worse of at least 26% (p=.05).

Primary hypotheses

Compared with unvaccinated women, women vaccinated prior to 18 years will have lower rates of (a) high-grade cytology and (b) high-grade histology.

The effectiveness of vaccination for lowering high-grade cytology and histology incidence rates will be dose dependent.

The effectiveness of vaccination for lowering high-grade cytology and histology incidence rates will be impacted by the age at which the first dose of the HPV vaccine was received (ie, prior to 18 vs after 18 years).

High-grade cytology and histology incidence rates will be impacted by ethnicity.

Secondary hypotheses

Compared with unvaccinated women, women vaccinated prior to 18 years will have lower rates of (a) low-grade cytology and (b) low-grade histology.

Statistical analysis

A two-sample test of proportions was used to compare proportions using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). To compare group differences in rates of high-grade cytology and histology, incidence rate ratio (IRR) analyses were implemented in R version 3.5.2 (R Core Team. 2013. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). Significance level was set at alpha =.05. Ninety-five percent confidence intervals are reported.

This audit protocol was approved by the New Zealand Health and Disability Ethics Committee (Ethics ref: 14/STH/141, 29 September 2014. 14/STH/141/AM02 Amendment to Protocol approved 22 February 2016) and had site authorisation.

Results

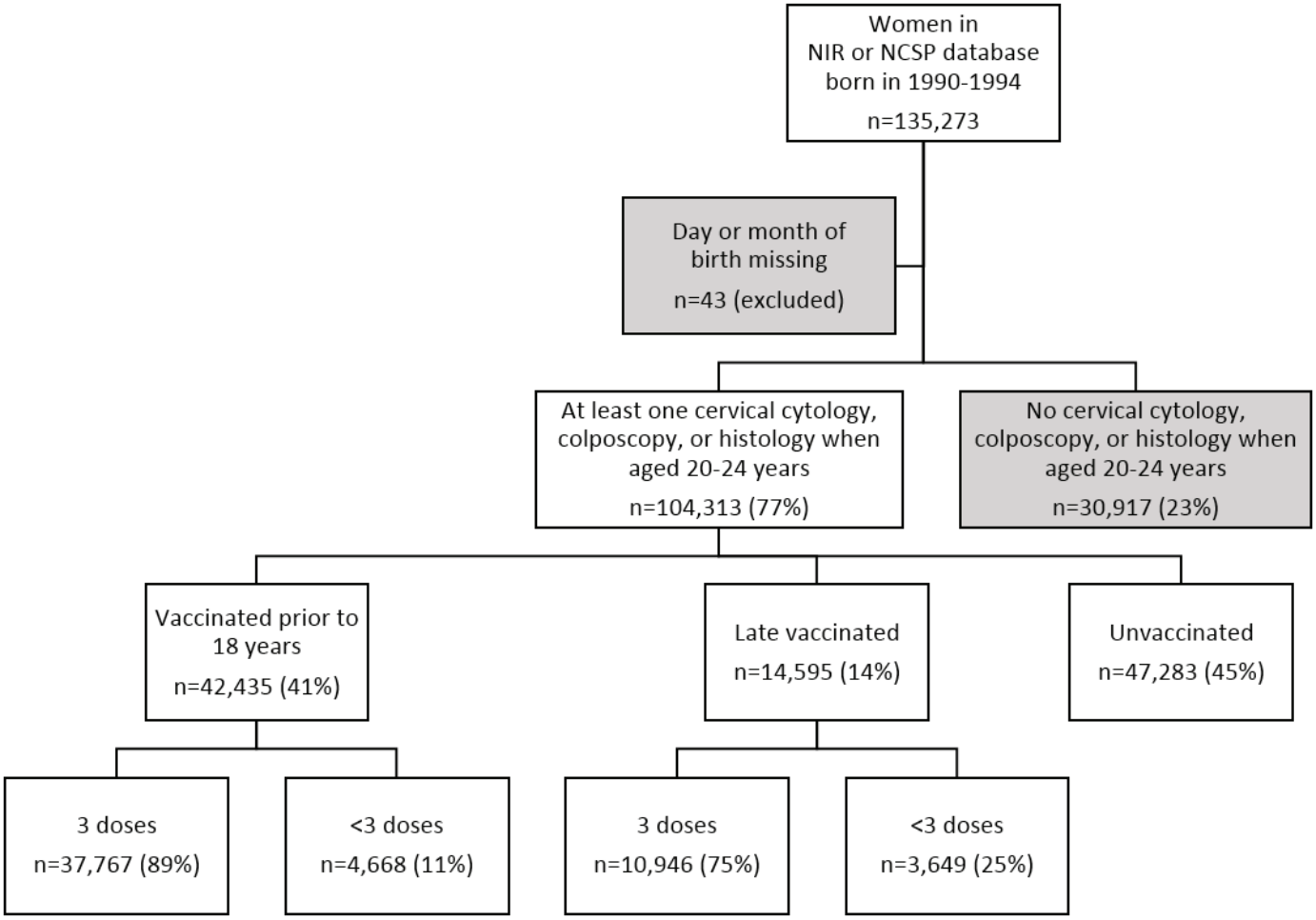
The combined NIR and NCSP dataset contained data for n=135,273 women born 1990–1994. Day or month of birth was missing in the dataset for n=43 women and these women were excluded. Of the remaining women, n=104,313 (77%) women had at least one cervical cytology sample, colposcopy or histology recorded when aged 20–24 years (see Figure 1).

Most women identified as New Zealand European or other European (64%). The remaining women identified as Māori (18%), Pacific (7%), Asian (7%) or other/not stated (4%).

N=42,435 (41%) women were vaccinated prior to 18 years, n=14,595 (14%) women were late vaccinated and n=47,283 (45%) women were unvaccinated.

A higher proportion of the women vaccinated prior to 18 years received all three HPV vaccine doses compared with the late vaccinated women (89% vs 75%, two-sample test of proportions z=41.3, p<.001, 95% CI 13, 15% difference).

Figure 1: Study analysis flow chart.



The mean age of vaccination decreased across birth cohorts (including both women vaccinated prior to 18 years and late vaccinated women) as most vaccinated women in these birth cohorts were vaccinated in 2008 or 2009 (Figure 2). Figure 2 includes the proportion of women who were not vaccinated and thus had no age of vaccination.

Incidence rate ratio (IRR) analyses included 376,402 person years of follow up.

The incidence of high-grade cytology was lower in women vaccinated prior to 18 years than in unvaccinated women (8.5 vs 11.3 per 1,000 person years [p1000py], IRR 0.75, 95% CI 0.70, 0.80, p<.001). The incidence of high-grade cytology was also lower in late vaccinated women than in unvaccinated women (9.7 vs 11.3 p1000py, IRR 0.86, 95% CI 0.79, 0.94, p<.001).

The incidence of high-grade histology was lower in women vaccinated prior to 18 years than in unvaccinated women (6.0 vs 8.7 p1000py, IRR 0.69, 95% CI 0.64, 0.75, p<.001). However, there was no difference in the incidence of high-grade histology in late vaccinated vs unvaccinated women (8.1 vs 8.7 p1000py, IRR 0.93, 95% CI 0.84, 1.02, p=.122) (see Figure 3).

When taking into account the number of HPV vaccine doses, the incidence of high-grade histology was lower in women who had all three doses (with at least one dose prior to 18 years) than in unvaccinated women (5.8 vs 8.7 p1000py, IRR 0.66, 95% CI 0.60, 0.72, p<.001). There was weak evidence for a lower incidence of high-grade histology in women who had had two vaccine doses (with at least one dose prior

Figure 2: Distribution of age of first dose of the vaccine (including both women vaccinated prior to 18 years and late vaccinated women) by birth cohort. The proportion of women born each year but not vaccinated and thus having no age of vaccination is shown by the bars labelled 'Not vaccinated'.

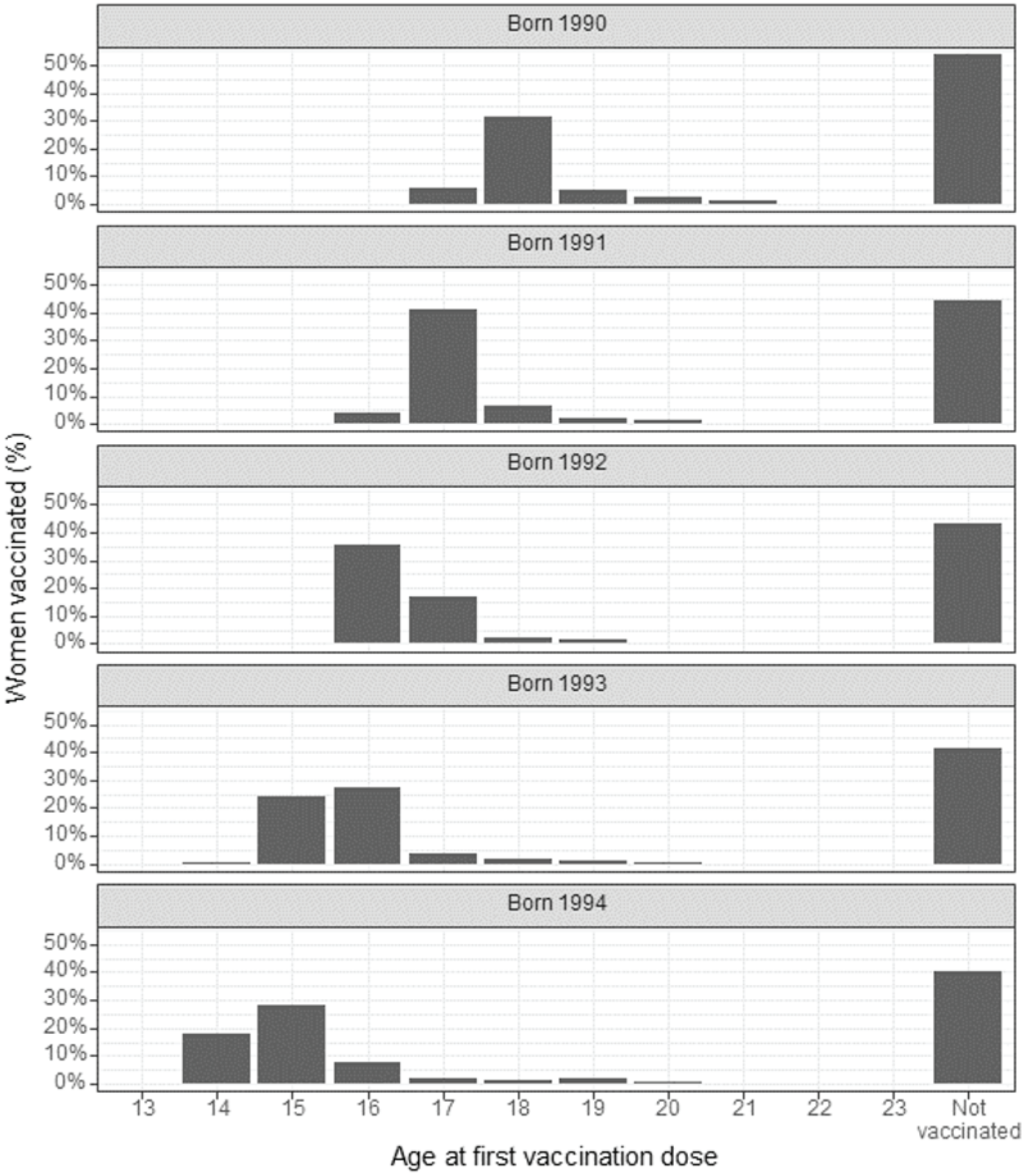


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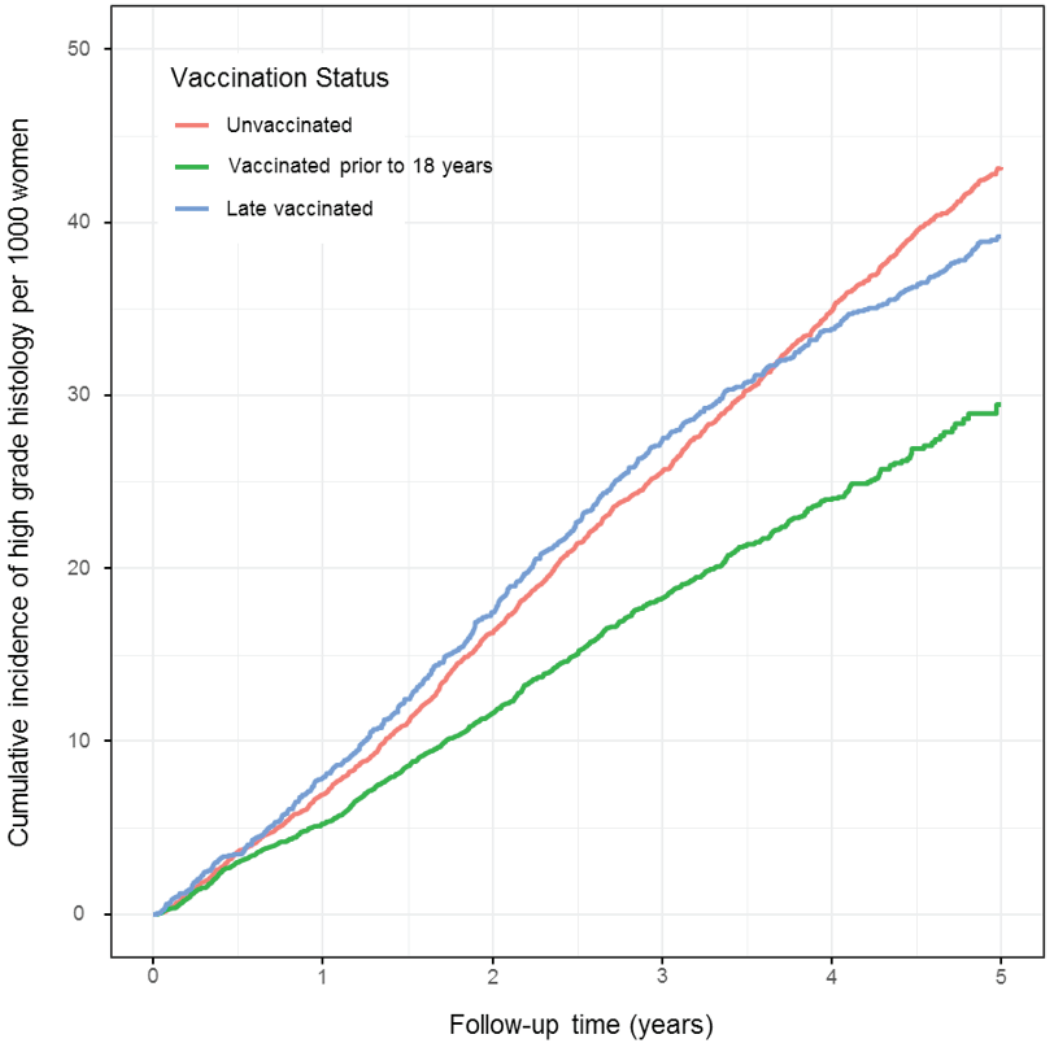
Figure 3: Cumulative incidence of high-grade histology in women aged 20–24 years by HPV vaccination status.



to 18 years) compared with unvaccinated women (7.0 vs 8.7 p1000py, IRR 0.81, 95% CI 0.63, 1.03, p=.07). However, compared to unvaccinated women, there was no evidence of a difference in the incidence of high-grade histology in women who had had only one dose (prior to 18 years) (9.7 vs 8.7 p1000py, IRR 1.1, 95% CI 0.85, 1.45, p=.43) (see Figure 4).

Proportions of women who were vaccinated prior to 18 years, late vaccinated or unvaccinated by ethnicity are given in Table 1. In screened women, Māori and Asian women were less likely to be vaccinated prior to 18 years than European women (Māori women 38% vs 42%, two-sample test of proportions z=9.67, p<.001, 95% CI 3, 5% difference; Asian women 33% vs 42%, two-sample test of proportions z=14.57, p<.001, 95% CI 8, 10% difference).

There was no evidence of a difference in the incidence of high-grade histology between screened European and Māori women overall (Cox proportional hazard ratio 0.96, 95% CI 0.85, 1.06, p=.40) or after taking vaccination status into account (Cox proportional hazard ratio 0.93, 95% CI 0.83, 1.03, p=.17). However, all other ethnicities had lower rates of high-grade histology (Cox proportional hazard ratio [range] 0.27–0.39, p<.001).

Figure 5 shows the incidence of high-grade histology over five years in women grouped by ethnicity.

Table 1: Proportions of screened women who were vaccinated prior to 18 years, late vaccinated, or unvaccinated by ethnicity.

Ethnicity	Vaccinated prior to 18 years	Late vaccinated	Unvaccinated	Total
European	28,309 (42%)	9,749 (15%)	29,102 (43%)	67,160
Māori	7,082 (38%)	2,435 (13%)	9,021 (48%)	18,538
Pacific	2,952 (41%)	957 (13%)	3,243(45%)	7,152
Asian	2,302 (33%)	859 (12%)	3,791 (55%)	6,952
Other or not stated	1,790 (40%)	595 (13%)	2,126 (47%)	4,511
Total	42,435 (41%)	14,595 (14%)	47,283 (45%)	104,313

There was no difference in the incidence of low-grade cytology in women vaccinated prior to 18 years compared with unvaccinated women (66.6 vs 65.0 p1000py, IRR 1.03, 95% CI 0.99, 1.06, p=.10) (Table 2). However, the incidence of low-grade cytology was lower in late vaccinated women than in unvaccinated women (61.2 vs 65.0 p1000py, IRR 0.94, 95% CI 0.91, 0.98, p=.002).

