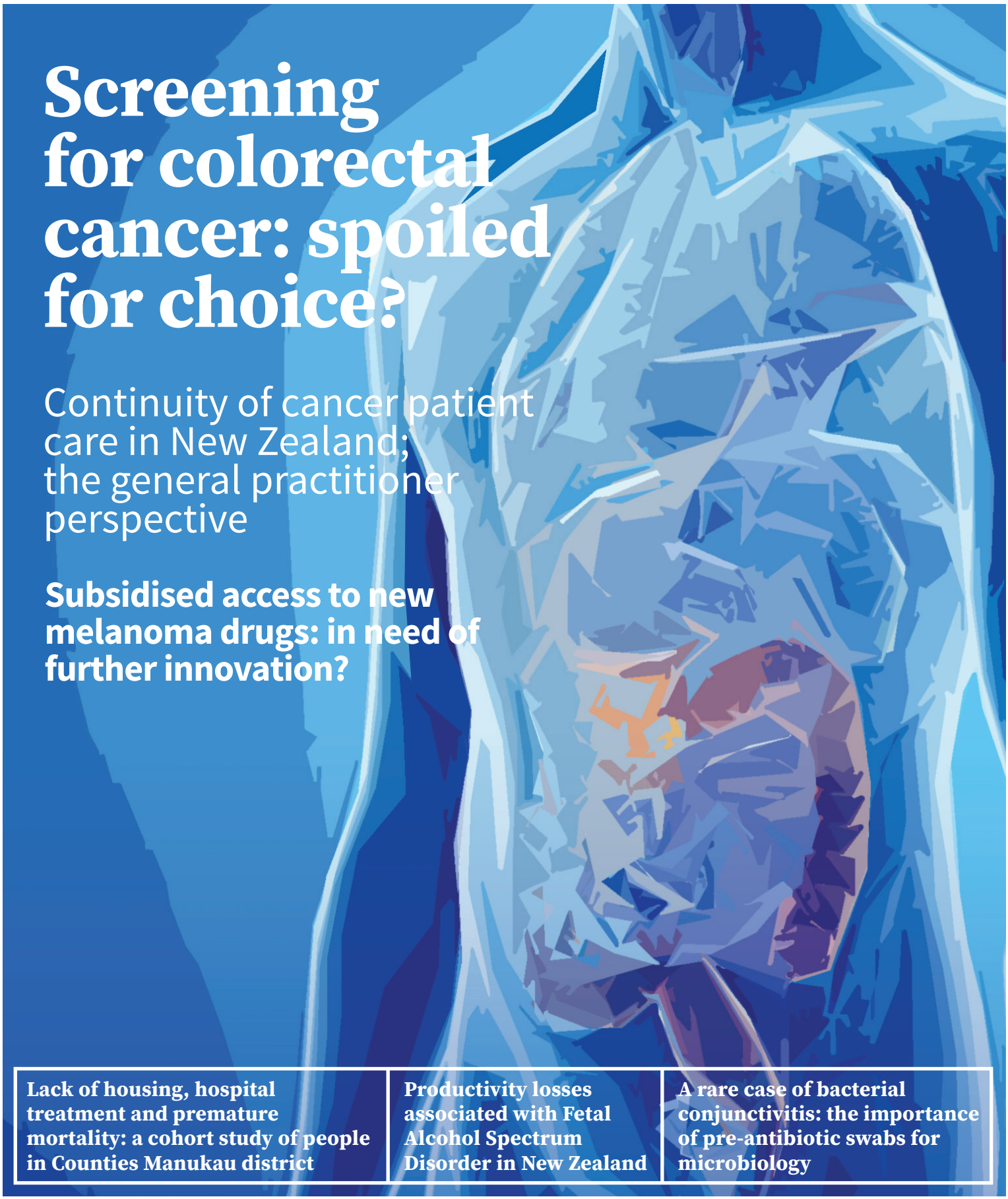
The
New Zealand
Medical Journal
Journal of the New Zealand Medical Association
Vol 129 | No 1440 | 19 August 2016



Screening for colorectal cancer: spoiled for choice?

Continuity of cancer patient care in New Zealand; the general practitioner perspective

Subsidised access to new melanoma drugs: in need of further innovation?

Lack of housing, hospital treatment and premature mortality: a cohort study of people in Counties Manukau district

Productivity losses associated with Fetal Alcohol Spectrum Disorder in New Zealand

A rare case of bacterial conjunctivitis: the importance of pre-antibiotic swabs for microbiology

The New Zealand
Medical Journal
Publication Information
published by the New Zealand Medical Association

To contribute to the *NZMJ*, first read:
www.nzma.org.nz/journal/contribute

Other enquiries to:
NZMA
PO Box 156
The Terrace
Wellington 6140
Phone: (04) 472 4741

To subscribe to the *NZMJ*, email
julie@nzma.org.nz

Subscription to the *New Zealand Medical Journal* is free and automatic to NZMA members.

Private subscription is available to institutions, to people who are not medical practitioners, and to medical practitioners who live outside New Zealand. Subscription rates are below.

All access to the *NZMJ* is by login and password, but IP access is available to some subscribers.

Read our Conditions of access for subscribers for further information
www.nzma.org.nz/journal/subscribe/conditions-of-access

If you are a member or a subscriber and have not yet received your login and password, or wish to receive email alerts, please email: julie@nzma.org.nz

The NZMA also publishes the *NZMJ Digest*. This online magazine is sent out to members and subscribers 10 times a year and contains selected material from the *NZMJ*, along with all obituaries, summaries of all articles, and other NZMA and health sector news and information.

Subscription rates for 2016

New Zealand subscription rates		Overseas subscription rates	
Individuals*	$298	Individual	$415
Institutions	$517	Institutions	$557
Individual article	$25	Individual article	$25

*NZ individual subscribers must not be doctors (access is via NZMA Membership)
New Zealand rates include GST. No GST is included in international rates.
Note, subscription for part of a year is available at pro rata rates.
Please email julie@nzma.org.nz for more information.
Individual articles are available for purchase by emailing nzmj@nzma.org.nz

ISSN 1175-8716

Methods of a national colorectal cancer cohort study: the PIPER Project

Melissa J Firth, Katrina J Sharples, Victoria A Hinder, Jerome Macapagal, Diana Sarfati, Sarah L Derrett, Andrew G Hill, Charis Brown, Papaarangi MJ Reid, Ross A Lawrenson, Carol Atmore, John P Keating, Mark Jeffery, Adrian H Secker, Charles De Groot, Christopher GCA Jackson, Michael PN Findlay

A national study looking at bowel cancer in New Zealand has previously been completed (the PIPER Project). The study included 5,610 patients and collected medical information about how each person was found to have bowel cancer and the treatment they received. This paper reports how the study was carried out. The information collected in the study will be used to look at the quality of care being provided to New Zealand patients with bowel cancer, and to find out if differences in care occur based on where people live, their ethnicity and their socioeconomic status.

Subsidised access to new melanoma drugs: in need of further innovation?

Michael Wonder, Rosalie Fisher

Melanoma is the most serious of the three forms of skin cancer. New Zealand and Australia have the highest melanoma incidence rate in the world. A number of new medicines (with different modes of action) for the treatment of patients with advanced melanoma are now available. These medicines are more costly and more effective than the existing treatments. These medicines are currently reimbursed in Australia and England. Only one these medicines is currently reimbursed in New Zealand and only since 1 July 2016.

Continuity of cancer patient care in New Zealand; the general practitioner perspective

Paul Kane, Marieke Jasperse, Richard Egan, Lynn McBain, E McKinlay, Susan Pullon, Patries Herst

As cancer therapies become increasingly effective, the number of cancer patients seeking long-term support from GPs is going up. This study investigated the perspective of GPs on issues around continuity of care for these patients. GPs who contributed noted they wanted more involvement with cancer patients but were not always clear as to their role. Poor communication with other facets of the healthcare system and barriers for patients in accessing GP care, are areas for improvement. Addressing these issues will improve the lot of cancer patients.

The incidence of Orofacial Cleft in live births in New Zealand

John MD Thompson, Peter R Stone, Megan Sanders, Harriette van der Zee, Barry Borman, Peter V Fowler

The overall incidence of oro-facial cleft in New Zealand over a ten year period was found to be 1.79 per 1,000 live births, higher than the norm for Western society. Māori rates are higher mainly due to a high rate of cleft palate alone (the highest known reported rate in the world). Different sex ratios were also seen in relation to Cleft Lip and Cleft Lip and Palate for Māori and Pacific compared to those normally reported. This data provides the basis for ongoing research in relation to outcomes of children born with oro-facial cleft. It also provides the impetus for further work understanding the environmental and genetic risk factors associated with oro-facial cleft.

Productivity losses associated with Fetal Alcohol Spectrum Disorder in New Zealand

Brian Easton, Larry Burd, Jürgen Rehm, Svetlana Popova

FASD, Foetal Alcohol Spectrum Disorders, arise from the drinking of alcohol by pregnant mothers damaging the brain development of the unborn child causing permanent cognitive damage which limit the child and impact on the child's family and society as a whole—by greater demand for health services, poorer educational performance, lower labour productivity and, in some cases, greater pressure on the justice system; it is thought that about one percent of the population suffer from FASD. The research estimates that the labour force productivity loss due to FASD-attributable morbidity and premature mortality translated to an aggregate loss in 2013 in the range from $49 million to $NZ200 million—between 0.03% and 0.09% of the annual gross domestic product. An effective preventive program, which made the public aware of drinking alcohol during pregnancy and discouraged pregnant women from drinking, would more than pay for itself in terms of productivity gains in the labour force; there would be additional public gains from reductions in demands on health services, more effective educational services and lower use of justice services, while family stress would be reduced.

Lack of housing, hospital treatment and premature mortality: a cohort study of people in Counties Manukau district

Simon Thornley, Roger Marshall

People who are treated in hospital and identified with a lack of housing are at high risk of death, with a life-expectancy about 20 years lower than the general population. Māori and Pacific people are over-represented in this population. Substance use and complications of use is common in this population. While cigarette smoking is likely to be responsible for the greatest burden of early death in this population, cannabis use in this group is also strongly associated with premature death.

In-hospital morbidity and brain metrics of preterm neonates born 1998–2009

Sarah L Harris, Nicola C Austin, Malcolm Battin, Roland Broadbent, John Horwood, Ross Keenan, Scott Wells, Carole Spencer, Patricia Graham, Lianne J Woodward, Brian A Darlow

Mortality and morbidity of infants born extremely premature in the antenatal steroid and early surfactant era have fallen. Morbidity following extremely preterm birth impacts on future health. Brain metrics is a novel simple, reproducible means of assessing brain growth in neonates born preterm. This study describes the survival, in-hospital morbidity, brain metrics and two-year neurodevelopmental outcomes of two extremely preterm cohorts and discusses the contribution of changes in clinical practice to these outcomes. The outcomes at hospital discharge of extremely preterm infants have improved since 1998 with better initial physiological stability, improved nutrition, decreased rates of chronic lung disease and improved brain metrics and neurodevelopment. This study adds to the accumulating data regarding the utility of brain metrics as a means of assessing brain growth in the preterm population and identifies multiple quality improvements in clinical care.

Little risk of severe complications associated with Zika infection in New Zealand

Gareth J Parry, Matthew Peacey, Eric J Buenz

Zika virus has established endemicity in the Pacific basin and has engendered considerable anxiety about its possible entry into New Zealand. Person-to-person infection through the mosquito vector is not possible in New Zealand but the country does not harbour the specific mosquito species. There is a low risk of sexual transmission or transmission through other body fluids. Serious complications associated with Zika infection include microcephaly and Guillain-Barre syndrome and individuals returning from an endemic area with a febrile illness should be checked for Zika infection and counselled regarding risk to the foetus and monitored closely if neurological symptoms occur.