The incidence of low-grade histology was lower in women vaccinated prior to 18 years than in unvaccinated women (13.3 vs 15.7 p1000py, IRR 0.85, 95% CI 0.80, 0.90, p<.001). However, there was only limited evidence of any difference in the incidence of low-grade histology in late vaccinated vs unvaccinated women (16.7 vs 15.7 p1000py, IRR 1.07, 95% CI 0.99, 1.14, p=.08).

Figure 4: Cumulative incidence of high-grade histology in women aged 20–24 years by HPV vaccine dose (with at least one dose prior to 18 years in Dose 1–3 groups).

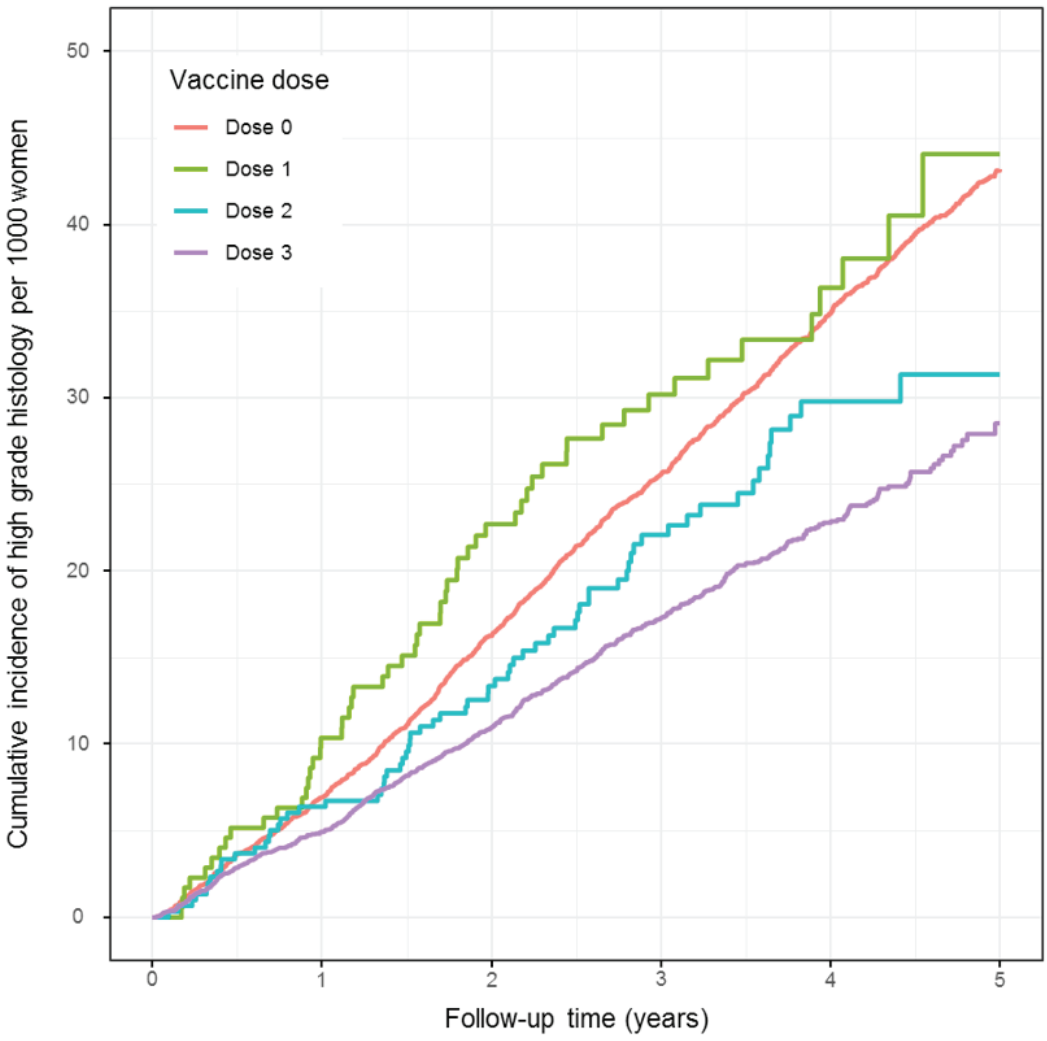


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Figure 5: Cumulative incidence of high-grade histology in women aged 20–24 years by ethnicity.

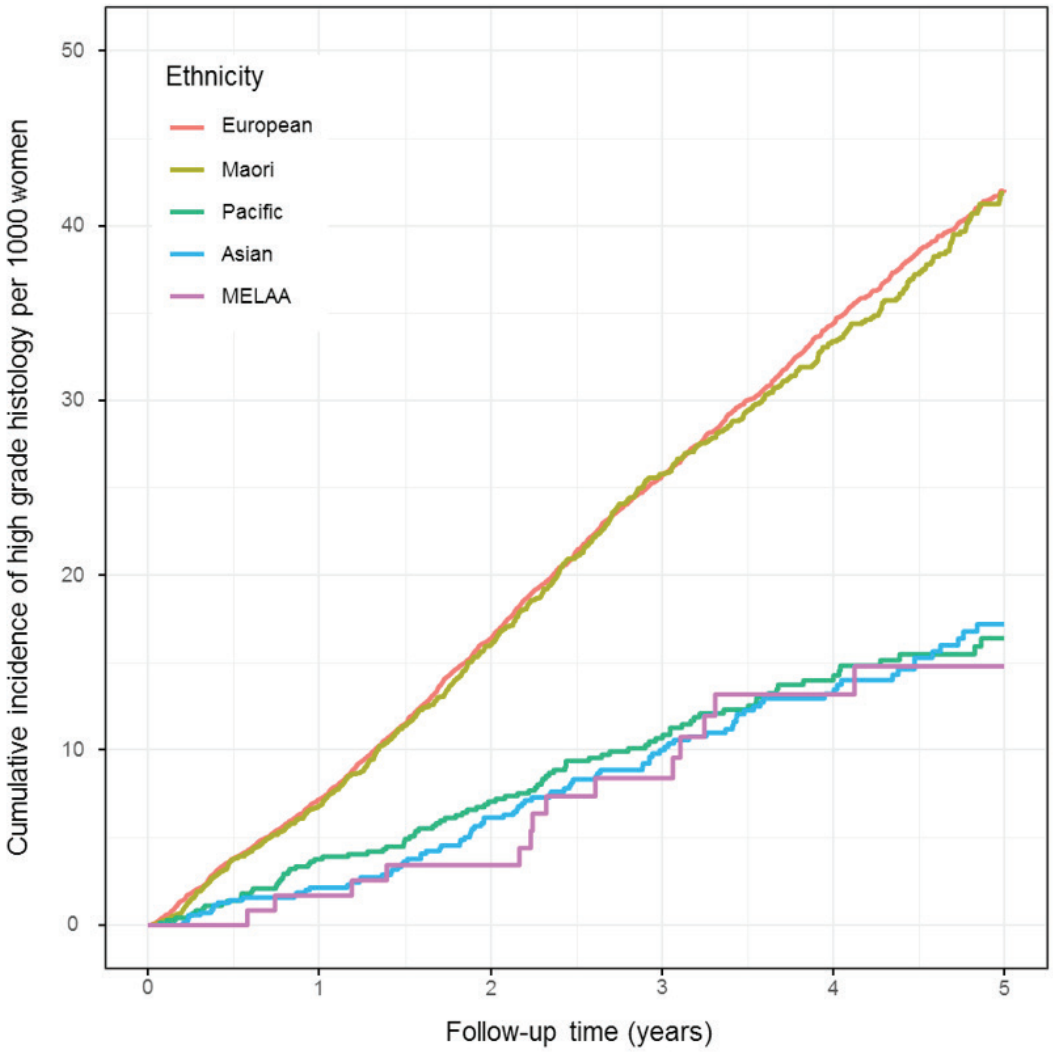

Table 2: Incidence of high-grade and low-grade cytology and histology by vaccination status.

	High-grade					Low-grade				
	Person-years of observation	N	Incidence per 1,000 person years (95% CI)	Incident rate ratio (95% CI)	p	Person-years of observation	N	Incidence per 1,000 person years (95% CI)	Incident rate ratio (95% CI)	p
Cytology										
Unvaccinated	174,742	1,981	11.3 (10.8, 11.8)	1.00		155,076	10,074	65.0 (63.7, 66.2)	1.00	
Late vaccinated	65,761	640	9.7 (9.0, 10.5)	0.86 (0.79, 0.94)	<0.001	56,727	3,470	61.2 (59.2, 63.2)	0.94 (0.91, 0.98)	0.002
Vaccinated prior to 18 years	133,895	1,135	8.5 (8.0, 9.0)	0.75 (0.70, 0.80)	<0.001	119,179	7,937	66.6 (65.1, 68.1)	1.03 (0.99, 1.06)	0.10
Histology										
Unvaccinated	175,748	1,537	8.7 (8.3, 9.2)	1.00		173,379	2,718	15.7 (15.1, 16.3)	1.00	
Late vaccinated	66,091	535	8.1 (7.4, 8.8)	0.93 (0.84, 1.02)	0.12	64,757	1,082	16.7 (15.7, 17.7)	1.07 (0.99, 1.14)	0.08
Vaccinated prior to 18 years	134,563	813	6.0 (5.6, 6.5)	0.69 (0.64, 0.75)	<0.001	132,909	1,768	13.3 (12.7, 13.9)	0.85 (0.80, 0.90)	<0.001

Discussion

Main findings

Compared with unvaccinated women, women who had at least one dose of the quadrivalent HPV vaccine prior to age 18 years had a 25% lower incidence of high-grade cervical cytology and 31% lower incidence of high-grade cervical histology when they were aged 20–24 years. For women vaccinated after 18 years, there was a 14% lower incidence of high-grade cytology compared with unvaccinated women; however, there was only a small relative decrease in high-grade histology rates within the time frame of the study.

Māori and Asian women in our cohort of screened women were less likely to be vaccinated prior to 18 years than European women while Pacific women had similar vaccination coverage to European women. There was no evidence of a difference in the incidence of high-grade histology between European and Māori women, either overall or after taking vaccination status into account. In contrast, Pacific and Asian women had lower rates of high-grade histology than European women.

We classified women as vaccinated prior to 18 years if they had had at least one dose of the HPV vaccine prior to age 18. However, most vaccinated women (89%) did receive all three doses and there was no substantial difference in the results if we excluded women who had had fewer than three doses.

Strengths and limitations

Missing data

Data was included from all women who consented to have their data held in either the NCSP or NIR. A small number of women may have consented for their data to be held on one register but not on the other, which could lead to incorrect assumptions being made about a woman (eg, cervical cytology history but no evidence of HPV vaccination [despite having received the HPV vaccine]). However, the number of women who would have been eligible for the audit but opted off either register is likely to be very small.[17]

During the audit period, 3–6% of the New Zealand population aged 20–25 years were recent immigrants (arrived within the past 12 months).[22] Some young immigrants may have been vaccinated prior to their arrival in New Zealand, but not recorded as vaccinated on the NIR. If a large enough number of young HPV-vaccinated immigrant women were included in NCSP register data and misclassified as unvaccinated, this could lead to an underestimate of the impact of vaccination on cervical cell abnormalities.

Our analyses took an inclusive approach to identifying Māori women (ie, the analyses included as Māori any woman who self-identified as Māori in any ethnicity response). However, ethnicity recording is not always accurate and there will inevitably be women who identify as Māori but who are not recorded as such. In addition, while screening coverage for Māori women (of all ages) is improving (increasing by about 8% between 2010 and 2017), coverage continues to be 20–25% lower than in non-Māori.[17] Thus, this study may underestimate the real incidence of high-grade abnormalities in young Māori women.

The potentially largest proportion of missing data will be from women who had neither an HPV vaccination nor a smear (but otherwise would have met the inclusion criteria for the study). These women would not be recorded in either register and, thus, were not included in the audit. While, the proportion of eligible women and girls receiving the HPV vaccine is slowly increasing in New Zealand, since the programme commenced in 2008, an estimated 39–56% of eligible women have not received the HPV vaccine.[18] In addition, only 52% of eligible women 20–24 years were screened in the three years prior to 31 December 2015.[23]

A factor that may impact our results is whether screening participation is different for those women who have undergone HPV vaccination. The data around this is conflicting.[24] HPV vaccination was associated with higher rates of screening participation in the US,[25] UK,[26,27] and Sweden[28] but decreased screening participation in Australia.[29] Unfortunately, we do not currently have the data to investigate this factor in young New Zealand women.

Exposure to HPV 16 or 18

Our analysis was limited to women born 1990–1994, as only women born in 1990 or later were eligible for the HPV vaccine and only those born in or before 1994 were

old enough to have been aged 20–24 years during the audit period. Women in our study who were born in 1990 had the most follow up data (ie, five years) as they were aged 20–24 years throughout the entire audit period. In contrast, women born in 1994 only turned 20 years in 2014, and thus, were limited to 1–2 years follow-up. The women with the most follow-up data (ie, those born in 1990–1991) were primarily 17 or 18 years old when vaccinated, meaning that a proportion of those women may have already been exposed to HPV16/18 prior to vaccination.

Women vaccinated over the age of 18 appeared to have limited benefit, however we cannot exclude a benefit for these women with longer-term follow-up as, although disease from existing infections was not prevented, further new infections will be.

Mean age of HPV vaccination decreased across each birth cohort in this study. Decreasing age of vaccination is likely to be associated with decreasing risk of pre-vaccination exposure to HPV. Thus, the impact of vaccination may be greater in later birth cohorts in this study and in later birth cohorts not evaluated in this study.

The herd effect is an important confounding factor to consider. Once there are a large number of vaccinated women within the population, the prevalence and transmission of vaccine HPV types will decrease. This herd effect offers protection to unvaccinated women. We have recently shown a substantial decrease in the proportion of unvaccinated young women with CIN2 who are HPV16/18 positive (66% in 2013 vs 17% in 2016).[13] Decreased HPV16/18 prevalence in unvaccinated young women has also been reported in the Australia[10,11] and Scotland.[12] The herd effect will be enhanced by the inclusion of HPV vaccination for males in New Zealand from 2017.

As age at first vaccination is influenced by birth cohort, and if incidence rates are dropping over time (due to herd effect), then those born earlier (and thus vaccinated later) will also be at higher risk of exposure (regardless of vaccination status). Factors such as a decreased mean age of vaccination and the introduction of the nonavalent HPV vaccination may lead to an even greater impact of the HPV vaccine on rates of high-grade cervical cell abnormalities in vaccinated women over time. There have also been increased rates of HPV vaccination in New Zealand, and coupled with the inclusion of HPV vaccination for males in New Zealand in 2017, both these factors may enhance the herd effect in New Zealand.

HPV vaccine effectiveness

The quadrivalent HPV vaccine has been demonstrated to be almost 100% effective in preventing HPV 16- or 18-related cervical abnormalities. In this study, women vaccinated prior to 18 years showed only a 31% reduction in high-grade abnormalities and little consistent reduction in low-grade abnormalities. This can be expected because while ~50–60% of high grade abnormalities in an unvaccinated population are associated with HPV 16 or 18,[5,6] a recent study of New Zealand women found that only 22% of high-grade abnormalities were positive for *only* HPV 16 and/or 18, with the remainder associated other high-risk HPV types.[6] Low-grade abnormalities are less likely to be associated with HPV 16 or 18 and therefore the impact of vaccination on the incidence of these abnormalities will be substantially less.

A US population-based study was undertaken following the 2007 introduction of the HPV vaccine. They showed an 11% annual decrease in CIN2 and a 41% annual decrease in CIN3 between 2007 and 2014 in adolescent women (aged 15–19 years).[16] They also noted a 6% annual decrease in CIN2 in women (aged 20–24 years) but no decrease in CIN3 in this age group. The individual HPV vaccination status of women was not evaluated.

An Australian study considered HPV vaccination status and found that compared with unvaccinated women, at least one dose of quadrivalent HPV vaccine was 26% effective against high-grade cervical abnormalities in young women attending their first cervical cytology screen, while the vaccine was 46% effective in fully vaccinated young women.[14] Similarly, a Scottish study observed a 50% decrease in CIN2 and 55% decrease in CIN3 among fully vaccinated women at their first cervical screen at age 20 or 21.[30] Therefore, the most substantial effects were seen in studies reporting decreases in high-grade cervical abnormalities in young fully-vaccinated women attending their first cervical cytology screen.

Conclusion

HPV vaccination has led to a significant reduction in high-grade abnormalities in women vaccinated prior to 18 years in New Zealand, which in turn can be expected to impact on rates of cervical cancer as this cohort ages. In this cohort of screened women, Māori were less likely to be vaccinated but, if vaccinated, vaccination offered similar protection for Māori and non-Māori women. As time progresses, we can expect the decreasing age of vaccination and higher coverage to increase the impact of vaccination and this will be further amplified by the herd effect. In 2017, the nonavalent vaccination became available, fully-subsidised, in New Zealand for both boys and girls. This vaccine will provide protection against the majority of disease-causing HPV types and vaccination of boys will compound the herd effect. The vaccination programme offers opportunities to reduce the incidence of, and inequities from, cervical cancer. This study also demonstrates that both HPV-vaccinated and unvaccinated women develop high-grade cervical disease and this underlines the need for cervical screening in both HPV-vaccinated and unvaccinated women and for the impact of HPV vaccination to continue to be monitored.

Competing interests:
Author CI reports a travel grant from Seqirus Ltd to present at a scientific meeting during the conduct of the study. Author MS is the Clinical Lead for Pathology with the National Cervical Screening Programme in the Ministry of Health in New Zealand. Author BL reports personal fees and non-financial support from CSL Biotherapies (NZ) Ltd and, outside the submitted work, she sits on the Pfizer board for women's health menopause.

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Career outcomes of students of an intercalated MBChB/PhD: experience from New Zealand

Yassar Alamri, Tim J Wilkinson

ABSTRACT

BACKGROUND: Medium- and long-term outcomes of an intercalated medical/PhD degree are less well-characterised for non-North American programmes than North American ones. We report on the career choices and academic accomplishments of MBChB/PhD students at one university 17 years after the programme's introduction.

METHODS: A list of all past and current intercalating students at the University of Otago was obtained. Participants were asked for details of their current position, scientific publications and career plans, as well as their opinions on the intercalated programme.

RESULTS: A total of 25 students (of whom eight were current students) had enrolled in the intercalated programme between 2001 and 2018. Ten students (40%) were women. The rate of enrolment remained relatively steady through the years at 1.4±1.0 students/year. The rate of completion was high at 88.2% (15/17). The congruence between students' PhD research topic and clinical specialty of interest was 52.4%. Most students (72%) published their research findings in local and international journals.

CONCLUSIONS: The programme is considered worthwhile by our students, most of whom continue (at various capacities) in academic work and produce a significant research output, although potentially in a field that is different to their PhD research.

Warnings of a globally declining cohort of physician-scientists have appeared in the literature over 15 years ago.[1] For example, the number of physician-scientists in British universities dropped by 12% between 1996 and 2001;[2] similar trends have been observed in other countries, including the US and Sweden.[3] Part of the solution has been the introduction of intercalated medical and research degrees by tertiary institutions. One of the aims of such programmes is the production of clinician-scientists who are well-established in research from an early stage and who (it is hoped) might continue on an academic/research-intense track. We have previously reviewed the various physician-scientist programmes around the world.[4] Among the unaddressed issues were medium- and long-term outcomes of such combined programmes—especially from outside North America.[4]

At the University of Otago, the MBChB/PhD programme commenced in 2001. It is open to "the most able of [Otago] medical undergraduates".[5] Applicants are required to have had prior research experience, usually in the form of BMedSc(Hons) degree. The PhD component of the intercalated degree is generally completed in one of two ways. The first option entails two research years, followed by research time interspersed with MBChB time (this choice is often used by students who decide to intercalate after their third medical year). The second option is three years of full-time research (students intercalating after their fifth medical year often opt for this). Once admitted into the intercalated programme, the student's clinical and academic progress is regularly reviewed by both the Academic Board of the Otago Medical School and the Graduate Research Committee.[5]

Since its introduction upwards of 17 years ago, the outcomes of Otago's MBChB/PhD programme, in terms of student characteristics and career/academic achievements, have not been ascertained. Therefore, the aims of the present study were to evaluate career choices and academic accomplishments of students of the intercalated programme, and to compare such parameters with those of other intercalated programmes internationally.

Methods

Study setting

A list of all past and current intercalating students was obtained from the Dean's Office, Otago Medical School, Dunedin, New Zealand. Potential participants were invited to complete an online survey via email. Two additional reminder emails requesting participation were sent in six-week intervals. This study was approved by the University of Otago Human Ethics Committee (reference D18/019).

Survey details

Participants were asked for details of their current position, scientific publications and career plans. In addition, they were asked for their opinion about the intercalated programme by rating statements on a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = neutral; 4 = agree; 5 = strongly agree). Each participant was assigned a unique code in order to preserve anonymity and prevent data duplication.

Statistical analysis

Descriptive statistics were used to analyse the data (expressed as means ± standard deviations, or medians and ranges). All analyses were performed using SPSS Statistics® software package (version 22.0.0.0).

Results

Student characteristics

Between 2001 and 2018, a total of 3,605 medical students graduated from the University of Otago. Over the same period, 25 students had enrolled in the intercalated programme. Of those, 22 responded to the survey (response rate 88%). Ten students (10/25; 40%) were women. Three (12%) were international students, with the remainder being New Zealand citizens or residents.

Admissions and graduations

The rate of enrolment remained relatively steady through the years at 1.4 ± 1.0 students/year. All but two students (23/25; 92%) entered medical school after high school; a similar majority (23/25; 92%) enrolled in the PhD degree after completion of the third year of the MBChB degree (the other two students intercalated after completion of the fifth year).

At the time of the study, eight students were in the research phase of their intercalated degree. Of the remaining 17, only two students withdrew from the programme, giving an attrition rate of 11.8%. The median total duration (full-time and part-time) from enrolment to thesis submission was 4.7 years (range, 3.2–10 years). It was difficult to ascertain an accurate full-time equivalent duration of PhD study in our students as some had alternated between full-time and part-time especially near thesis submission.

Research topics and outcomes

Topics of PhD research varied widely; the most common supervising departments were: surgery and anaesthesia (n=7), medicine (n=5), pathology (n=3) and anatomy (n=3). The type of research was almost equally divided between basic science (8/18; 44.4%) and clinical (10/18; 55.6%) research. Most studies (72%) were published in local and international journals. The median number of all publications per individual was 3 (range, 0–62).

Postgraduate careers

Of the 15 students who had graduated from the MBChB/PhD programme, two had completed, and 10 were still undertaking, medical specialty training. The remaining three alumni elected to continue on the research track: two as post-doctoral fellows and the third as a research associate professor. All students remain in New Zealand except four: three are in Australia and one in Canada.

For 21 students whose long-term specialty of choice was known (as expressed by the student or noted from specialty training choice), the congruence between their PhD research topic (eg, Parkinson's disease research) and specialty of interest (eg, choosing neurology or neurosurgery) was 52.4%. Of the 22 students who responded to the survey, three (13.6%) wanted future

Table 1: Summary of responses to survey questions on student attitudes towards the intercalated MBChB/PhD programme at the University of Otago.

Statement	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Mean (SD)
The MBChB/PhD programme is clearly advertised as an option for interested students	5 (22.7%)	7 (31.8%)	5 (22.7%)	3 (13.6%)	2 (9.1%)	2.8±1.3
The MBChB/PhD at Otago University is well set-up	2 (9.1%)	10 (45.5%)	3 (13.6%)	5 (22.7%)	2 (9.1%)	2.9±1.3
The allotted duration for research (PhD component) is adequate	0 (0%)	8 (36.4%)	7 (31.8%)	3 (13.6%)	4 (18.2%)	3.2±1.2
The support (financial, intellectual/supervision, integrating with MBChB component) from the University is adequate	1 (4.5%)	6 (27.3%)	7 (31.8%)	6 (27.3%)	2 (9.1%)	2.9±1.1
The university should continue to offer this intercalated MBChB/PhD programme	0 (0%)	2 (9.1%)	1 (4.5%)	7 (31.8%)	12 (54.5%)	4.4±1.0
If given the chance, I would do it again	1 (4.5%)	3 (13.6%)	4 (18.2%)	7 (31.8%)	7 (31.8%)	3.9±1.2

involvement in research to make up <25% of their time, 12 (54.5%) for 25–50% of their time, five (22.7%) for 50–75% of their time and two (9.1%) for >75% of their time.

Attitudes towards the intercalated programme

Agreement was relatively high among the 22 respondents that the University should continue to offer the intercalated programme, and most agreed that they would do it again. Responses in general were more neutral or unfavourable with regards to the current programme's set-up and support available for students. The results are summarised in Table 1.

Discussion

Overall remarks

In the present study, we report the career choices and academic accomplishments of students of Otago's MBChB/PhD intercalated programme. As far as the authors are aware, the combined MBChB/PhD degree at the University of Otago is one of the longest continuously running such programmes in Australasia. Hence, our findings may be of interest to institutions contemplating establishing such intercalated programmes. We compare the outcomes presented in the present study with those of other programmes in Table 2.

Despite a relatively steady rate of enrolment, the total number of current and previous MBChB/PhD students remains low compared with other combined programmes. For example, the University of Sydney enrolled 31 MBBS/PhD students between 1998 and 2003 before the University discontinued the programme in 2014 after changing its primary medical degree to 'MD'.[6] New Zealand medical students were also shown to intercalate (including non-PhD research degrees) less frequently than their counterparts elsewhere. Park and colleagues reported on the

Table 2: Comparing outcomes of three medical/PhD intercalated programmes.

	University of Otago	University of Cambridge[10]	Medical Scientist Training Programme[14]
Location	New Zealand	England	24 centres in the US
Established	2001	1989	Various (as early as 1964)
Cohort size* (n)	25	153	5,969
Proportion of female students	40%	32.7%	37%
Completion rate	88.2%	91.6%	90%
Estimated proportion expressing plans for significant future research involvement	86.4% (≥25% full-time equivalent)	90%	77.3%

*At the time of reporting.

low uptake of intercalated research degrees by medical students at the University of Auckland.[7] Myriad reasons were proposed, including financial, organisational and the selection process among others. We are in the process of collecting qualitative data from MBChB/PhD students and their supervisors exploring the reasons behind the observed low uptake.

The proportion of female students in our cohort (40%), on the other hand, is very encouraging as it is higher than most medical/PhD cohorts reported elsewhere (typically between 25–35%).[6] The PhD completion rate in our cohort (15/17; 88.2%) is almost identical to that of other health sciences-related PhD (88%) at the University of Otago, and is comparatively very high with respect to many other tertiary institutions.[8]

Academic achievements

Our students have been very successful in publishing in peer-reviewed journals. It is expected that students who graduated several years ago and chose an academic career would produce more publications than current students or those who chose research-light careers. The overall rate of publications (72%) is substantially higher than our previous report of published BMedSc(Hons) students at Otago (32.7%).[9]. Data on publication rates of other medical/PhD programmes are relatively scarce: "most" of the University of Cambridge MB/PhD students published their findings[10] while 93% of Swiss MD/PhD students were co-authors in at least one peer-reviewed article.[11]

Postgraduate careers

The retention rate (ie, remaining within New Zealand) of the students was high (21/25, 84%). In 2016, the Medical Council of New Zealand reported the mean retention rate of New Zealand graduates 10 years after graduation to be 65.7%,[12] although this figure includes both intercalating and non-intercalating medical graduates.

Most MBChB/PhD students (17/22, 77.3%) wanted to continue to be heavily involved in research (≥25% full-time equivalent). Only half of our students had matching research field and specialty choice. Although the reason(s) underlying this are unclear, we propose an explanation: whereas the specialty of choice is likely significantly driven by personal interest,[13] the area of research is limited by the advertised list of proposed topics from supervisors. Hence, we suspect students who have a strong personal interest in one specialty (eg, orthopaedic surgery) will choose corresponding research topics (eg, radiological evaluation of the human pelvic anatomy) should one be available. For those who have no personal interest in any one specialty, they may choose a research topic that interests them at the time, with the choice of future specialty left until completion of the clinical component of their MBChB degree and/or working as a doctor in the future. This is because a PhD may be viewed as an "apprenticeship" into research, and the skills obtained are not necessarily restricted to the investigated research topic.

Data on specialty choice of medical/PhD students elsewhere are heterogeneous and indicate a complex interaction of academic (eg, focus of degree-awarding institution) and non-academic (eg, amount of debt and perceived specialty-earning potential) factors.[14] Relatively little data exist on the direct comparison of a student's PhD research topic to their clinical specialty of choice. In an analysis of 24 MD/PhD programmes in the US, the majority of students had completed their PhD research in laboratory-based biology/medicine, and most students decided to train in internal medicine, neurology, paediatrics or pathology—without an apparent correlation between the two.[15] The authors speculated that these specialties have historically provided trainees with protected research time compared with other specialties.[15] Similarly, most graduates of University College London's intercalated programme were reported to choose a career in internal medicine without reference to their PhD research topic.[16]

Attitudes towards the programme

Overall, the students were satisfied with and supportive of the intercalated programme—although we realise this view could be biased as it is of individuals who have heavily invested time, psychological and cognitive resources. More students than not agreed that the programme was under-advertised as an option for interested medical students, and several were hopeful of better execution of the combined degree—both in terms of structural integration with the MBChB degree, as well as increased supports (financial and supervisory) for the students.

There are several potential reasons for the reported difficulties by students. Given the small number of students who had enrolled in the combined-degree programme, it is possible that administrative staff are not as cognisant of such difficulties experienced by students. However, the programme may be expected to improve over time as problems are identified and resolved. One of the benefits of surveying the programme's students is the identification of limitations and ways to rectify them. Similar problems have been reported from even more established intercalated programmes. For example, up to 44% of MD/PhD graduates of Swiss universities reported suboptimal supervisory mentoring during their course of study/research.[11] In addition, financial constraints remain an obstacle for most intercalated medical/PhD programmes.[3] Given the apparent need to elaborate on these responses about the programme, a future qualitative study of intercalating students and their supervisors has been planned.

Limitations

There are a number of limitations to our study that warrant consideration. The results presented originate from a single institution in New Zealand, and may therefore not be generalisable. In addition, while every effort was made to obtain a 100% response rate, this was not achieved. However, the response rate in this study far exceeds response rates (~35–45%) typical of graduate medical education research.[17] Finally, a significant number of the intercalating students were current students (8/25; 32%). Although their perspective and experiences may differ from those who had completed the programme, their inclusion was necessary in order to provide a fuller reflection of the programme at our institution.

Conclusions

The outcomes of this intercalated MBChB/PhD programme help fill a research gap by showing some of the medium-term benefits.[3] While some of the measured career outcomes are similar to those of well-established intercalated programmes elsewhere, we also found unique insights into the MBChB/PhD cohort. The programme is considered worthwhile by our students, most of whom continue (at various capacities) in academic work and produce a significant research output, although potentially in a field that is different to their PhD research. Future studies should focus on acquiring qualitative data in order to probe why students and alumni of the programme made the career choices they did. In addition, comparative data about the make-up of intercalating students–both locally (ie, the proportion of indigenous medical students) and internationally (eg, comparison with Australia) ought to provide meaningful and robust comparisons in order to identify keen and capable students early, as well as target students from under-represented groups.

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Media representation of chronic pain in Aotearoa New Zealand—a content analysis of news media

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ABSTRACT

AIM: To analyse how the New Zealand news media has reported on chronic pain and identify whether this publicly available information is reflective of best practice.

METHODS: A content analysis of news media published between January 2015 and June 2019, with a primary focus on chronic pain was undertaken. The Factiva, EBSCO and ProQuest databases, alongside popular New Zealand news websites were searched.

RESULTS: Two hundred and forty news articles were included; the overarching themes identified in content analysis were (1) the lived experience and the impact of chronic pain (n=119/240), (2) pain management strategies with information on pharmacological (ie, opioids and medicinal cannabis) (n=107/240) and non-pharmacological strategies (eg) psychological therapies (36/240), physical activity (34/240), pain education (34/240), (3) the systemic issues influencing chronic pain healthcare pathways (n=79/240).

CONCLUSION: Living with chronic pain is predominantly represented as a struggle, with a lesser focus on the ability to successfully self-manage and live a meaningful life. The limited emphasis on each of the non-pharmacological strategies suggest that the reports failed to communicate that these strategies should be a key component of self-managing chronic pain. New Zealand healthcare providers and researchers can collaboratively work with the media to provide evidence-based information on both non-pharmacological and pharmacological pain management strategies.

Chronic pain is the leading cause of disability worldwide.[1] It affects one in five New Zealanders and the annual prevalence is rising.[2] Chronic pain disproportionately affects older adults, females, Māori and those living in areas of high deprivation.[2] Not only does chronic pain burden individuals, but also society, costing the New Zealand economy an estimated annual cost of $14.8 billion in 2016 with projections of $24 billion by 2048.[3]

There are many types of chronic pain where no single cause can be determined.[4] Chronic pain is not always well understood, perhaps due to its variety of causes and ambiguous definition.[5] The International Association for Study of Pain has recently published the International Classification of Disease, Eleventh Revision (ICD-11)[4] definition for chronic pain based on biopsychosocial framework and classified pain conditions into chronic primary pain where chronic pain is the primary disease (eg, fibromyalgia, chronic migraine and chronic low back pain) and chronic secondary pain where pain is a symptom of an underlying condition (eg, pain caused by cancer or post-trauma/surgery or inflammatory joint diseases such as rheumatoid arthritis).[4]

Best practice care recommends healthcare providers adopt a biopsychosocial framework fostering adaptive behavioural change for people living with chronic pain.[6] Best practice care can vary across chronic pain conditions but generally includes a combination of non-pharmacological and

pharmacological strategies.[7] Non-pharmacological strategies such as psychological therapies (eg, cognitive-behavioural therapy, acceptance and commitment-based therapy and mindfulness-based therapy), pain neurophysiology education, physical activity and distraction techniques used alone or in combination are recommended as preferred management strategies for chronic primary pain[8] and chronic musculoskeletal pain.[9] Pharmacological strategies are recommended for some chronic pain conditions such as chronic cancer pain as part of palliative care and for managing chronic neuropathic pain.[10] For other pain conditions, selected pharmacological strategies are recommended to be used with care and caution due to their potential side-effects and limited effectiveness long-term.[7] For all chronic pain conditions, active self-management strategies (ie, non-pharmacological strategies) are recommended as primary pain management strategies, modified to be appropriate for the type of pain condition, presence of other comorbid health conditions (eg, depression), and psychosocial profile of the person. People treated using active self-management strategies have shown improved long-term functional outcomes as compared to those who adopt an attitude of reliance on others to fix their pain.[11]

There are barriers for many people with persistent pain to achieve optimal management of chronic pain usually supported by accessing specialised pain services as they are offered only in secondary or tertiary services.[12] Further, Māori and Pasifika and other ethnic minorities are underrepresented in accessing tertiary pain services in New Zealand.[13] In addition to access barriers, knowledge deficits, lack of awareness and misconceptions relating to pain management among healthcare providers contribute to inadequate pain management.[14] Further, lack of validation of symptoms from healthcare providers, family and friends has been perceived as a major barrier by people living with chronic pain to effectively self-manage their symptoms.[15]

Media representation can influence societal beliefs in regard to condition management and attitudes towards those living with long-term health conditions.[16] With an average of 3.1 million New Zealanders reading newspapers within a one-week period, news media has the potential to disseminate public health messages and influence public health behaviour.[17] An exploratory study[18] from the US analysing multimedia sources that focused on chronic pain (ie, newspaper reports, video blogs, memes and a movie 'Cake') from 2010 to 2015 found varying representations of chronic pain. While the authors concluded that the type of media source can influence the key messages delivered, the study did not intend to analyse if the contents reflect best practice care to influence beliefs at societal level. Another review on multimedia campaigns, including newspaper and video, about chronic pain has shown these can change beliefs and behaviours of the public and healthcare providers about chronic pain.[19] Given the potential for media accounts of chronic pain to influence experiences and/or understandings of chronic pain for people with pain, their family and communities and the beliefs of healthcare providers,[20] the aim of this study was to explore the representation of chronic pain in New Zealand news media.