Why are those most in need of Sudden Unexplained Infant Death (SUDI) prevention information the least likely to receive it? A comment on unconscious bias and Māori health

Carla A Houkamau, Kathrine Clarke

This paper expands discussions of unconscious bias into the New Zealand health care arena. We review international research which links health provider bias to inequitable health outcomes for ethnic minorities as well as local data which indicates Māori may be vulnerable to bias. Our focus is on outcomes from the 2014 *Well Child/Tamariki Ora (WCTO) Programme Delivery Report* which shows Māori are less likely to receive SUDI prevention information from their Well-child health provider than other ethnic groups in New Zealand.

Screening for colorectal cancer: spoiled for choice?

Diana Sarfati, Caroline Shaw, Melissa McLeod, Tony Blakely, Ian Bissett

Deciding on the best test to use in a bowel cancer screening programme for New Zealand is not entirely straightforward due to limitations in the research base and local factors. Reviewing the modelling literature from overseas shows that other countries are also encountering these issues, however the models consistently show that bowel cancer screening is a cost-effective intervention compared to no screening and that immunochemical faecal occult blood testing is likely to be the best choice in New Zealand currently. However this may change in the future as more research is undertaken.

A change in focus in colorectal cancer in New Zealand: not *should* we screen, but *who* and *how* should we screen?

J Gandhi, TW Eglinton, FA Frizelle

New Zealand's rate per capita of colorectal cancer is among the highest in the world, with a median annual age standardised rate per 100,000 for males of 55.2 (range 50.8 to 56.2) and for females 44.1 (range 42.5 to 45.0).[1] Colorectal cancer was the third most commonly diagnosed cancer in New Zealand in 2012 with 3,016 cases, behind only breast cancer (3,054) and prostate cancer (3,129).[2] It was the second most common cancer for both males and females in New Zealand, behind prostate and breast cancer respectively, and had the second highest number of deaths from any cancer (1,283 in 2012), with only lung cancer leading to more deaths (1,628).[2]

Despite this significant burden of disease, single institutional data suggests that the outcome from colorectal cancer has steadily improved over the last 20 years[3] but still lags behind similar countries such as Australia. Given that the prognosis of colorectal cancer is related primarily to stage at diagnosis, screening can play a major role in improving outcomes and has been implemented in many countries. With such a burden of disease, the lack of a bowel cancer screening programme in New Zealand has been of huge concern. The New Zealand Government has now, finally, after 17 years of avoiding doing so, announced the roll-out of a national colorectal cancer screening program over the next three years. This has shifted the debate from *should* we screen to *how* and *who* we should screen. Two articles published in this edition of the NZMJ further enlighten these aspects of the debate.[4,5]

Firstly, the PIPER study[6] has demonstrated what is really happening in New Zealand to patients with colon and rectal cancer. The PIPER study is a comprehensive description of the outcome and management of New Zealanders with colorectal cancer and its methodology is described in this issue of the journal.[4] It is a national retrospective cohort study of a selected sample of New Zealand residents diagnosed with colorectal adenocarcinoma in New Zealand from 1 January 2007 to 31 December 2009. The researchers identified 5,667 eligible patients. A full copy of the results can be found on the University of Auckland Faculty of Medical and Health Services website.

The PIPER study[6] found 4,193 (74%) patients were diagnosed with colon cancer, and 1,401 (25%) with rectal cancer. Most patients were of European extraction, with 8% recorded as Māori, 3% as Pacific, and 2% as Asian. The mode of first presentation was to the emergency department (ED) for 34% of patients with colon cancer, with 44% for Māori and 51% for Pacific patients. In the UK, 21% of CRC patients have this mode of admission. For patients with rectal cancer, the mode of first presentation was to the ED for 14% of patients; 21% for Māori and 24% for Pacific patients, while 8% of patients with colorectal cancer presented with a bowel obstruction.[6] This information is consistent with earlier work showing the unequal impact of cancer across Maori and Pacific Island communities.[7,8,9]

As discussed, the stage of CRC at diagnosis is the single most powerful prognostic variable and is the principal determinant of treatment. PIPER confirmed New Zealand has a relatively higher proportion of patients diagnosed with stage IV (metastatic) disease than other countries—

Australia has 19% and 17% stage IV for colon and rectal cancer respectively, and the UK has 17% for both stage IV colon and rectal cancer. Higher proportions of metastatic disease were seen in Māori and Pacific patients; the proportions diagnosed with stage IV colon cancer were 32% and 35% for Māori and Pacific respectively, and for rectal cancer were 29% and 22% respectively.[6]

These outcomes highlight one of the important challenges for management of CRC in New Zealand, which is how to reduce inequities in cancer-related outcomes. Colorectal cancer is one of the few cancers for which incidence rates are lower among Māori, but rates among Māori are tending to increase towards those of non-Māori. Māori patients tend to be younger at diagnosis and have more comorbidities. There is evidence relating to health service factors that contribute to poorer colorectal cancer survival among Māori. Fewer Māori are referred to oncologists in comparison to non- Māori; fewer are offered chemo and of those who are referred, fewer get chemo started within 8 weeks.[10]

The Ministry of Health's document on *Standards for Service Provision for Patients with Bowel Cancer in New Zealand*[11] provides a starting point for ensuring there is harmonisation of best practice in the care of patients with colorectal cancer. The objective of the standards is to promote nationally coordinated and consistent standards of service provision across New Zealand, with a focus on equity. These standards, however, are still being implemented, and many aspects are yet to be fully applied especially aspects around equity.

The inequities identified in PIPER and previous research need to be carefully considered in the roll-out of a national screening programme. Screening is typically taken up by the white middle class, especially females. In the pilot, while 56.8% of the target population took up the screening trial, only 46% of those who identified as Māori and 30% of Pacific Islanders. This compared with 59.7% that identified as of European descent.[12] Previous work on this[13] has shown participants were largely positive about potential colorectal screening; however, various access barriers exist. These include patient-clinician engagement and communication; lack of provision for patient's privacy during screening; and patients feeling discouraged to take part in screening. Factors enabling screening include having an established relationship with their general practitioner; screening clinicians taking time to build rapport, answer questions and share information; screening practices that were inclusive of Māori cultural norms; and possessing high health literacy.