Methods

Using a content analysis approach,[21] the following methodological framework was used:
1) identifying the research question, 2) study selection, 3) identifying relevant articles, 4) charting data and 5) collating, summarising and reporting the results.

Identifying the research question

The research question guiding our review was: How is chronic pain represented in popular news media in New Zealand?

Study selection

Primary data were collated from print and online media available in the New Zealand public domain. Media articles were included if: they contained any reference to chronic pain in concordance with the ICD-11 definition of chronic pain,[4] and published in major New Zealand newspapers, magazines or radio podcasts since 1 January 2015 until 30 June 2019. Relevant radio podcasts were transcribed by the research team. Media articles were excluded if the focus was on acute pain or if access required paid subscriptions.

Identifying relevant articles

Primary search

To identify potentially relevant printed news media articles, Factiva, EBSCO and ProQuest databases were searched on 10 June 2019. Search terms included [*"chronic pain"* or *"persistent pain"* and *"New Zealand"]* (see search strategies in Appendix 1). Search terms were developed with an experienced librarian and refined by team discussion after pilot searches. New Zealand newspapers and magazines identified were: The Press, The Dominion Post, NZ Herald, The Nelson Mail, NZ Doctor, Taranaki Daily News, Waikato Times, The Timaru Herald, The Southland Times, Manawatu Standard, North & South, NZ Listener, The Daily Post, Sunday News, The Marlborough Express, Bay of Plenty Times, Sunday Star Times, Wanganui Chronicle and NZ Newswire. Three authors searched all the databases (YK, DM and LE), duplicates were removed with the remaining primary articles used for screening. Five authors (CA, DM, LE, MS and YK) screened the first 20 news articles from the primary search and discussed findings to ensure consistency before full screening.

Secondary search

A secondary search was performed on websites with Google search engine using primary search terms. The sites searched included major independently owned New Zealand print newspapers (Otago Daily Times and NZ Herald), major commercial or independent radio and/or television media outlets (One News Now, Newshub, Māori Television, Sunday Star Times, Radio New Zealand and Newstalk ZB*)* along with New Zealand news media websites (Stuff, Spinoff, Noted, Scoop, Voxy, Newsroom). These represent major New Zealand news outlets with an online presence.

Charting the data

Articles that met the initial criteria were charted on Microsoft Excel Sheet® and consequently entered into EndNote X9 library (Clarivate Analytics). The initial screening involved screening of headlines and texts (LE, DM and YK). After the initial screen, the full text of the news articles were examined to exclude duplicates that were not identified in EndNote by meta-data, and articles that did not have a primary focus on chronic pain. Authors then worked in pairs to establish congruence about the inclusion of uncertain articles. A third author (HD) adjudicated any disagreement (n=16). The remaining news articles were included for the content analysis.

Content analysis

A conventional approach to content analysis was used where categories were inductively derived from the data to identify overarching themes within the texts.[21] As per this inductive approach, the emergent codes and supporting quotes were established after in-depth reading of texts. Each author made notes of their impressions of these texts, as this iterative process continued, codes were derived that captured more than one key thought.

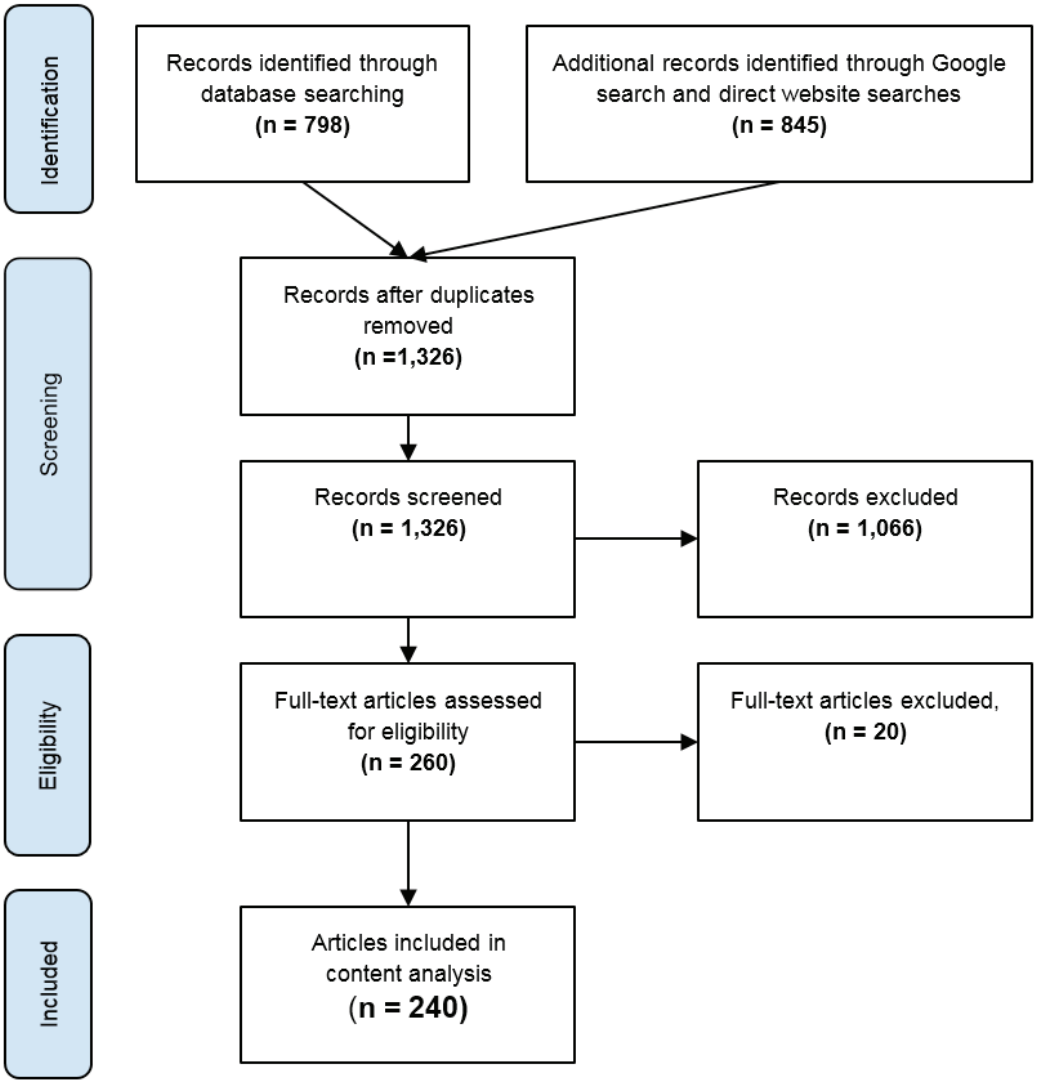
Coding of data was completed to extract and classify relevant data from the included media.[21] To minimise the subjectivity of text interpretation, four of the authors piloted this using 20 news media articles to establish analytic concordance (LE, DM, YK and MS).[22] Once finalised, the authors worked in pairs to identify key themes and sub-themes within the texts. The final themes and sub-themes were finalised by a consensus meeting involving the entire research team. To ensure credibility of the analysis, another author (JY) independently coded and thematically analysed a randomly selected subset of 20 included articles to produce themes for comparison.

Results

After the database search and screening, 240 articles were included for content analysis as shown in Figure 1. Most of the articles were excluded as they were not focusing on chronic pain.

The three overarching themes identified in content analysis were (1) the lived experience and the impact of chronic pain, (2) how chronic pain is managed, (3) the systemic issues influencing healthcare pathways of chronic pain management. The findings are presented in Tables 1–5, with a selection of example quotes from the news articles. The frequency of news articles published since 2015 and the types of news sources are presented in Appendix 2.

Figure 1: News article selection process.



The lived experience and the impact of chronic pain

Almost half of the included articles (n=119/240) reported on personal experiences of living with chronic pain, the impact of pain on quality of life and the attitudes towards managing pain (Table 1).

Chronic pain was reported as a disabling long-term health condition impacting on an individual's quality of life (n=69/240) and their sense of identity (n=54/240). Chronic pain impacted daily life by affecting an individual's sleep, ability to participate in social activities and most frequently, placing stress on relationships (Table 1). Another sub-theme encompassed the constant burden of chronic pain, forcing many to stop or reduce working, leading to financial hardship (n=50/240).

An additional subtheme identified was attitudes towards managing pain. We identified two key attitudes among people with chronic pain (Table 1). The first was more a negative attitude towards pain (n=44/240) where chronic pain was described as 'debilitating' and a cause of 'suffering'. Such articles reported primary reliance on pharmacological options, particularly opioids, for managing their symptoms, which frequently led to dependence and

addiction. Chronic pain was portrayed as challenging to manage, with people often looking for a 'quick fix'. As well as experiencing the negative effects of chronic pain, there were some articles (n=28/240) which reported people demonstrating a positive attitude towards living well with pain. Positive attitudes were expressed in the form of people taking active responsibility for their pain management, remained hopeful, and had support and motivation to manage their symptoms. Despite the positive attitudes towards managing pain, very few reports focused on the time, patience and work required to self-manage chronic pain (n=13/240).

How is chronic pain managed?

Information on chronic pain management strategies focused on both passive approaches such as pharmacological management (n=107/240) with opioids (n=67/240) and medicinal cannabis (n=65/240) (Tables 2 and 3), and active approaches such as non-pharmacological management strategies (n=97/240) (Table 4). Articles addressing opioids or cannabis products as treatment options often did so in the context of possible legalisation of cannabis products for medicinal use (n=59/240).

The sub-theme of opioid-based painkillers (n=67) included reports of opioids as ineffective for chronic pain, leading to dependence and addiction, producing unwanted side-effects, being prescribed with inadequate information, explanation or advice about alternatives, and overall being perceived as harmful and dangerous (Table 2). In contrast, the sub-theme of medicinal cannabis use for chronic pain (n=65) was portrayed as an effective and safe treatment option with minimal or absent side effects as compared to opioid-based analgesics (Table 3). The expense and inability to source medicinal cannabis legally were highlighted. Medicinal cannabis was portrayed as a solution withheld from people with pain by the New Zealand government and reported as being a last resort, with people reluctantly accessing it illegally. Finally, few articles (n=15/240) mainly from healthcare providers reported a lack of robust scientific evidence supporting the benefit of cannabis products in chronic pain and warranted further research before recommending therapeutic use (Table 3).

Around 40% of the articles (n=97/240) reported on active approaches such as non-pharmacological management strategies and the importance of holistic treatment, avoiding singular focus on pain (Table 4). Holistic approaches for the management of chronic pain included patient-centred care within a multidisciplinary framework (n=36/240), incorporating pain education and acceptance of pain (n=34/240). Other non-pharmacological strategies included use of psychological therapies such as cognitive behavioural therapy, mindfulness and meditation (n=36/240), and encouragement of physical activity (n=34/240). The effectiveness of these non-pharmacological approaches was occasionally noted by both health professionals and people living with chronic pain (Table 4).

Systemic issues influencing healthcare pathways of chronic pain management

Various healthcare system challenges were reported (n=79/240): lack of healthcare service resources (n=45/240), lack of understanding and not being listened to by healthcare providers (n=30/240), ethnocultural differences that exist when seeking medical care (n=10/79), and delays in receiving diagnosis (n=27/240).

Chronic pain was portrayed as a condition that is not well understood by both healthcare providers and patients (n=28/240). People without diagnosis recalled experiences where they were perceived as 'malingering', 'attention-seeking' or drug-seeking by healthcare providers (n=13/240). This contributed to people 'feeling frustrated' and 'not being listened to' when interacting with healthcare providers. Reports of being passed between specialists were also mentioned (n=15/240). These reported experiences led to people giving up seeking medical attention, negatively impacting their prognosis. Many articles highlighted the challenging and lengthy process required to receive a diagnosis. Formal diagnosis was reported to provide relief and validation of their symptoms.

Table 1: Theme #1: The impact and lived experiences of chronic pain.

Sub-themes	Description	Example 1*	Example 2*	Example 3*
Impact on the person	Chronic pain impacts the person's whole life by changing the person and those around them.	"Chronic Illness completely changed my life and who I was as a person."[23]	"She's in chronic pain. She's lost in it. She has no quality of life."[24]	"Her pain is the central fact of their family life."[25]
Impact on daily life	Chronic pain affects quality of life negatively and forces people to give up their meaningful activities.	"It's like living half a life. I get home at the end of day wiped out. There's so many things I don't do because I am so sore and tired."[26]	"It has completely taken my quality of life. I just watch TV now."[27]	"I've lost my health, my job, my marriage and my home."[28]
Impact on work and financial situations	Inability to work leads to deterioration or loss of financial wellbeing.	"People have to make choices about how they exist that may worsen their illness, such as not heating their houses to the level they should."[29]	"Severe pain causes frustration, anxiety, depression, it affects people's social life, their family life, their financial life, it has a big impact on their whole life."[30]	"I just want to live a normal life and be able to get on with what normal people do, like going to work."[29]
Positive attitudes towards chronic pain	Positive attitudes associated with successful coping strategies and ability to focus on living a meaningful life despite pain.	"It may take a while, it doesn't happen overnight, but it can and will get better."[23]	"I have chosen a really positive mindset. I've dealt with severe chronic pain and still managed to create a life for myself. The coping strategies I've been using for years still apply."[31]	"You can do two things. Sit around and let it take over your life, or get up and live with it, not let it beat you."[32]
Negative attitudes towards chronic pain	Negative attitudes associated with difficulty coping and decreased quality of life.	"I'm lying on a bed and no one cares, and no one is speaking up for me."[24]	"I rehearsed nuanced replies: Not too bad. Not so good. As good as. Waiting and hoping."[33]	"I live with chronic pain, 24 hours a day, seven days a week, 365 days a year. I am perpetually teetering atop a dark chasm called complex regional pain syndrome "[34]
Management requiring time, money and effort	People looking for a quick fix but chronic pain management takes time and sustained effort.	"As I say to people, it didn't take you five minutes to get to where you are, and it's going to be hard work and going to take you time to get out of it,"[35]	"The pain journey can take time, and if you've had a problem for 20 years, it can become very seared in your consciousness."[36]	"I just gritted my teeth and pushed through, knowing that even though my back hurt like hell this week, it's worth it to be pain-free in time. Patience and hard work. There is no quick fix, super exercise or magic pill. Nothing worth having is gained easily."[37]

Table 2: Theme #2: Sub-theme: Opioid-based treatment of chronic pain.

Sub-themes	Description	Example 1*	Example 2*	Example 3*
Opioid-based painkillers not effective for chronic pain	Personal and professional opinions about effectiveness: commonly prescribed opioid-based painkillers only working short term or not helping at all.	"She was told the treatment regime would be ongoing and 'it was just going to be the new me'. After a couple of months the medication's effects wore off and the pain returned worse than ever."[38]	"[She] had previously been on a large amount of strong opiates, using "uppers and downers" for chronic pain related to fibromyalgia. She said they didn't 'touch the sides' of her pain and kept her as a 'zombie'."[39]	"He says using strong opioids like fentanyl for chronic, non-cancer pain is inappropriate. The drugs tend not to work well when used over a significant period of time, and the side effects increase."[40]
Dependence and addiction	Constant use of opioid-based painkillers led to dependence and addiction.	"After four years of opioid use I am addicted and due to my high tolerance of this drug, it is now all but useless as an analgesic for me."[41]	"When we see a name of Endone, codeine or OxyContin, people think it's just a painkiller—but it's opium-based. And people get addicted to opium or heroin."[42]	"There's a sense [among patients] that, because a drug is prescription or over the counter, it's less harmful, less risky and they wouldn't sell it to you if there was a problem. But all opioids can have the effect of you developing a physiological dependency, because you develop tolerance and when you take them away you get all those withdrawal symptoms."[43]
Side effects	Accounts of experience with opioid-based painkillers producing harmful side effects, such as drowsiness, depression, nausea, constipation, that impact the life as much, if not more, as the chronic pain itself.	"But it [Tramadol] is potent, and has side effects. As a fairly small woman, the drug has a powerful effect on me, and whenever my pain increases to a level that I have to go back on it, I have to plan to take my first pill with a decent 12 hours on the other side in which I can either sleep or lie on the couch feeling nauseous and stoned out of my mind (and not in a good way). The last time I went back on to Tramadol, back in January, I couldn't stand up for about eight hours."[44]	"The pills all managed [his] pain—initially—but as his resistance grew, the dosages were increased and the side effects worsened. Eventually his life was a nightmare of constipation, drowsiness, depression and memory loss."[45]	"Those drugs left him with no energy, feeling depressed, his memory was shot and he was sleeping at least 14 hours a day…'I was that sedated, I couldn't really live a normal life. That's why they [doctors] took me off it and put me on methadone.' He would remain on methadone for five years. It managed his pain for the first six months, but when the dosage needed to be increased, the side-effects worsened."[45]
Information and risks not given by healthcare providers	Not enough information about painkillers is given to people with chronic pain which impacts the consent as the risks and side-effects were not fully explained.	"...she saw her doctor about her chronic pain and mental health issues. He gave her 150 tramadol tablets for the pain, as well as antidepressants. 'He just prescribed it and from then on I didn't need to see him again ... I just had to call up for a re-script'."[43]	"Doctors would give him opioid prescriptions without advising of the side effects and potential for addiction."[45]	"I got a whole stack of them while I was in hospital ... and then afterwards I got a whole stack and a prescription. It was weird, some doctors would warn against it—like 'I won't give you too much of this' and others were quite free—'here you go' kind of thing."[46]
Prescribed without alternative	Opioid-based painkillers are prescribed as the only solution, other options not being explored.	"The tramadol gets me through that bad time and then I get on with it. I've got a headache today, I know I'm going to be exhausted tonight, and I know that I'm going to need to take some morphine just to have a break from the pain tonight. I don't like it, I don't want to, but I have to, because there isn't the alternative."[47]	"Doctors recommended strong pain relief, including high doses of tramadol and codeine medication as the only treatment."[38]	"Long-term opioids for most pains aren't terribly useful, but the script just gets continued, or the patient turns up saying 'oh I got this from the hospital', so the doctor just continues it."[43]
Drugs are harmful and dangerous	Overall perception of opioid-based painkillers being harmful and dangerous.	"I was in such a bad place mentally; every day I was on the edge of taking the maximum amounts of opiates you can without having a cerebral seizure. I would think about my children and [I was] frightened."[48]	"I was looking at my little girl and I thought if I keep taking all these pharmaceuticals, I'm not going to last to see her get married, my liver function will crap out."[49]	She says people don't realise how dangerous opioids can be. "I still feel the effects of it even now. It's done nothing but ruin my body in a way I can't take back."[43]

Table 3: Theme #2: Sub-theme: Medicinal cannabis use for chronic pain.