In addition to engaging different populations in CRC screening, now that a national programme has finally become a reality, another focus of debate has reignited on how to most appropriately screen the population.[14] Multiple options exist, ranging from faecal occult blood tests, through radiological investigations, to flexible sigmoidoscopy and colonoscopy. In the second CRC-focused paper in this issue, these options are outlined and discussed. Safarti et al[5] conclude that the proposed national population-based biennial FIT-based programme is consistent with international evidence and entirely in line with similar decisions made in countries with similar health care systems and resource constraints.

It is reassuring that a national bowel cancer screening programme is now within our grasp and that the chosen test is appropriate to maximise the impact on bowel cancer outcomes. The challenge for the programme will be to ensure these outcomes are maximised across all New Zealanders, in particular Māori and Pacific peoples.

Author information:
J Gandhi, FRACS Colorectal fellow CDHB etc; TW Eglinton, MMedSC FRACS Assoc Prof of surgery, colorectal surgeon; FA Frizelle, FMMedSC FRACS Professor of colorectal surgery, Colorectal surgeon.
Corresponding author:
FA Frizelle FMMedSC FRACS Professor of colorectal surgery, Colorectal surgeon.
frank.frizelle@cdhb.health.nz
URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6969

REFERENCES:

1. Ministry of Health. Cancer: new registrations and deaths. 2007. Table 5. Available on www.moh.govt.nz.
2. Ministry of Health, "Selected Cancers 2012, 2013, 2014," October 2015. [Online]. Available: http://www.health.govt.nz/publication/selected-cancers-2012-2013-2014.
3. Pamela Buchwald, Claire Hall, Callum Davidson, Liane Dixon, Frank Frizelle. The four cohort study: improved survival for rectal cancer compared to colon cancer. ANZJ Surg. 2016 in press
4. Michael Wonder, Rosalie Fisher. Methods of a national colorectal cancer cohort study: the PIPER Project. NZ Med J. 2016;1440: (25–36)
5. Diana Sarfati, Caroline Shaw, Melissa McLeod, Tony Blakely, Ian Bissett. Screening for colorectal cancer: spoiled for choice? NZ Med J. 2016 Aug 19;129(1440): 120–128
6. Christopher Jackson, Katrina Sharples, Melissa Firth, Victoria Hinder, Mark Jeffery, John Keating, Adrian Secker, Sarah Derrett, Carol Atmore, Dale Bramley, Charles De Groot, Wendy Stevens, Diana Sarfati, Charis Brown, Andrew Hill, Papaarangi Reid, Ross Lawrenson, Michael Findlay. The Piper study https://www.fmhs.auckland.ac.nz/assets/fmhs/sms/ctnz/docs/THE%20PIPER%20PROJECT%20Final%20deliverable%20report%207%20August%202015%20(HRC%2011_764%20FINDLAY).pdf)
7. Robson B, Purdie G, Cormack D. 2010. Unequal Impact II: Māori and Non-Māori Cancer Statistics by Deprivation and Rural–Urban Status, 2002–2006. Wellington: Ministry of Health.
8. Hill S, Sarfati D, Blakely T, et al. Ethnicity and management of colon cancer in New Zealand: do indigenous patients get a worse deal? Journal of Epidemiology Community 2009;63; 6: 3205–14
9. Hill S, Sarfati D, Robson B, Blakely T. Indigenous inequalities in cancer: what role for health care? ANZ J Surg. 2013;83:36–41
10. Sarfati D, Hill S, Blakely T, Robson B, Purdie G, Dennett E, Cormack D, Dew K. (2009). The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: A retrospective cohort study. BMC Cancer, 9, 116. doi: 10.1186/1471-2407-9-116
11. Standards for Service Provision for Patients with Bowel Cancer in New Zealand Available on http://www.health.govt.nz/our-work/diseases-and-conditions/cancer-programme/faster-cancer-treatment-programme/national-tumour-standards
12. Bowel Screening pilot. Available on http://www.health.govt.nz/our-work/diseases-and-conditions/cancer-programme/bowel-cancer-programme/bowel-screening-pilot.
13. Pitama S, Cave T, Huria T, Lacey C, Cuddy J, Frizelle F. Exploring Maori health worker perspectives on colorectal cancer and screening. N Z Med J. 2012 Jun 8;125(1356):75–84.
14. Cox B. Flexible sigmoidoscopy is the best approach for a national bowel screening programme. N Z Med J. 2016 Feb 19;129(1430):14–7.

Opioid rain: opioid prescribing is growing and practice is diverging

Alan Davis, Kieran Davis, Catherine Gerard, Sunita Goyal, Gary Jackson, Chris James, Elizabeth Loe, Bev Nicolls, Mary-Anne O'Rourke, Carl Shuker, Leanne Te Karu

A fit, active, 57-year-old man of petite build, just 1.6 m tall, and weighing 50 kg, with "a long history of clean, drug-free living" is found dead in an elevator—his death is attributed by the coroner to a fatal overdose of self-administered fentanyl.[1,2]

Prince, the singer, songwriter, multi-instrumentalist and musical icon, died from an overdose of a strong opioid that in patch form is funded for use in New Zealand. Other strong opioids funded here include methadone, morphine, oxycodone and pethidine. A "strong" opioid is one classed as step 3 on the World Health Organization (WHO) analgesic "ladder" for cancer pain management, after weak opioids (tramadol, codeine and dihydrocodeine are subsidised in New Zealand) at step 2, and non-opioids (such as nonsteroidal anti-inflammatory drugs and paracetamol) at step 1.[3]