Sub-themes	Description	Example 1*	Example 2*	Example 3*
More effective, better strategies for chronic pain	Medical cannabis is an effective treatment for chronic pain, based on personal/anecdotal evidence.	"I can make a cup of tea in the morning, which will ease my pain, I can eat a cookie in the day and I can have a little cone at night and that will take care of everything, instead of taking approximately 16 pharmaceutical opiates to get through the day."[49]	"And then a friend who has cancer shared some of his high CBD cannabis pills with her. That was life-changing. It meant I wasn't in so much pain and could get up and do stuff."[50]	"Ask anyone who has tried medicinal cannabis for chronic pain if it works. Feedback from the 170 patients I started on CBD shows half report very good to excellent response. Many have suffered pain for years or decades, unresponsive to standard treatments with associated side-effects."[51]
Less side effects	Medicinal cannabis does not produce any side-effects and is a desirable alternative with less impact than opioid-based painkillers.	"Not a cure or anything but a great alternative to opiates. It means pain relief that doesn't affect me in a bad way. A natural solution without all these massive side effects."[52]	"Other drugs upset my system so badly. I have tried all the pills, none of them agree with me. Tramadol put me in hospital, damaged my pancreas. I rely on cannabis—it's the only thing that doesn't upset me."[53]	"It's a 'strange feeling' to be pain-free and without nasty side effects, he says. His energy levels have returned, he is lucid and aware of his surroundings—and he even walks the dog. 'My life's fantastic. I am getting up early, I am more active, I can actually remember stuff now'."[45]
Legal medical grade expensive and inaccessible	The only legal cannabis option is inaccessible requiring numerous bureaucratic hurdles, and is expensive.	"To get a prescription for their patient, a doctor and a specialist must apply to the Ministry of Health, with [Associate Health Minister] making the final call. [He] has been approved to receive the drug, an oral spray, but it is enormously expensive. 'When the script arrived, I took it to the pharmacy and they wanted $1,400' she says, "and I just didn't have that money."[47]	"Technically speaking a legal form of medical marijuana is available in New Zealand. It's a mouth spray called Sativex. But at approximately $1,200 a month it is out of most people's reach. The other thing about Sativex is that it's almost impossible to access. [She] tried and was knocked back."[52]	"If it was a realistic affordable opportunity then I would definitely apply, it should be more accessible for people who need it."[52]
Solution being withheld by government from people	Debate around medicinal cannabis for chronic pain transforms into debate about government creating obstacles and withholding an effective and cheap treatment for chronic pain sufferers.	"Millions of taxpayer dollars are shelled out annually to fund thousands of daily doses of methadone for drug addicts without question, yet they drag the chain when it comes to offering people in real pain, with chronic conditions a viable alternative".[55]	"[She] tried marijuana and finds it transformative. "It works and it's a crime that it's not available to us"[52]	"He said blocking access to cannabis for medicinal purposes was a breach of human rights."[49]
Last resort, people forced to illegal means	Failure to decriminalise cannabis for all medicinal uses forces sufferers of chronic pain seeking pain relief to turn to illegal practices.	"People who take marijuana for pain relief are still technically criminals, and those who are supplying it to them are putting their lives on the line. Co-leader of the Aotearoa Legalise Cannabis Party is one of those people who are risking it all to relieve her own chronic pain and others who are suffering in her community. 'I'm not just doing this for myself—it's for everyone. The law sucks. They're just making criminals out of us'."[56]	"This month she revealed she takes cannabis oil to relieve the pain. She had exhausted all legal pain relief."[47]	"Campaigners have been calling on the Government for some time to provide safe legal access to cannabis-based pain relief. 'Legitimate and high-needs patients [name omitted] are forced to go to the blackmarket by the high bar for access of a comparatively safe analgesic'."[53]
Minimal scientific evidence presented	Professional opinions based on the scientific evidence referring to lack of evidence or lack of strength of this evidence to support the use of medicinal cannabis for chronic pain.	"Experts from the University of Otago say there's little or no evidence it works. 'It's not a silver bullet, we all wish there was a silver bullet for chronic pain'."[57]	"The international data on which one could make an informed decision about the effect of medicinal cannabis on chronic non-cancer pain is in fact very poor. The conclusions have been oversold."[58]	"'We found no evidence that cannabis use improved patient outcomes,' the researchers wrote in Lancet."[59]

Table 4: Theme #2: Sub-theme: Non-pharmacological management of chronic pain.

Sub-themes	Description	Example 1*	Example 2*	Example 3*
Holistic focus	Chronic pain is complex, requiring a holistic approach to management. Some opinions expressed the inadequacy of relying solely on pharmacological management strategies, and the need of individualised treatment.	"We know that chronic pain is a much more complex phenomenon which requires a holistic approach to management that is tailored to the individual's circumstances. To rely only on medicines is just not going to work."[60]	"We have to look at the big picture and support the whole person and not just the limb."[30]	"We start to look at pain as a pie with lots of different segments," ... "We work with these people in areas where we can make a difference. It's very individual and might be a combination of medication, physical therapy and some psychological input."[61]
Multidisciplinary input	There is a need for multidisciplinary input when managing chronic pain in order to improve health outcomes for individuals.	"Multidisciplinary management more than doubles return-to-work rates for patients and substantially reduces opiate use and annual medical costs."[62]	'We know that linking people to integrated, multidisciplinary models of care will improve outcomes of health and wellbeing—evidence shows this reduces the amount of pain medication required and can reduce the burden on other health services."[63]	"A multidisciplinary approach to chronic pain management is widely considered best practice. This involves medical doctors, physiotherapists, psychologists and nurses, among others."[64]
Physical activity	Physical activity can be successfully incorporated in the management of chronic pain and help improve the individual's quality of life.	"Running has been key to helping a former Olympian overcome chronic pain. 'I really like running. I can't get it out of my system. 'Every little step is a step forward and it's something to celebrate—just like the Olympics'."[65]	"If I could tell anyone with fibromyalgia one thing it would be to get out there, get active and give it a go. Not doing anything makes the pain so much worse and makes it so much harder to find the motivation to get better. Slow and steady wins the race and small steps are all it takes to begin to improve the quality of your life."[23]	"We may not have a cure but improving our quality of life through exercise and other effective measures sure is worth it to have pain more manageable and regain the ability to work away at doing some of the things we were able to do before we got ill."[23]
Psychological Strategies	Psychological treatment can be included as a strategy for non-pharmacological management of chronic pain.	"Mindfulness-based cognitive therapy, which uses meditation and other therapeutic techniques, has been extensively studied as a treatment for preventing relapses of depression. This therapy is also becoming established as a valuable skill for pain sufferers."[66]	"CBT (a therapy offered by psychologists) can be really useful in coming to terms with a change in lifestyle that CP may have caused."[67]	"She has done acceptance and commitment therapy and participates in a weekly mindfulness and meditation session at the service. Separately she sees a physiotherapist She still has pain but copes by managing her life well—doing things she enjoys and that keep her mind busy, while still staying calm."[68]
Understanding and acceptance	Understanding chronic pain mechanisms and accepting the process of working towards good quality of life despite the pain is an important aspect of managing pain.	"When it comes to pain, all the outcome data shows that knowledge is more effective than anything else."[36]	"Understanding how pain works and the value of the strategies—such as pacing or increasing daily activities, relaxation and meditation—reinforced the participants' ability to self-reflect and accept how they might live well with chronic pain. It also fostered their ability to continue to use the strategies they had learnt."[69]	"Instead of trying to find answers, I'm trying to live with what I've got. It's a constant balancing act for me—to not allow my pain to rule my life and bring me down."[68]

Table 5: Theme #3: Systemic issues in healthcare associated with chronic pain.

Sub-themes	Description	Example 1*	Example 2*	Example 3*
Importance of getting a diagnosis	Many individuals wanted a formal diagnosis to validate their chronic pain for themselves and others. A diagnosis aids self-management.	"Before being diagnosed, people were sceptical and somewhat cynical of my experiences. They would tell me to get over it. I finally had a diagnosis and I was so relieved."[70]	"Being diagnosed gave me a sense of relief in terms of I now had a name for my pain, a reason and real diagnoses for the way I felt."[71]	"They seek to make sense of their pain, their diagnosis and what is important in life."[70]
Not being understood or listened to by healthcare providers	When dismissed by healthcare providers, people with chronic pain are made to believe that the pain they are feeling is not real and is all in their head.	"Those not in wheelchairs, or whose pain comes and goes, are often misunderstood and dismissed. Every patient I have ever met has been made to feel that the pain is all in their head. Someone doesn't believe them. But the pain is real."[73]	"I think doctors sometimes don't take people seriously and you will see women complain more about pain in more places, more often and say it's more intense. They often don't get taken as seriously."[74]	"There are still doctors out there who think this is all in our heads or that it's depression...that it wasn't as bad as I was making it out to be."[75]
Lack of understanding about chronic pain	Chronic pain is not well understood by healthcare professionals in New Zealand, where people with chronic pain are sometimes left without answers.	"Clinicians generally demonstrate inadequate knowledge and inappropriate beliefs about pain. Insufficient pain-related competencies may limit how well healthcare professionals provide effective treatments."[76]	"I felt like no one understood. The people who you're meant to trust the most with your health are doctors. You'd think that they would do anything to get to the bottom of what was wrong with an 18-year-old girl in chronic pain."[77]	"I have been told by previous employers, WINZ and a past gynaecologist that it's all made up and it shouldn't hurt."[78]
Lack of resources	There is limited availability of pain specialists and pain clinics, unable to meet the treatment needs of people with chronic pain in New Zealand.	"Pain management is often the ambulance at the bottom of the cliff. We are grossly under-resourced."[79]	"With an ageing population this is only going to go up and skyrise, we need more resources to tackle persistent pain in this country."[80]	"He has begged the health minister for more resources as thousands of New Zealanders live in misery after being shut out of specialist medical services."[81]
Ethnocultural barriers	There are disparities with regards to who is more likely to seek/receive medical help for chronic pain within ethnoculturally diverse groups.	"Ethnic minority groups not accessing chronic pain services were complex. [They] are less likely to seek help for chronic pain despite having greater needs than Pakeha."[82]	"Many Pasifika people in New Zealand do not seek hospital help to cope with chronic pain."[83]	"Ethnic minority groups tend to be significantly under-represented and show more severe symptoms. It would be relatively easy to integrate Māori, Pacific and Asian cultural practices, because multidisciplinary chronic pain services are holistic by nature. One of the only things missing is a spiritual component."[64]

New Zealand's lack of resources for chronic pain diagnosis and management was a frequent sub-theme reflected in New Zealand news media (n=45/240). Specific issues reported were lack of pain specialists in practice, a shortage of funding available, need for further training of healthcare providers, a need to open more accessible multidisciplinary pain clinics, improving access to existing pain clinics and addressing the prolonged waiting time for appointments with pain specialists.

Ethnocultural issues were also noted (n=10/240), with ethnic minorities having difficulty receiving a diagnosis. Some reports suggested Māori, Pasifika and Asian communities in New Zealand were less likely to seek medical help, regardless of their severity of pain, due to lack of culturally-responsive healthcare services.

Discussion

This content analysis found that chronic pain is often represented in media by focusing on the burden of living life with pain. There were also some reports of people adopting active approaches to successful self-management. The limited emphasis of each of the non-pharmacological strategies such as psychological therapies, physical activity, and pain education and acceptance suggests that the reports failed to communicate that non-pharmacological strategies including active self-management should be prioritised to live well with chronic pain. Reporting on opioids focused on the risk of dependence and adverse effects, however reports regarding medicinal cannabis products largely presented this as a desirable therapeutic option with only limited reporting on lack of scientific data supporting these benefits. There was no reporting of the potential adverse effects of cannabis products. Many reports accurately reported health system limitations leading to challenges with access to appropriate care for chronic pain management that meets health needs particularly for ethnoculturally diverse communities.

The New Zealand news media commonly reported on the impact of living with chronic pain. Chronic pain was portrayed as a condition that is poorly understood unless a person experience it themselves. This has been reported in 69 articles where people with chronic pain reported loss of social roles due to pain impacting their ability to engage in daily tasks. Previous research looking at news media depictions of mental health in New Zealand and Australia found similarities when media reports on personal experience.[84,85] People with mental health issues experienced a sense of vulnerability where they too felt an inability to control their own life, affecting their participation within their communities.[84,85]

New Zealand news media frequently presented chronic pain as a debilitating condition, with only a few reports suggesting the potential for coping well with ongoing pain with adequate support. However, evidence suggests chronic pain can be successfully managed with multidisciplinary health professional input.[11] This is represented in a few of the included reports that captured positive experiences of people coping well with pain due to receiving multidisciplinary input from pain services in New Zealand. Further, media reporting has the potential to change public misconceptions, address myths and provide hope and support by offering helpful information.[20] Similar to our finding, negative portrayal of people living with mental health conditions in the media was previously reported in New Zealand,[86] which led to the development of a media reporting guideline for accurate portrayal of people living with mental health conditions in New Zealand.[87]

In addition to limited coverage of each of the non-pharmacological approaches, there was limited information on clinical effectiveness of non-pharmacological strategies. Non-pharmacological self-management strategies have sufficient evidence to support their effectiveness for chronic pain management.[88] However, much of the information published in the media recommended seeking support from health services or pharmacological strategies instead. As a result, the New Zealand public may not be receiving balanced coverage about potential effective management strategies with a robust evidence base. There was however a clear portrayal of the limited capacity of, and access to specialist pain services. This is not unique to New Zealand; a telephone-based study (n=4,839) conducted in Europe reported that very few people had been introduced to effective pain management strategies despite the high-quality evidence supporting non-pharmacological strategies.[89]

The extensive reporting of people's experiences with opioids used for pain management suggest best practice pain management, with avoidance, or at least minimisation of opioid use, may not be widely practised in New Zealand despite existing guidelines.[90] Current guidelines recommend not using opioids as a primary pharmacological treatment option in people with chronic non-cancer pain and recommends opioid use only in people with cancer pain and in people with failed non-pharmacological treatments (eg, complex cases).[90] Further, having a care monitoring plan in place is recommended in current opioid users due to the risk of opioid-induced dependence, addiction

and other complications (eg, constipation, sedation, depression).[90] Some news articles reported opioids were often prescribed as a second-line treatment due to the inability to access specialist pain services (Table 2), this may have contributed to the lack of understanding patients have in regards to best practice care.

The media representations of pharmacological strategies were dominated by personal experiences of people with chronic pain reporting positive benefits from using medicinal cannabis. This coincides with the consideration of the New Zealand government to change legislation surrounding access to medicinal cannabis products.[91] All personal experiences in the media focused on the positive effects of cannabis with fewer side effects as compared to opioid-based analgesics suggesting that cannabis use is a safer treatment strategy to manage chronic pain in those using opioids. There is however limited evidence to suggest cannabis as a substitute for opioids[92] and a lack of high-quality evidence to support the use of cannabis for chronic pain.[93] This lack of evidence was reported in only a few articles featuring input from healthcare providers. Interestingly, there was no reporting on potential adverse effects of medicinal cannabis use especially for young people such as cognitive deficits, dependency and mood changes,[94,95] which may outweigh the purported benefits. Therefore, current media reports may not reflect evidence-based information about the clinical effectiveness of medicinal cannabis for chronic pain management. Readers have to be mindful of such information in media reports and consult their healthcare providers for management approaches that would best suit their chronic pain condition.

News media accurately reported that New Zealand is under-resourced for specialist pain management services and has a definite shortage of pain specialists. The UK recommends one pain specialist per 100,000 individuals, while in New Zealand there are only 12 full-time equivalent specialists, falling short of the population-based recommendation of 45 specialists.[3] Not only there is a shortage of pain specialists but also pain clinics in New Zealand. Media reporting also failed to emphasise the potential role for the primary care sector and other allied health professions (eg, physiotherapy, psychology and occupational therapy) in supporting people with chronic pain to adopt non-pharmacological self-management strategies. The prevalence of chronic pain in New Zealand is growing, but the capacity for patients remains inadequate, resulting in long wait lists to access healthcare services.[3] All these reasons may contribute to the difficulty for chronic pain patients to receive their diagnosis and best practice care.