However, the benefits of opioids for chronic non-cancer pain have limited evidence, while the harms are increasingly apparent, including tolerance, adverse effects, aberrant behaviour, addiction, falls, overdose and death.[4–8]

In the US, commentators are describing a "prescription opioid overdose crisis" and an "epidemic" of addiction, abuse and overdose.[9,10] The US Centers for Disease Control and Prevention (CDC) have released a new guideline for prescribing opioids for chronic pain in response to the astonishing figures:[11–13]

- Since 1999, sales of prescription opioids in the US have quadrupled.
- In 2012, prescribers wrote 82.5 opioid pain relief prescriptions per 100 people in the US.[14]
- From 1999 to 2014, more than 165,000 Americans are estimated to have died from a prescription opioid overdose.[11]
- An estimated one in five American patients with non-cancer pain or pain-related diagnoses is prescribed an opioid. This figure doubled between 2000 and 2010 while non-opioid analgesic prescribing remained unchanged.[11,15]
- Wide regional variation in prescribing rates in the US is "unlikely to be attributable to underlying differences in the health status of the population."[14]

In the UK work examining prescribing patterns suggests similar growth patterns to the US,[16,17] but does the UK have "an epidemic of prescription opioid misuse and mortality"? Commentators suggest—due to the lack of reliable data—"maybe not" or "not yet".[18]

"Opioids are neither an easy nor necessarily effective solution to the problem" of persistent pain, and indeed—fraught with problems of measurement—research has shown a 90–100% failure rate for strong opioids in treatment of chronic non-cancer pain.[19]

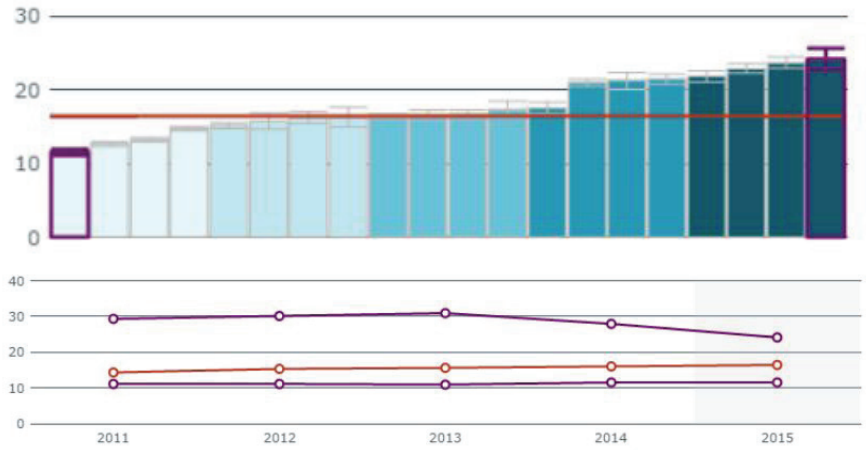
Thus opioids are a classic contender for wide variation in prescribing practice: evidence is patchy and evolving, indications are ambiguous and subject to individual interpretation, and patient preference is not well-informed. So what's going on in New Zealand?

Opioid use in New Zealand—new data in the Atlas of Healthcare Variation

The opioid domain of the New Zealand Atlas of Healthcare Variation has been updated today with 2014 and 2015 data, tracking ten indicators of opioid use nationally and by district health board

ISSN 1175-8716

Figure 1: Strong opioid dispensing rates by DHB, total 2015 and by year, rate per 1,000.



Legend: Red = national mean; purple = DHBs with widest variation in rates

(DHB).[20] How do we compare internationally and between different parts of the country?

Sixteen point four people per 1,000 were dispensed a strong opioid in New Zealand in 2015, a figure that has remained doggedly stable since 2011 (14.3 per 1,000) despite the increasing awareness of opioid-related harms and growing literature attesting to their dubious effectiveness in managing chronic non-cancer pain. Moreover, within that persistently "false flat" national mean (it may look level but is in fact a steady incline) lie 12,000 more people on a strong opioid between 2011 and 2015, and a more than twofold difference in the opioid dispensing behaviour of DHBs (see Figure 1).

By way of contrast, rates of opioid prescribing in Japan and many continental European countries have barely increased at all.[21] International comparison suggests that other developed countries are able to manage without such high rates of opioid use but also that we are not alone in this problem (see Table 1).

Differences between comparable countries is one thing, but a twofold difference in the dispensing behaviour of DHBs raises questions. The purpose of atlases of variation in healthcare practice is not to assert that one or another figure is necessarily wrong, but given two such wildly varying practices both can't be right.[22] Atlases are the starting point in exploring varying practice where evidence is ambivalent or not being acted upon, where we find out where we sit in comparison with each other and how our practice changes over time.

So what's going on?

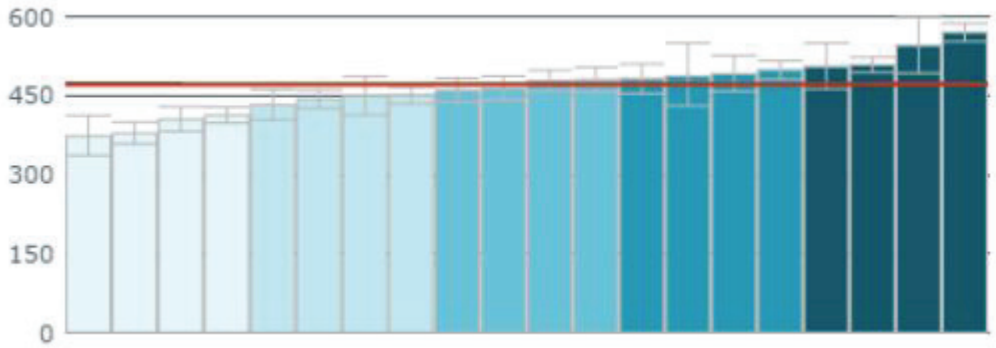
Table 1: Selected opioid consumption by country; 2014.[21]

Country	Milligrams (mg) morphine/ capita	mg oxycodone/capita	Morphine equivalent excluding methadone/ capita
Canada	134	84	732
US	74	194	502
Australia	35	151	358
UK	49	92	264
Scandinavia*	33	48	212
New Zealand	45	27	155
Japan	2	4	24

NB. Consumption refers to amounts distributed to the retail level, not amounts dispensed to, or used by, patients. "Morphine equivalent" is an aggregate measure of the following strong opioids: fentanyl, hydromorphone, morphine, oxycodone, and pethidine.

* Weighted average: Denmark, Finland, Iceland, Norway, Sweden.

Figure 2: People dispensed a strong opioid who had a public hospital event, by DHB, rate per 1,000, 2015.



New data and what we can know

Digging deeper into the new data there are some striking findings.

Strong opioid prescribing continues to increase, and of those dispensed a strong opioid in 2015, most received morphine. The number of people dispensed morphine has significantly increased since 2011, from 7.5 to 11 per 1,000—approximately 17,600 more people in absolute numbers. More than 10% of those on morphine were taking it for six or more weeks.

Rates of both strong and weak opioid dispensing were higher in people of European or other ethnicity (as compared with Māori, Pacific or Asian ethnicities), and higher in women and people aged 80 and over (on which more later).

Another of the indicators in the atlas is people dispensed a strong opioid who had a public hospital event in the eight days prior. Nearly half of all New Zealanders dispensed a strong opioid had recently attended a public hospital as an inpatient or outpatient, suggesting these prescriptions are generated in hospital (see Figure 2).

The good news—oxycodone

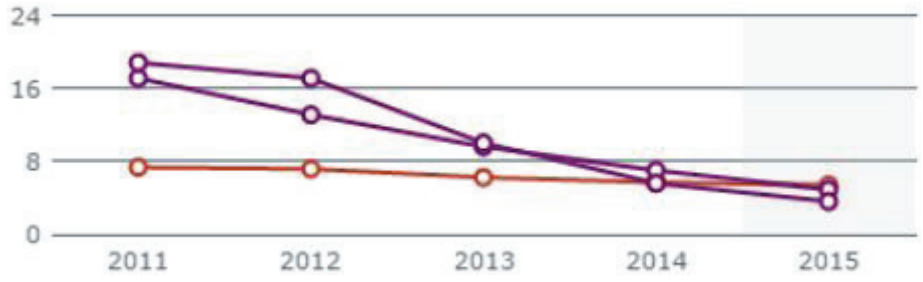
But there is good news in what can be achieved in New Zealand.

Oxycodone is a strong synthetic opioid that was introduced to New Zealand in the early 2000s as a "new and improved" morphine—fewer side effects and less stigma and patient resistance. The drug was heavily marketed in the US in the 1990s on the basis of evidence now refuted, leading to federal charges against a manufacturer and the largest fine ever paid by a pharmaceutical company.[5] Dispensing rates of oxycodone in New Zealand increased by 249% between 2007 and 2011,[6] before mounting international evidence for adverse effects, addiction, emergency admissions, overdoses and mortality began to influence prescribing practice.[23–25]

The Atlas has shown significant reductions in oxycodone dispensing with a rate of 5.4 people per 1,000 receiving the opioid in 2015, down from 7.3 per 1,000—7,800 fewer people in absolute numbers, compared to 2011. In DHBs where dedicated campaigns have sought to address optimal prescribing, the outcomes have been particularly positive. Nelson Marlborough and Wairarapa DHBs have reduced their dispensings of oxycodone by 60–70% and fallen below the national mean (see Figure 3).

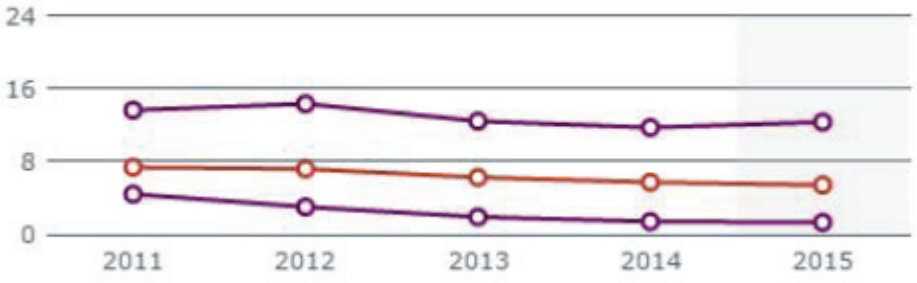
It's not all good news though. There remains extensive—more than threefold—

Figure 3: People dispensed oxycodone by DHB: total by year, rate per 1,000.



Legend: Red = national mean; purple = Nelson Marlborough and Wairarapa DHBs

Figure 4: People dispensed oxycodone by DHB: total by year, rate per 1,000.



Legend: Red = national mean; purple = DHBs with widest variation in rates

variation between many DHBs in oxycodone prescribing: 1.3 people per 1,000 (and falling) in Capital & Coast DHB; 12.3 per 1,000 in Bay of Plenty in 2015 (see Figure 4). Explicable through demography or differences in patient preference, or are people doing things differently? If so, why?