There was an increasing frequency in coverage on chronic pain within New Zealand's news media. We can expect that this number may continue to rise due to chronic pain becoming increasingly relevant with the current cannabis bill discussion,[91] and increasing prevalence with New Zealand's ageing population.[2] This study emphasises the need for New Zealand healthcare providers to be cognisant of the potential for chronic pain reporting by the media to challenge and change people's beliefs about pain mechanisms and shape patient expectations around management strategies. As few articles included healthcare providers' views, there is a role for experts to make themselves available to journalists to provide information about evidence-based treatments; and the potential need for public education campaigns with evidence-informed information about chronic pain.[20] Media guidelines are available for the portrayal of people with mental health issues in New Zealand to ensure that journalists provide a safe, accurate and respectful representation of this condition.[87] This idea has been developed by a New Zealand campaign "Like Minds, Like Mine" where a human rights approach was taken towards enabling people to be free of discrimination and their disabilities being represented.[96] A similar approach could be adopted for long-term conditions such as chronic pain, due to its high prevalence and impact in New Zealand. Further, journalists could refer readers to a wide variety of evidence-informed, quality-appraised, educational resources fostering pain self-management accessible to the New Zealand public via the internet.[97,98]

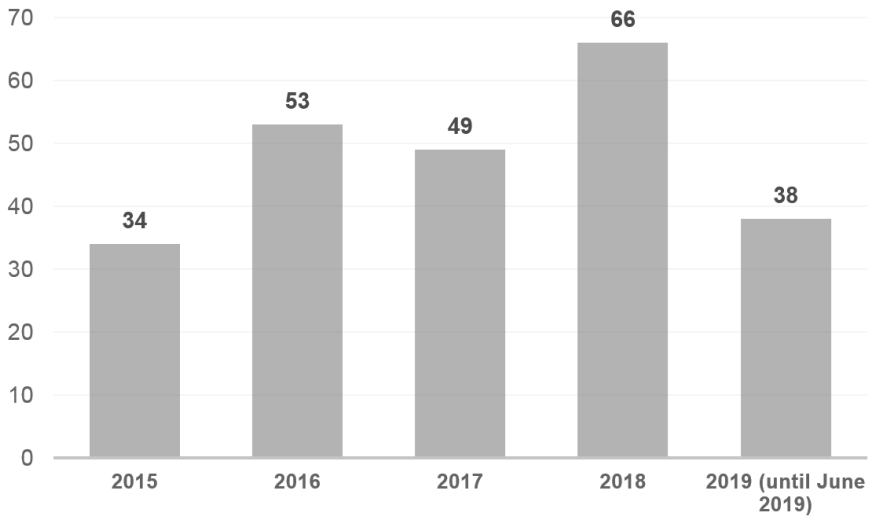
The strengths of this study include the coverage of all paper and online New Zealand news media. Due to the country's size it was achievable to include data from 2015, resulting in a large sample size. Independent parallel coding and coding verification added rigor to the analysis. Limitations include the limited generalisability outside New Zealand due to local socio-political considerations. Public debate around legalisation of cannabis before the general parliament election 2017, and subsequent reports on the Misuse of Drugs (Medicinal Cannabis) Amendment Act passed in 2018 influenced the frequency of the cannabis coverage in media related to chronic pain. It is also possible that in countries with higher rates of opioid prescription and unintentional overdose, media reporting may emphasise opioid risk more prominently.

This content analysis identified that chronic pain may have been represented in a somewhat unbalanced manner by popular news media in New Zealand. Many news outlets focused on the struggle associated with living in chronic pain, with a lesser focus on the ability to successfully manage pain and live a meaningful life. Further, the greater emphasis on pharmacological strategies over non-pharmacological approaches suggest that the reports failed to communicate that non-pharmacological strategies should be a key component of self-management for living well with chronic pain. Given the potential for news media reports shaping patient's health beliefs and treatment expectations, New Zealand healthcare providers and researchers can collaboratively work with the media to provide evidence-based information on both non-pharmacological and pharmacological pain management strategies.

Appendix 1

Example of search strategies used for the review	
Database	**Search Strategy**
EBSCO	Select Databases: Australia/New Zealand Reference Centre, Health Source - Consumer Edition, Newspaper Source plus, Newswires, WebNews. 1. (TX ((chronic* OR persist*) N3 pain)) AND ((TX chronic* N3 pain*) AND (TX Zealand*)) 2. Limited to News and Magazines; 2015–2020 3. Include New Zealand newspapers/ Exclude Australian newspapers (by publication)
ProQuest:	1. ("chronic pain" OR "persist* pain") and'' New Zealand*" 2. Source type: Newspapers, Magazines, Language: English, Location: New Zealand

Appendix 2



Frequency of news articles on chronic pain published since 2015

Sources of articles included			
Newspaper/website	**Primary**	**Secondary**	**Total**
The Dominion Post	15		15
The Press	11		11
New Zealand Herald	15	27	42
The Daily Post	2		2
New Zealand Doctor	7		7
New Zealand Listener	5	5	10
Waikato Times	2		2
Taranaki Daily News	4	1	5
Sunday News	2		2
The Timaru Herald	3		3
The Nelson Mail	9		9
The Marlborough Express	1		1
North & South	3		3
Bay of Plenty Times	10		3
Sunday Star Times	3		3
The Southland Times	1		1
Manawatu Standard	2		2
Wanganui Chronicle	1		1
NZ Newswire	1		1
1 News Now		3	3
The Spinoff		3	3
Stuff.co.nz		48	48
Scoop		19	19
Newstalk ZB		3	3
Otago Daily Times		8	8
Newsroom		2	2
Voxy.co.nz		18	18
RNZ		7	7
Newshub		5	5
TVNZ.co.nz		1	1
Whale Oil Beef Hooked		1	1
Total	**240**		

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New Zealand should introduce nationwide pulse oximetry screening for the detection of critical congenital heart disease and other hypoxaemic conditions in the newborn

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ABSTRACT

The mortality risk for infants with critical congenital heart disease (CCHD) unrecognised at the time of birth is high. Pulse oximetry has been utilised as a screening tool for the detection of these anomalies in the newborn as the majority will have a degree of hypoxaemia. This screening strategy has a moderate sensitivity and excellent specificity for the detection of CCHD, and a low false-positive rate. Respiratory and infective diseases are responsible for a large number of positive test results. The early recognition of these diseases can also improve health outcomes. Different approaches have been taken to introduce screening, ranging from hospital-led initiatives to mandatory state-wide policies. A study conducted in New Zealand demonstrated that sector-led screening initiatives are unlikely to result in equitable outcomes. In this midwifery-led maternity setting a nationwide pulse oximetry screening programme with adequate human and material resources should be introduced.

In the last decade, advances in antenatal screening have been made leading to improvement in the detection of critical congenital heart disease (CCHD) in the fetus.[1,2] Furthermore, new developments in the field of interventional cardiology continue to offer those affected by cardiac disease a better chance of survival and an improved quality of life.[3,4] Antenatal detection of a severe cardiac anomaly enables physicians and parents to plan and prepare for the birth and to discuss subsequent management pathways if they wish to continue with the pregnancy. Birth at a centre capable of providing cardiac intervention provides the affected infant with the best chance of survival.[5]

The mortality risk for those with severe cardiac anomalies that are unrecognised at the time of birth do, however, remain high as survival often depends on the patency of the ductus arteriosus that enables the mixing of oxygenated blood with deoxygenated blood. This vessel starts to constrict shortly after birth as a result of the rise in blood oxygen content and will generally close within 24–48 hours after birth. Time is therefore of the essence, as unrecognised cardiac disease can result in sudden cardiovascular compromise and death.

The newborn physical examination is a screening assessment that can potentially identify infants with an underlying

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cardiac anomaly. However, even in the most experienced hands the sensitivity of this examination for the detection of cardiac disease is modest.[6] In New Zealand this assessment is done on the first day after birth by the lead maternity carer, who is most often a midwife. Cardiac disease may not cause visible cyanosis, but a degree of hypoxaemia will be present in the majority of infants with severe anomalies. This has led to the logical conclusion that pulse oximeters (devices measuring oxygen saturation levels) can be utilised as a screening tool for the detection of CCHD in newborns.

The first research in this field emerged in the early 2000s[7,8] and now, nearly 20 years later, the value of pulse oximetry as a screening tool for CCHD has been firmly established. A Cochrane systematic review of 21 studies that included 457,202 participants was published in 2018.[9] Pulse oximetry was found to be highly specific (99.9%; 95% confidence interval [CI] 99.7% to 99.9%) and moderately sensitive (76.3%; 95% CI 69.5% to 82.0%) for the detection of critical cardiac disease with a very low false-positive rate (0.14%). This review showed that six out of 10,000 apparently healthy late preterm and term infants will have CCHD and that pulse oximetry screening can detect five of them. The reviewers therefore concluded that current evidence supports the introduction of routine pulse oximetry screening for CCHD.

Importantly, there is also evidence to show that pulse oximetry screening improves survival for infants with congenital cardiac disease. Abouk et al reported a 33.4% (95% CI, 10.6–50.3%) decline in cardiac-related deaths in American states with mandatory screening policies between 2007 and 2013.[10]

As a result of the mounting evidence in favour of universal pulse oximetry screening, several developed countries have formulated a consensus statement in favour of its implementation. Perhaps the most widely cited is the recommendation made by the United States Secretary of Health and Human Services in 2011 to add pulse oximetry screening to the country's Recommended Uniform Screening Panel.[11] More recently statements have been published by a European workgroup,[12] and in Canada,[13] Spain[14] and Nordic countries.[15] Research has also been conducted in developing countries to investigate the feasibility and unique challenges associated with introducing pulse oximetry screening in those settings.[16–18]

An ideal screening test has a high sensitivity, a high specificity and a low false-positive rate. In pulse oximetry screening, both the timing of screening and the site(s) used to do the test can impact on the accuracy of the test. The Cochrane review on pulse oximetry screening found greater variability in sensitivity than specificity across studies, but could not find an explanation for this heterogeneity in sensitivity.[9] No significant difference in test accuracy was found when comparing measurements obtained from the foot alone (post-ductal) with measurements taken from both the foot and the right hand (post- and pre-ductal). Nonetheless, there are many advocates for two-limb testing as there are reports in the literature of infants diagnosed with coarctation of the aorta or interrupted aortic arch based solely on a difference between pre- and post-ductal oxygen saturation.[19,20] This difference, when present, is produced by right to left shunting across the ductus arteriosus as a result of the pressure gradient between the pulmonary circulation and the aortic arch beyond the level of obstruction. This is an important consideration in the New Zealand context where fewer than 40% of the 15 infants born each year with either coarctation of the aorta or an interrupted arch are diagnosed before birth.[21]

The incidence of specific cardiac anomalies among population groups and its relationship to the sensitivity of pulse oximetry has not been investigated yet. It is well understood that cardiac anomalies produce varying degrees of hypoxaemia depending on the anatomy of the defect with, for instance, aortic arch anomalies less likely to produce hypoxaemia in the first few days after birth than transposition of the great arteries.[22] The incidence of left heart obstructive lesions is significantly higher in the New Zealand European population compared with all other ethnic groups in the country.[23] The ethnic composition of communities and its relationship with disease incidence may therefore contribute to the variation in the test's sensitivity that has been reported.

Furthermore, test accuracy may be influenced by human error.[24,25] Computer-based tools have been shown to result in improved accuracy compared with manual interpretation of screening algorithms. Oster et al reported that 81.6% of mock screening scenarios (using a two-limb strategy) were manually correctly interpreted compared with 98.3% when using a computer-based tool. This difference was most pronounced for "fail" scenarios (65.4% manual vs 96.1% computer).[25] A single-limb screening strategy was used in the New Zealand feasibility study.[26] The simplicity of performing the test on one limb was an important consideration in this setting where significant concerns were raised about the impact of the test on the workload of midwives. This factor, combined with the lack of evidence suggesting a higher sensitivity when using a two-limb strategy and in the absence of a computer-based programme that can store and interpret the test results, resulted in a decision by the Steering Committee that a single-limb strategy was most appropriate for the New Zealand setting.

Test accuracy studies have also investigated the impact of the timing of the test, with screening conducted <24 hours after birth reportedly resulting in higher false-positive rates, but with no significant impact on sensitivity or specificity.[9] We have demonstrated a relationship between the false-positive rate and not only the timing of the test, but also infant activity. Infants tested <4 hours of age were significantly more likely to have a low oxygen saturation level in the absence of pathology (2.8%) compared with 1.9% that were tested after 24 hours (p=0.005).[26] It is generally recommended that pulse oximetry should be conducted on infants that are calm and alert, but the relationship between infant activity and oxygen saturation levels has not previously been investigated. Our research showed that conducting the test while infants are unsettled or asleep will result in a significantly higher proportion of low oxygen saturation levels in the context of no underlying pathology when compared to tests conducted when infants are awake and settled. We were the first to demonstrate that breastfeeding does not result in a higher false-positive rate. This finding demonstrates that the bonding between a mother and infant does not have to be interrupted in order to perform the test. When pulse oximetry screening is conducted in the first 24 hours after birth, the number of false-positive results can be limited if the test is conducted after four hours and while infants are settled or breastfeeding.[26] This is an important finding as infant activity is a variable that can be adjusted more easily than the timing of the test, which is often dictated by the setting in which screening is undertaken. Jurisdictions characterised by early postnatal discharges have to conform to an early screening strategy.[26,27]

False-positive test results are to a large extent attributed to conditions such as respiratory or infective diseases that can also produce hypoxaemia. Early screening in particular presents an opportunity to detect and treat these conditions. The study we undertook showed that 33 of 48 (69%) infants with a positive screening result had a respiratory or infectious disease.[26] This is in keeping with others that reported that pneumonia, septicaemia and transient tachypnoea are some of the most common causes of low oxygen saturations on the first day of life.[28,29] Detecting these 'false-positives' is of benefit to the affected infants as some of these conditions are potentially life-threatening if treatment is delayed. Undertaking pulse oximetry screening before discharging newborns home can also avert the morbidity, cost and anxiety associated with later urgent transfer. During the course of our study, pulse oximetry screening prevented the discharge of several infants with congenital pneumonia and sepsis, and an infant with supraventricular tachycardia.[26] Clinicians are in agreement that no newborn with unexplained persistent hypoxaemia should be discharged home.[30] It is therefore surprising that the UK National Screening Committee recently decided against routine pulse oximetry screening in the UK due to, among other reasons, concerns about potential overdiagnosis and treatment of infants with false-positive test results.[31] A pilot study conducted in the UK found that seven out of every 1,000 infants that are screened will be healthy despite failing to reach target saturations on the first day. Contrary to this up to 80% of infants that are admitted to a neonatal unit following a positive test

have a non-cardiac condition that requires treatment.[32]

In the last decade New Zealand has made significant improvement in the antenatal detection of cardiac anomalies with >70% of fetuses with critical anomalies currently diagnosed during pregnancy.[21] The yield from pulse oximetry screening may therefore be less than in other jurisdictions with lower antenatal detection rates. However, even with high-quality antenatal screening there will always be infants born with CCHD who have not had an antenatal diagnosis either because the lesion was not detected or because of lack of access to appropriate ultrasound investigation. We have estimated that five previously undiagnosed infants with CCHD can be identified each year if pulse oximetry screening is offered in New Zealand.[21] Different approaches have been used globally to introduce screening, ranging from hospital-led initiatives to mandatory state-wide policies.[10,15,16,33] New Zealand has a midwifery-led model of maternity care and women can choose whether to give birth at home, a primary maternity unit or a hospital. Women who birth in a hospital are frequently discharged either home or to a primary unit within hours of the birth. Ensuring that pulse oximetry is offered to all, regardless of the chosen place of birth, will be an important determinant of the success of a screening programme.

Midwives' central role in the care of mothers and babies on the first day postpartum place them in the ideal position to perform pulse oximetry screening. Consultation with New Zealand midwives revealed concerns over the impact on workload and additional resource requirements.[34] The New Zealand College of Midwives and Ministry of Health are working jointly to address the current midwifery workforce shortage and its impact on maternity services. The parties recently agreed to a process for the co-design of a new funding model and contracting of community Lead Maternity Carer midwives.[35] The recognition of the value of midwives' work has also been stressed by the Midwifery Employee Representation and Advisory Services in their advocacy for pay equity for midwives.[36]

Staffing and resource constraints are likely to detract from equitable service delivery. We found significant ethnic and regional disparities in the delivery of pulse oximetry screening in a research setting. Screening rates were lowest among Māori and Pacific infants from the most deprived areas. Furthermore, only 6% of infants born at home were tested. There was also an association between the type of maternity carer and screening rates, with the lowest rates recorded for infants whose mothers failed to register with a carer.[37] The additional demands placed on midwives by a screening programme and the resource requirements therefore require careful consideration.

Reassuringly, there is no evidence to suggest that positive test results will place excessive pressure on child health services in New Zealand. Referral pathways are already in place to ensure that any infant suspected of cardiac or other diseases are assessed and treated appropriately. In our study, 48 of 16,644 (0.28%) infants that underwent pulse oximetry screening had a positive result. Eleven (23%) of those were found to have no underlying pathology. Four (36%) of these infants were admitted to a neonatal unit for investigations and/or observation. The median (range) duration of these admissions was one day (0–2). Over the course of the study 11 echocardiograms were performed, of which four may be considered unnecessary. These four scans were performed by paediatricians and neonatologists and did not impact on cardiac services.[26]

Conclusion

Pulse oximetry is a safe, easy-to-use and effective tool that can identify serious diseases in the newborn before the onset of symptoms. The research conducted in New Zealand supports the introduction of a national screening programme. Such a programme should be adequately resourced, with both equipment, consumables and funded time in order to perform the screening test. The programme should be subjected to monitoring in order to identify deficiencies and to enable quality improvement and equitable access to the test. Uniform guidelines and educational

material should be developed to guide screening practices and to raise awareness among consumers and healthcare professionals. As such, the programme should be governed by the Ministry of Health's National Screening Unit. The best outcomes will be achieved if antenatal ultrasound, the newborn physical examination and pulse oximetry are all offered as screening tests. There must be ongoing efforts to improve the quality of each of these screening tests.