A special case: ageing, aged residential care (ARC) and fentanyl

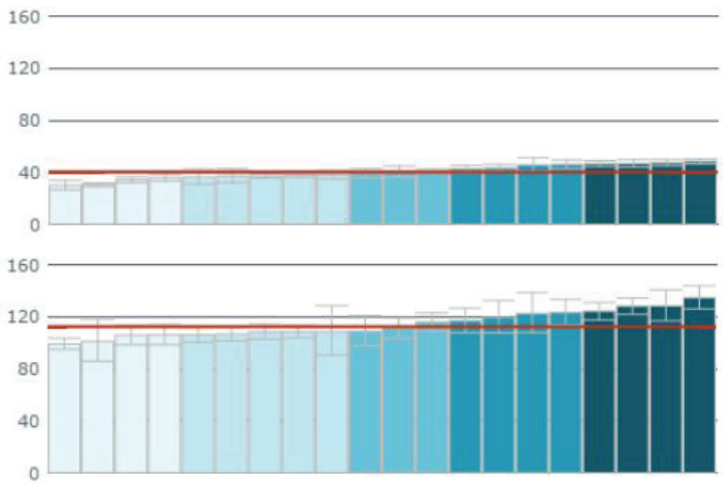
Engagement and awareness appears to be driving a rationalisation in oxycodone prescribing, but elsewhere are some alarming findings. Adverse effects of strong opioids are more frequent in the older population, including constipation, falls, changes to mental status, and nausea.[26,27] Yet strong opioid prescribing rates for those over 80 years are six to seven times higher than the rates for those under 65 (see Figure 5). Furthermore, these prescribing rates are rising: in the 80+ age group, 105.4 people in 1,000 were prescribed a strong opioid in 2013; a year later that figure was 111.4 per 1,000. In 2015 it was 112.3.

On top of this, rates of prescribing are higher in aged residential care (ARC) than in the community. Access to primary care support, allied health and pain management specialists, and pharmacists is problematic for ARC so treatment may not be ideal in this vulnerable group. Pain is under-reported in the cognitively impaired so it is in fact even possible we are under-treating some ARC patients.[28]

Fentanyl is a strong opioid recommended for people with chronic cancer pain as an alternate option after morphine and depending on patient circumstances. Fentanyl is convenient: a three-day patch that doesn't require qualified staff for twice-daily administration. However, the drug has the potential for severe adverse effects such as significant respiratory depression in opioid-naive patients or those with chronic obstructive pulmonary disease (COPD).[29] It is cautioned in those with hepatic or renal impairment, or bradyarrhythmias.[29] Fentanyl can have life-threatening opioid toxicity in those with chronic skin conditions[30] and can be addictive like other opioids. Elderly patients have increased sensitivity.[29]

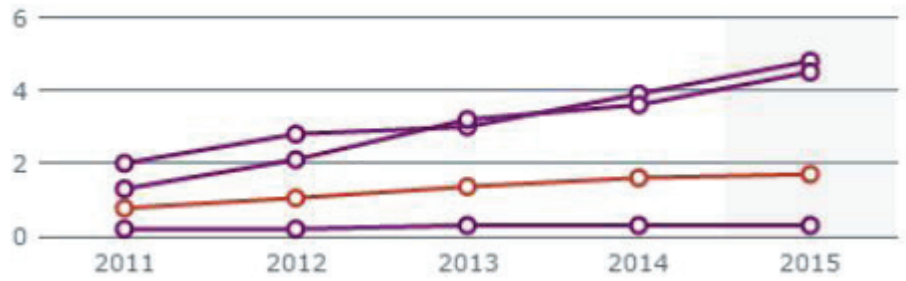
The Atlas shows fentanyl dispensing is rising year on year in roughly half of all DHBs despite clear evidence of consistently

Figure 5: Strong opioid dispensing rates by DHB and age group: rate per 1,000 for age 65–79 (above) and 80+ (below); 2015.



NZMJ 19 August 2016, Vol 129 No 1440
ISSN 1175-8716
www.nzma.org.nz/journal

Figure 6: People dispensed fentanyl by DHB: total by year, rate per 1,000.



Legend: Red = national mean; purple = selected DHBs

low usage in one large DHB. In fact, fentanyl dispensing varied sixteen-fold between DHBs in 2015 (see Figure 6).

Is it possible that fentanyl is being used in lieu of oxycodone as awareness grows of the dangers of the latter but not the former?

Further preliminary analysis has been conducted by the Atlas expert advisory group comparing dispensing rates of morphine, oxycodone and fentanyl to people 65 and over living in ARC versus those in the community. (Those in ARC receiving higher levels of care, such as rest-home hospital, dementia or psychogeriatric care, were excluded to increase comparability between groups.) The results are shown below (Figure 7).

All strong opioids were prescribed more in ARC than the community; morphine up to five times so. Oxycodone dispensing trended downwards in both settings but all other strong opioids increased over the three years and increased more rapidly in residential care. Dispensing of fentanyl in ARC almost doubled.

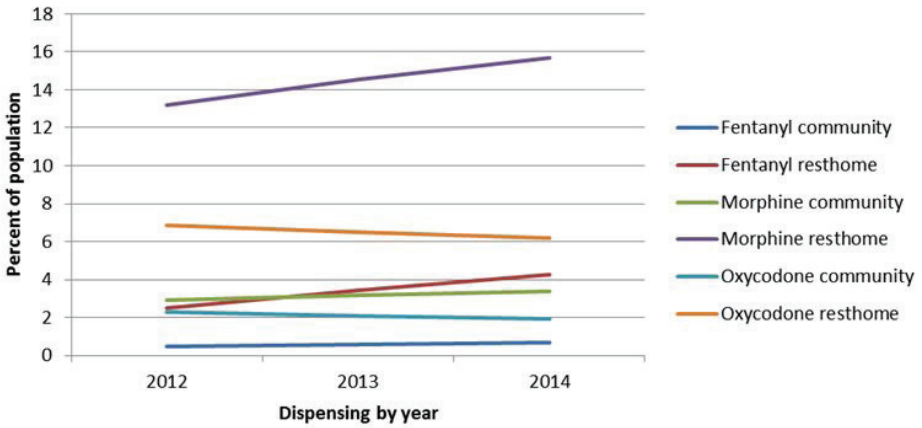
Why it's hard: "If all variation were bad, solutions would be easy"[31]

General practitioners (GPs) prescribing in ARC describe some of the complicated issues at play.[32]

In general, more people at higher acuities are being admitted to ARC and receiving palliative care. Meeting their needs, particularly in smaller DHBs, is challenging as the problem is multi-faceted and structural. Staffing issues and lack of access to specialist pain and palliative services means requests for relief from bad pain are often met by nurses or clinicians unaware of the pain history, and who may not have the time or training to design a tailored pain management program or initiate de-escalation of analgesia. (It is instructive to note there are only 11.5 full-time equivalent pain specialists in New Zealand,[33] and GP ARC visits can be three months apart.) Plus there are communication deficits and issues of cognitive impairment in patients with moderate to severe dementia.