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Teeth or no teeth: exploring punitive measures for adults smoking in cars containing children in Aotearoa/New Zealand

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ABSTRACT

This viewpoint welcomes the recent announcement of the Government of Aotearoa/New Zealand to ban smoking in cars with children. However, it notes that the thorny issue of enforcement and punishment remains. Internationally there is a deficit on research on this issue. The experiences of the UK and Ireland are examined, where there was little or no enforcement of such laws, as well as a comparison with the State of Victoria in Australia, where the law was more robustly enforced. This viewpoint argues that enforcement is an important element in safeguarding the health and wellbeing of children.

One generation plants the trees; another gets the shade. - Chinese proverb

Smoking remains the world's leading causes of preventable mortality and morbidity. Alongside the human cost are the significant economic costs of smoking.[1] Therefore, all actions to de-normalise and remove this threat are important. Hence the recent announcement that Aotearoa/New Zealand is to ban smoking in cars with a child present is welcome,[2] particularly as it will undoubtedly help protect the most disadvantaged children.[3] Although there is some resistance to such legislative approaches among libertarian/laissez-faire advocates,[4] the Government is to be commended for this move. It is a bold and mature step for any Government because, in line with the Chinese proverb above, although it will undoubtedly yield returns into the future, these will not become apparent for some time. Introducing this important legislation closes what has been termed "an enormous gap in the law" elsewhere.[5] In assessing the issue of parents' smoking in cars with children, an obvious parallel is the infamous statement by RJR Tobacco Executive Charles Harper:

At the 1996 shareholders' meeting of cigarette and food manufacturer RJR Nabisco, a woman in the audience asked company chairman Charles Harper whether he would want people smoking around his children and grandchildren. Mr. Harper responded, "If the children don't like to be in a smoky room … they'll leave." When the woman responded, "An infant cannot leave a room," Mr. Harper answered, "At some point they learn to crawl, okay? And then they begin to walk" (RJR Nabisco 1996).[6–7] Given that children are strapped in by seat belts and are, to all intents and purposes, almost incarcerated in cars while being driven by parents/guardians, the similarity with the quote above is obvious.[8] The issue of a smoking ban in cars containing children has been heavily researched in New Zealand, with most of the literature focusing on attitudes towards such a ban or estimates of youth exposure to tobacco smoke. However,

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one notable lacuna in this extensive literature is the issue of the enforcement of and punishment resulting from such legislation. New Zealand is not alone in this deficit. In a review of legislative measures to improve health it is interesting to note Pawson et al's conclusion that "there is virtually no available data pertaining directly to the policing of smoking in cars".[9] However, on the basis of the precautionary principle, legislation and subsequent enforcement is required, albeit accompanied by ongoing evaluative research.

It is generally agreed in legal circles that there are five purposes of punishment: specific and general deterrence; incapacitation; rehabilitation; retribution; restitution.[10] In relation to fines for misdemeanours, the usual reason given is that of general deterrence/prevention.[11] In Ireland for example, the powers of the Police (An Garda Síochána) in relation to the fines for this offence are clearly outlined:

An Garda Síochána will issue a fixed charge notice. The amount of that fixed charge is €100. The person will have 28 days to pay that amount. If they do not pay within the 28 days, the amount payable will increase to €150 to be paid in a further 28-day period. If they do not pay any fine within the 56 days then a prosecution will be initiated.[12]

However, the philosophy of general deterrence presumably only works if sanctions are actually administered, or at least there is a perception of such a threat. Analysis of information from the UK and Ireland, however, reveals the almost total absence of such sanctions. Analysis after the law had been in existence for 12 months in Ireland revealed that nobody had been fined.[13] Reports after a similar period in the UK noted just one fine having been given alongside a minimal number of warnings:

Only Northumbria Police gave a figure other than zero for fines, reporting one case involving a driver. Three forces—the Met Police, Dyfed Powys and Devon and Cornwall—gave figures on warnings, with two, six and three respectively.[14]

It is notable that in other jurisdictions this offence has been much more rigorously enforced. In the State of Victoria (Australia) for example, where the fine for smoking in a car with children is $289, it was noted that "During the first 12 months, police reported 318 offences were recorded, rising to 350 in 2012–2013".[15] Commenting on these figures the author of that report acknowledged that "it is difficult to know if the increasing number of offences related to a rise in incidence or reflected more effective enforcement of the law".[16]

Discussion of the lack of fines metered out in Ireland revealed some interesting responses. For example, the National Director of Population Health indicated that the legislation was assumed to tap into habitual respect for and obedience to the law:

"it was not envisaged that this initiative would have to be driven by fear of prosecution. It is the law and we believe that the vast majority of smokers, and particularly parents, are responsible and comply with legislation".[17]

In a similar vein, the Irish Minister for Health has stated that the Irish police force will not have to enforce the law themselves, instead relying on public shaming: "peer pressure from other drivers who will look across and see a kid in a car and an adult smoking".[18] Given the widespread and well acknowledged problems relating to other traffic-related offences such as speeding, driving without insurance and/or tax, driving while using a mobile phone and illegal parking, this would appear to be an odd appraisal. Perhaps the most notable response to the lack of any fines having been issued in Ireland came from the former Senator and oncologist John Crown, who drew up the legislation. He stated that the fact that no fines for the offence had been issued was "wonderful news … It's really fantastic. The purpose of the legislation was not to make money from prosecutions but to encourage education and create a bit of debate".[32] Senator Crown is undoubtedly correct in that the legislation was never meant to be a revenue stream for government. However, his description of the zero prosecutions outcome as "wonderful" and "fantastic" does appear to have an Orwellian Newspeak ring to it (where instead of such a finding being very bad it might for example be termed 'Doubleplusungood').[19] It must be acknowledged that enforcement of laws in Ireland, as well as professionalism and discipline within the Irish police force, are ongoing

issues.[20–21] Concerns have been raised in both the UK and Ireland about the willingness and ability of police to enforce this legislation.[22–24]

It is hard to pinpoint exactly why both the UK and Ireland have introduced laws outlawing smoking in cars with children, while almost steadfastly refusing to enforce them. However, some of the reasons may include the pervasiveness of smoking, alongside the perceived futility of enacting a law for vehicles, while it remains legal in other contexts, such as the family home. Another reason may include the general perceived inconsequentiality of the offense, particularly in relation to more acutely serious offences. This issue may be combined with police concerns over a public backlash, with offenders and bystanders potentially challenging police with statements or sentiments along the lines of "Have you not got anything better to do?". The general workload and administrative burden of the police force should also not be underestimated as an impediment to enforcement. However, the reality may be that many of the broader coalition of politicians involved were simply more interested in appearing concerned about the issue and striving to score political kudos from the theatrics of dynamic action, rather than actually wishing to implement change.

It is very interesting to note that reports related to the proposed legislation in New Zealand appear to offer a wider spectrum of proposed police interventions than observed elsewhere:

> Police will be able to require people to stop smoking in their cars if children (under 18) are present … They will also be able to use their discretion to give warnings, refer people to stop-smoking support services or issue an infringement fee of $50.[2]

Such interventions therefore would encompass, not just general and specific deterrence but also aspects of rehabilitation[10] such as "educational and vocational programs, treatment centre placement and counselling".[11] As such, the legislation should meet less resistance from both the police and the public in Aotearoa/New Zealand. It should be acknowledged that the New Zealand Police have worked hard to improve their professionalism in recent years.[25]

However, whatever the sensibilities about enforcement of such legislation, it is imperative to remember both the deadly impact of cigarettes, and the responsibilities of New Zealand as a signatory to the United Nation's Convention on the Rights of the Child (UNCRC). Articles 3, 6, 19 and 24 of the UNCRC clearly have implications for the introduction and effective enforcement of legislation banning smoking around children.[26]

It is imperative that the impact of the proposed legislation is evaluated carefully. Such research should include ongoing observation-based analysis, as well as self-report data from both children and adults about exposure. Further research should also examine both support for the legislation and the level of support for penalties for those that break this law. Longer-term research will undoubtedly examine the possible impact of such legislation on smoking rates among young people and cancer epidemiology into the future. However, the difficulties in trying to disentangle the impact of various initiatives probably render such research as hopelessly optimistic.

Although the proposed legislation banning smoking in cars with children is certainly welcome, thought must also be given to how it is going to be implemented and enforced. The evidence is clear from other driving related behaviours that legislation without enforcement is meaningless. Evidence from Ireland and the UK points to police inaction, a scenario that appears in stark contrast to States within Australia. The ethical arguments supporting robust intervention are clear,[27] and there is wide public support for this measure. A range of possible penalties for breaking the law have already been suggested for New Zealand, that go well beyond those currently in place in either the UK or Ireland. However, whatever the proposed penalties or interventions finally adopted, enforcement is essential. Finally, this process should be accompanied by in-depth and ongoing research examining the impact of this important legislation.

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Nil.

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Murphy's law in force: sequential adverse events encountered during the treatment of Pneumocystis pneumonia (cotrimoxazole-induced acute peripheral neuropathy and primaquine-induced methemoglobinemia)

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ABSTRACT

Methotrexate monotherapy is a common management strategy in rheumatoid arthritis (RA). Treatment with immunosuppression can lead to opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP). The treatment options for PJP include cotrimoxazole, clindamycin-primaquine and dapsone. Though these drugs are generally well tolerated, they can result in potentially severe adverse effects. Sometimes several undesired events may occur in a single patient, reminding us of Murphy's law. Herein, we report a case which exemplifies this adage. A 50-year-old female developed PJP, while on methotrexate therapy for RA and was treated with cotrimoxazole. The latter resulted in painful peripheral neuropathy, which improved after cotrimoxazole was stopped. Salvage therapy for PJP with primaquine-clindamycin, lead to another serious adverse event, methemoglobinemia. Withdrawing the offending drug resulted in dramatic improvement.

A 50-year old woman with rheumatoid arthritis (RA) on methotrexate therapy (15mg per week) for the preceding two years presented with fever, dry cough and breathlessness of one-week duration. She had a heart rate of 110 beats/minute, blood pressure 110/60mmHg, respiratory rate 34 breaths/minute and oxygen saturation by pulse oximetry (SpO2) of 74%. Chest radiograph suggested the presence of bilateral symmetrical and basal predominant perihilar infiltrates with peripheral sparing (Figure 1A). Computed tomogram (CT) of thorax revealed bilateral diffuse ground glass opacities and areas of consolidation (Figure 2A). There was no mediastinal lymphadenopathy or effusion. Hemoglobin was 10.3g/dL; total leukocyte and platelet counts were 11,400/mm^3, and 224,000/mm^3, respectively. Echocardiography, renal function and liver function tests were normal. A possibility of *Pneumocystis jirovecii* pneumonia (PJP) was considered. She was unfit for bronchoscopy, and induced sputum examination did not identify any organism, including *Pneumocystis*. Empiric treatment with cotrimoxazole (trimethoprim 960mg and sulphamethoxazole 4,800mg/day in three divided doses) and prednisolone was started. She improved, and was

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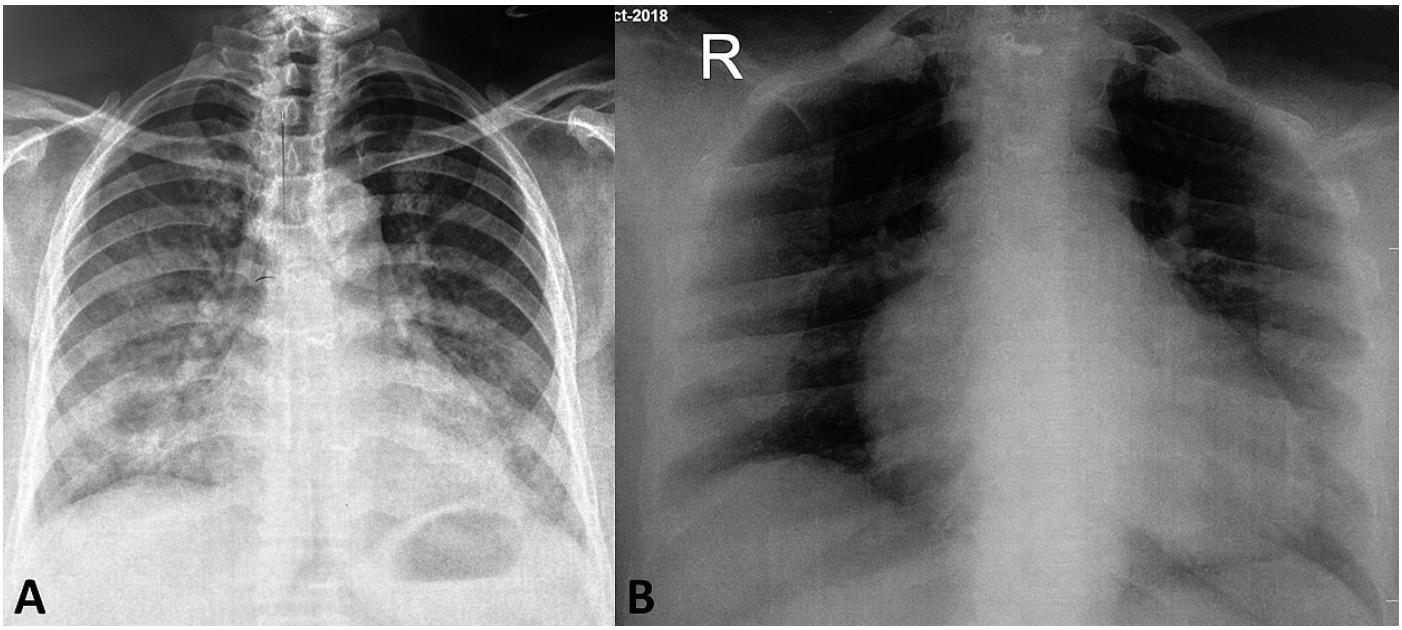
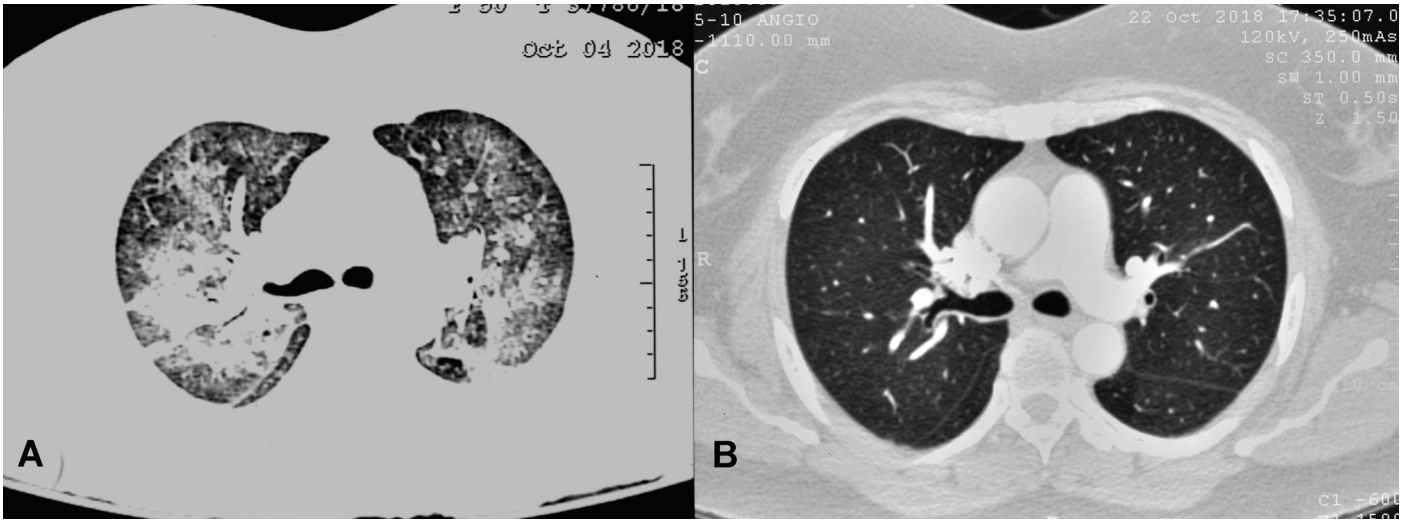
Figure 1: Chest radiograph (A) at presentation showing diffuse bilateral symmetrical basal predominant infiltrates, with peripheral sparing. (B) Unremarkable chest radiograph obtained during the second hospitalisation for breathlessness.



discharged after seven days. Three days later, she noted "needle and pin" sensations, along with weakness involving both her hands and legs. A nerve conduction study suggested axonal sensorimotor neuropathy. Antinuclear antibodies, antineutrophil cytoplasmic antibody, hepatitis B surface antigen, hepatitis C virus and human-immunodeficiency virus antibodies were not detected in the serum. Cotrimoxazole-induced peripheral neuropathy was suspected and the drug was stopped. Neuropathic symptoms resolved and she regained full muscle power in five days. Clindamycin-primaquine (primaquine 30mg base orally once/day and clindamycin 600mg orally thrice/day) was initiated for PJP. Six days later, she reported to the emergency with dyspnea. There was no fever, cough, chest pain, palpitation or orthopnea. Her SpO2 on room air was 90%, BP was 120/90mmHg, respiratory rate was 30 breaths/minute and heart rate was 110 beats/minute. Chest radiograph did not show any lung parenchymal opacities (Figure 1B). CT pulmonary angiography did not reveal acute pulmonary embolism and the

Figure 2: (A) Computed tomography (CT) of the thorax, performed at the initial presentation showing bilateral diffuse ground glass opacities and consolidation. There was no mediastinal lymphadenopathy or effusions. (B) CT scan performed during the second admission, which was normal.



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lung parenchyma was unremarkable (Figure 2B). On arterial blood gas analysis (on inspired oxygen fraction of 0.3), the partial pressure of arterial oxygen (PaO2) and the estimated arterial oxygen saturation (SaO2) were 100mmHg and 98%, respectively. The "saturation gap" (SaO2-SpO2 gap) suggested methemoglobinemia (primaquine-induced), which was confirmed by co-oximetry (14.8%). She improved after stopping clindamycin-primaquine and is currently doing well at six months of follow-up.

Discussion

PJP is a rare complication of methotrexate monotherapy.[1] The treatment options include cotrimoxazole, clindamycin-primaquine and dapsone. Also, cotrimoxazole, dapsone, atovaquone and rarely pentamidine are the drugs recommended for prophylaxis (either primary or secondary) against PJP in immunosuppressed individuals.[2] The use of these drugs may sometimes cause serious adverse events including cytopenias, neuropathy, renal failure and rarely methemoglobinemia. The index patient experienced several rare adverse events sequentially, highlighting the epigram "Murphy's law"—when things can go wrong, they will.[3] Cotrimoxazole is generally well tolerated and adverse effects are mild. Painful peripheral neuritis is unusual with sulfonamides,[4–6] and generally attributed to the sulpha component.[5] Polyneuritis usually presents as painful paresthesias, followed by distal muscle weakness occurring within 1–2 weeks of therapy (range, two days after starting treatment to one month after discontinuation of therapy). The lower limbs are more frequently affected than upper limbs, and the symptoms can re-occur on reintroducing the sulpha drugs. The symptoms usually improve after the culprit drug is withdrawn, though residual weakness may persist in some. In the index case, painful paresthesias occurred after 10 days of therapy, followed by muscle weakness, and she recovered completely after withdrawing the offending drug.

Salvage therapy with clindamycin-primaquine resulted in another uncommon complication, methemoglobinemia, suspected on the basis of the 'saturation gap'. Methemoglobin absorbs both the wavelengths used in pulse oximetry (660nm and 940nm, usually absorbed by deoxyhemoglobin and oxyhemoglobin, respectively), leading to an erroneous estimation of oxygen saturation. Co-oximetry is a spectrophotometric analysis of blood, where absorbance at multiple wavelengths is measured to give an estimate of oxyhemoglobin, deoxyhemoglobin and various dyshemoglobins (including carboxyhemoglobin and methemoglobin).[7] This technique is employed whenever there is a discrepancy between pulse oximetry and the estimated oxygen saturation obtained from blood gas analysis (saturation gap). More accurate determination of methemoglobin levels is possible with the use of Drabkin's agent and the method of Evelyn-Malloy.[8,9] In most cases of methemoglobinemia, withdrawal of the offending drug is sufficient. Supportive therapy (oxygen supplementation or assisted ventilation) or specific therapy with (methylene blue) may be required in some.[10]

Peripheral neuropathy is a rare complication of cotrimoxazole therapy. Primaquine-clindamycin is an alternative for treating PJP, but can cause methemoglobinemia in susceptible individuals. A high index of suspicion and withdrawal of the offending drug usually results in improvement.

Learning points

- The commonly used treatment of PJP can result in unusual complications (cotrimoxazole-induced painful neuropathy) and a high index of suspicion is required to recognise these rare adverse events.
- Drug-induced methemoglobinemia is an important differential diagnosis to be considered in unexplained hypoxemia.
- Timely recognition and withdrawal of the offending drug is essential in managing this potentially life-threatening condition.

Competing interests:
Nil.

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Antenatal rubella serology is useful for reassuring pregnant women that they are likely to be immune to measles

Timothy K Blackmore, Maxim Bloomfield, Sarah Burge, Kirsty Low, Marina Dzhelali, Annette Nesdale

New Zealand is currently experiencing a significant measles epidemic, initially centred in Auckland, but with increasing numbers appearing elsewhere.[1] There have been numerous public health messages advising people who have been in particular places such as cafes, schools, workplaces and aircraft to be alert to the possibility that they may have been exposed to infectious measles.

A recent review of severe measles in Auckland indicated that some pregnant women with measles went into premature labour, and there has been a high proportion of measles cases admitted to hospital.[2,3] These factors have compounded concern for pregnant women, and driven them to seek information about their immune status for measles. The only measles-containing vaccines available in New Zealand also contain mumps and rubella attenuated live viruses (MMR) and are therefore contraindicated in pregnancy. Many pregnant women do not have their immunisation records and are left concerned that they may be non-immune. Laboratory testing for measles IgG antibodies offers a way of testing immunity, but there may be limited laboratory capacity to perform testing outside of public health contact tracing for measles outbreak control.

All pregnant women in New Zealand are currently recommended to have rubella IgG antibody screening at the first antenatal visit. MMR vaccine was introduced in New Zealand in 1990,[4] so it is reasonable to assume that New Zealand-born women born after 1990 with antibodies to rubella will have them as a result of MMR rather than single antigen vaccine or natural infection. We therefore planned to conduct a small pragmatic study to establish whether the already available rubella antibody results could be used to predict measles immunity, and hence provide a way of reassuring pregnant women who are not sure of their vaccination history.[5,6]

One hundred and four first antenatal blood samples from routine requests were collected and tested. Names were not recorded, but the national health index number was used to determine ethnicity and whether New Zealand-born status from the national minimum dataset. Rubella and measles IgG testing was conducted using Architect Rubella IgG assay (Abbott Laboratories, Lake Forrest, Illinois, US) and Virclia Measles IgG assay (Vircell, Granada, Spain), respectively, as routinely used in our laboratory. Results were interpreted according to the manufacturers' recommendations. The study received expedited approval from the regional ethics committee.

The population characteristics are shown in Table 1.

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Table 1:

	Total	Overseas born	Unknown birth country
NZ European	45	0	6
NZ Māori	31	1	3
Samoan	10	4	2
Indian	5	1	4
Other European	5	3	2
Other Asian	2	1	1
African	1	1	0
Response unidentifiable	1	0	0
Fijian	1	1	0
Tokelauan	1	0	0
Middle Eastern	1	1	0
Pacific Island not further defined	1	0	0
Grand total	**104**	**13**	**18**

Approximately 30% of subjects were either born overseas or the information was not available, making it impossible to make assumptions about whether or not they received MMR in childhood.

As shown in Table 2, 71% and 89% of participants had serological evidence of immunity to rubella and measles, respectively. If equivocal rubella results are included in the immune group, rubella serological immunity increased to 89%.

The important finding is that only two women with immune levels of rubella IgG lacked detectable measles antibodies. One person was born in Fiji in 1992, where measles-rubella vaccination was introduced in 2003. The other was identified as New Zealand European, born in New Zealand in 1990, but we did not have any vaccination history. Our study was too small for further subgroup analysis.

A study of antenatal serology from Montreal showed higher rates of immunity to rubella and measles, but also found that rubella non-immunity predicts measles non-immunity. Interestingly they found that routine measles antibody testing showed that 28% of women were "non-immune" to measles, but when tested with the reference plaque reduction assay, the number of

Table 2:

	Measles IgG				
	All	Immune	Non-immune	Percent Immune by rubella status	95% CI
Rubella immune	71%	72	2	97%	90–100
Rubella equivocal	18%	15	4	80%	54–94
Rubella non immune	11%	6	5	55%	23–83
	100%	**93**	**11**	**89%**	**82–95**

Measles immunity groups are presented according to rubella immunity status.
Interpretation of rubella immunoglobulin G (IgG, IU/ml): < 5, non-immune; 5-10, equivocal; > 10, immune.

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non-immune dropped to 4.3%.[6] Our study therefore probably undercalls measles immunity, which would only strengthen the conclusion that a woman with immune levels of rubella antibodies is unlikely to non-immune to measles.

Another study of the relationship between rubella and measles immunity in pregnant women by Kennedy et al is interesting, because despite finding similar numbers to our study and that of Martel et al,[6] they reached the conclusion that rubella antibody levels are not useful for predicting measles immunity.[7] We believe the statistic used was misleading, which looked at all rubella results. Our hypothesis, supported by our findings, was that high levels of rubella antibodies would be a reasonable presumptive indicator of receiving MMR, and hence predictive of immunity.

We believe these results provide evidence to inform those providing advice to New Zealand-born pregnant women born after 1 January 1990 who may not be able to source their childhood vaccination records. Rubella IgG levels >10 IU/ml are predictive of vaccine-induced measles immunity, and provide a readily available way of identifying women who do not need to worry about measles if there are increasing numbers of measles cases in the community. We would still recommend measles antibody testing for a woman who has been in close contact with a known case, particularly if there is uncertainty about whether she has received two doses of MMR. These results also highlight a high proportion of women who don't have detectable rubella antibodies on first antenatal serology and hence the need to offer MMR vaccination after delivery.

Routine serological testing is generally insensitive for detecting vaccine-induced immunity and there is inter-assay variation at lower levels of IgG.[8–10] Receipt of two doses of properly administered and documented MMR is considered to provide immunity to measles and rubella in almost all cases, regardless of serological testing.[11] Even using routine serological methods, this small study suggests that New Zealand-born pregnant women born after 1 January 1990 (after the combined MMR vaccine was introduced in New Zealand) who are unsure of their vaccination history can be reassured that they are likely to be immune to measles if they have high levels of rubella IgG on antenatal testing.

Competing interests:
Nil.
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Response to Ben Gray: Sun protection policy in New Zealand

Bronwen McNoe, Anthony Reeder

We recently published findings from an ecological study of school sun protection policies.[1] In a critique of our publication,[2] Gray incorrectly states that we collected ethnicity data, but failed to utilise it in the data analysis. Our study and analyses were conducted at the school level, whereas ethnicity is a personal characteristic. It would have been possible, using Ministry of Education data, to categorise schools based on the proportion of European children on their roll, for example. However, we do not believe that this would be appropriate.

First, ethnicity does not necessarily equate with skin phototype, which is a crucial factor for skin cancer prevention. A national telephone survey of 396 randomly selected participants included 57 who identified as Māori, and these encompassed the full range of untanned skin colour from very light to very dark.[3] Some reported susceptibility to sunburn and almost 20% reported experiencing sunburn the previous summer weekend—five becoming red and tender or sore, the most severe category.[3] Admittedly that sample was small, but we mention it to highlight that assumptions about skin type cannot be made on the basis of ethnicity.[4]

Second, even schools with low proportions of European children still include sizeable numbers of those children who are most vulnerable to skin damage from exposure to UV radiation. For example, approximately one-quarter of New Zealand primary schools are listed as having less than 25% of their school roll identified as European and yet these schools still represent 15,000 children of European ethnicity (http://www.educationcounts.govt.nz/home).

New Zealand has extremely high rates and numbers of cutaneous melanomas and other skin cancers. The epidemiological evidence of the causal association of ultraviolet radiation exposure and subsequent skin cancer development is very strong. Childhood and adolescence are thought to be particularly important times both for preventing DNA damage which may initiate carcinogenesis and for establishing recommended lifetime sun protection practices.

Although in our increasingly multicultural society it would be better not to use what Gray calls a "one- size-fits-all" policy approach to sun protection, pragmatically this is the reality, given the lack of resourcing for skin cancer primary prevention. The Government currently invests only $600,000 per annum (including salaries) to fund skin cancer primary prevention programmes through the Health Promotion Agency (personal communication Health Promotion Agency 2019). The responsibility for advocating for sun protection in schools is entirely devolved to a charitable organisation with no government funding and limited resources. There is no Government investment to support sun protection, such as the provision of shade or sun protective hats in existing schools. This is despite Australian evidence that investment in their SunSmart skin cancer prevention programme is cost effective.[5]

The cost of treating this largely preventable group of skin diseases continues to escalate. Last year, funding for Keytruda to treat stage 4 melanoma, alone, cost our public health system $23.4 million.[6] The cost for treating the 90,000 cases of Keratinocytic cancers per year is unknown,[7] but likely to be substantial. In Australia, which has five times our population, the annual cost of treating skin cancer is $900 million.[8,9] Modest investment in primary prevention would help ensure that the proportional New Zealand equivalent could, increasingly

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as disease rates fell, be directed to making a valuable contribution to addressing other health issues.

Concern about vitamin D deficiency is of course an issue, but most New Zealanders can obtain sufficient vitamin D through incidental sun exposure. When this is not the case, as the Consensus Statement notes (https://www.health.govt.nz/publication/consensus-statement-vitamin-d-and-sun-exposure-new-zealand), for example among the institutionalised elderly or those who wear full-body clothing coverage as part of cultural practices, supplementation may provide the best option. A recent study of rickets among children in New Zealand found that most cases occurred among children with mothers of African, Asian or Middle Eastern origins and concluded that "*Preventative targeted vitamin D supplementation, as per existing national guidelines, was lacking in all cases reported.*"[10] That represents a failure in primary healthcare. The other side of the coin is that we cannot afford to fail to protect vulnerable young school children from exposure to harmful levels of solar ultraviolet radiation, a type 1 human carcinogen. Finally, it should be noted that the SunSmart schools programme operates in terms 1 and 4 when the risk of skin damage is highest and school boards endeavour to develop appropriate policies in consultation with their communities.

Competing interests:
Nil.

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Unilateral Renal Haematuria

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Several cases of unilateral renal haematuria have come under my care which are of sufficient interest to warrant publication from several points in their histories and treatment.

(1) R. was a married man of about forty with an uneventful medical history. About eight months ago he came to the genito-urinary clinique with a complaint of blood in the urine. Examination of the urine showed blood alone as an abnormal constituent of the urine. There were no casts, pus, or organisms.

Cystoscopic examination showed bloody urine spurting from the right ureter. The jet from the left ureter was apparently normal. The right ureteral orifice seemed slightly congested, the left normal. The pulse and temperature were normal. The bodily examination showed an easily palpable, movable right kidney, slightly enlarged, but painless and insensible, otherwise the examination was negative. He was advised to undergo further examination, as the possibility was renal tumour, and an operation advisable. But he promptly disappeared from my ken, and I did not see him again for many months. Subsequently he was referred back to me by Dr. Whetter, as the haematuria had continued unabated, and latterly had been accompanied by renal colic on the right side.

His condition was unchanged except that he was thinner and felt poorly, and the examination again revealed only the blood in the urine and the palpable right kidney.

I cystoscoped him again and catheterised the left ureter. The right ureter was spurting blood and was slightly congested. The urine from the left kidney was quite normal. X-ray photographs were negative.

My provisional diagnosis was malignant disease of the right kidney, tuberculosis and calculi being negatived by the absence of pus and organisms and the X-ray photographs.

On 21st March, 1918, I explored the right kidney, which, except for the thickening of the capsule which so commonly accompanies movable kidney, appeared normal. I explored the kidney substance completely by incision and found nothing. I therefore closed the kidney and fixed it posteriorly by Thompson Walker's method.

His convalescence was normal. The renal colic, which I put down to the passage of clots, disappeared, and the urine became completely bloodless by the end of a week. He left the hospital in three weeks, and has remained since quite well.

(2) M.J.W., aet. 54, strained his back a year ago, and was off work for some weeks in consequence. A few weeks later he noticed blood in the urine, and this had been present ever since. He had no pain, but lost weight and felt weak.

Examination, apart from the facts of obvious anaemia, an insensitive palpable right kidney, and blood in the urine, disclosed nothing. The urine contained blood, transitional cells, and scanty polymorphs—no tubercle bacilli or other organisms.

Cystoscopy revealed blood spurting from the right ureter, and none from the left. Ureteral catheterisation yielded "profuse blood-transitional cells, scanty polymorphs, no tubercle bacilli" from the right ureter, and "scanty blood (probably due to the slight traumatism of catheterisation), scanty polymorphs, transitional cells, no tubercle bacilli" from the left ureter.

On 24th February, 1919, I explored the right kidney and found it normal except for the same thickening of the capsule referred to in Case 1. I incised the kidney and found nothing and removed a piece for microscopical examination. I fixed the kidney to the posterior wall, removing a part of the posterior capsule for the purposes of the fixation. By 28th February the urine was free

from the appearances of blood, and, healing without complications, he was ultimately discharged, apparently completely cured.

(3) P.K., a young girl, aet. 13, had had haematuria with right-sided renal colic accompanied with the passage of blood clots for a considerable time. Dr. Irving, with whom I saw her, had tried varied and many remedies. There had been some loss of weight and languor. The right kidney was palpable. The urine contained blood, but no casts, pus, or organisms, and X-ray photograph showed no stone. Cystoscopy and ureteral catheterisation showed the blood limited to the right side. The palpable kidney and localisation of the haematuria, combined with her age, were suspicious of malignancy. Exploration of the right kidney was therefore advised.

Dr. Irving informs me that her kidney was explored by Dr. Barnett, of Dunedin, and, thorough examination being negative, it was moored in its place. The immediate and subsequent result was complete recovery.

The features which these cases above noted have in common are—(1) Limitation of the haematuria to one side; (2) right kidney in all; (3) kidney easily palpable; (4) absence of pus, casts, and organisms; (5) two had renal colic on the right side; (6) there was clotting of blood in all of them; (7) my own cases had thickening of the capsule; (8) all were treated by nephrotomy; (9) all have apparently perfectly recovered.

They differ from those cases classed as essential haematuria in the facts that—(1) there were blood clots; (2) pain was a feature.

It is difficult to account for the bleeding, in view of the relief obtained by operation. It is also not possible to do other than credit the exploration of the kidney with the cure, as their histories were prolonged and the result immediate. Whether the fixation alone, or the nephrotomy in addition, produced the favourable result is a matter of speculation. Certainly one is obliged to incise the kidney for the exclusion of tumour, varix, or papilloma. On the other hand, the negative finding thus made excludes these causes and makes one wonder how incision could be effective in view of the linear character of nephrotomy and the obvious limitation of the severing of any dilated vessels unobserved to a definite linear area.

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