A lack of shared knowledge on the part of clinicians *and* patients not only of effec-

Figure 7: Percentage of population 65 and over dispensed morphine, oxycodone and fentanyl in the community versus those living in aged residential care (rest home) by year to 2014.



Source: Health Quality & Safety Commission routine data analysis 2016. NZ resident population derived from StatsNZ population projections.

tiveness but also side effects of strong opioids exacerbates the problem. Patients and residents, for example, can resist morphine because they fear it signals they're dying, but often don't want a so-called "weak" opioid—they want the best, which means the strongest. Strong opioids do not necessarily mean strong analgesia.

There are others who are not even aware they are on an opioid.

Change is possible

Nelson Marlborough and Wairarapa DHBs show that where the problem is clear, improvement is possible. The Find My Patients query tool in primary care patient management systems, developed by the Health Quality & Safety Commission, can be used by GPs to identify patients in their own practice who are prescribed a strong opioid:[34]

A) for at least a month, by individual medicine

B) and who have diagnosed COPD where strong opioids are either contra-indicated or have a caution

C) have no co-prescribed stimulant laxative to deal with the common side effect of constipation.

The first step is finding out where as a DHB one stands, how that prescribing practice compares with others and how it has changed over time. The Atlas can help.

Author information:
Carl Shuker, Principal adviser, Publications Health Quality & Safety Commission Level 8, Customs House, 17–21 Whitmore Street, Wellington.
Corresponding author:
Carl Shuker, Principal adviser, Publications Health Quality & Safety Commission Level 8, Customs House, 17–21 Whitmore Street, Wellington.
carl.shuker@hqsc.govt.nz
URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6990

REFERENCES:

1. Sutherland S. Why the pain drug that killed Prince can be especially dangerous. Scientific American. 6 Jun 2016. http://www.scientificamerican.com/article/why-the-pain-drug-that-killed-prince-can-be-especially-dangerous/.
2. Midwest Medical Examiner's Office. Death investigation. Minnesota, USA: 2 Jun 2016. http://www.anokacounty.us/DocumentCenter/View/10066.
3. World Health Organization (WHO). WHO's cancer pain ladder for adults. http://www.who.int/cancer/palliative/painladder/en/.
4. Savvas S, Gibson S. Pain management in residential aged care facilities. Aust Fam Physician. 2015 Apr;44(4):198-203. http://www.racgp.org.au/afp/2015/april/pain-management-in-residential-aged-care-facilities/.
5. Martin L, Laderman M, Hyatt J, Krueger J. Addressing the Opioid Crisis in the United States. IHI Innovation Report. Cambridge, Massachusetts: Institute for Healthcare Improvement; April 2016. http://www.ihi.org/resources/Pages/Publications/Addressing-Opioid-Crisis-US.aspx.
6. bpacNZ. Identifying and managing addiction to opioids. Best Practice Journal. 2014:64.
7. Söderberg KC, Laflamme L, Möller J. Newly initiated opioid treatment and the risk of fall-related injuries. A nationwide, register-based, case-crossover study in Sweden. CNS Drugs. 2013 Feb;27(2):155–61. doi: 10.1007/s40263-013-0038-1.
8. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA. 2016 Jun 14;315(22):2415–23. doi: 10.1001/jama.2016.7789.
9. McCarthy M. Doctors are urged to limit opioid prescribing. BMJ 2016;352:i1614.
10. Von Korff MR. Long-term use of opioids for complex chronic pain. Best Pract Res Clin Rheumatol. 2013 Oct;27(5):663–72. doi: 10.1016/j.berh.2013.09.011. Epub 2013 Oct 5.
11. US Centers for Disease Control and Prevention

(CDC). CDC Guideline for Prescribing Opioids for Chronic Pain. 2016. http://www.cdc.gov/drugoverdose/prescribing/guideline.html.

12. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65:1–49.
13. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths--United States, 2000-2014. MMWR Morb Mortal Wkly Rep. 2016 Jan 1;64(50-51):1378–82.
14. Paulozzi LJ, Mack KA, Hockenberry JM; Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC. Vital signs: variation among States in prescribing of opioid pain relievers and benzodiazepines - United States, 2012. MMWR Morb Mortal Wkly Rep. 2014 Jul 4;63(26):563–8.
15. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. Med Care 2013;51:870–8.
16. Health and Social Care Information Centre. Prescriptions dispensed in the community: Statistics for England 2002–2012. 2013. www.hscic.gov.uk/searchcatalogue?productid=12055&returnid=1683.
17. Zin CS, Chen LC, Knaggs RD. Total number of prescriptions and number of patients stratified by non-cancer and cancer pain CPRD 2000–2010. Pharmacoepidemiol Drug Safe. 2012;21:(suppl 3):403.
18. Stannard C. Opioids in the UK: what's the problem? BMJ. 2013 Aug 15;347:f5108. doi: 10.1136/bmj.f5108.
19. Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. BMJ. 2013 May 3;346:f2690. doi: 10.1136/bmj.f2690.
20. Health Quality & Safety Commission. Atlas of Healthcare Variation. Opioids. http://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/opioids/.
21. University of Wisconsin-Madison. Pain & Policy Studies Group. Opioid Consumption Data. http://www.painpolicy.wisc.edu/opioid-consumption-data.
22. Rayner HC. Tackling practice variation. Lessons from variation can help change health policy. BMJ. 2011 Apr 8;342:d2271. doi: 10.1136/bmj.d2271.
23. Dhalla IA, Mamdani MM, Sivilotti MLA, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. Can Med Assoc J. 2009;181:891–6.
24. Maxwell JC. The prescription drug epidemic in the United States: a perfect storm. Drug Alcohol Rev. 2011;30:264–70.
25. bpacNZ. Oxycodone: how did we get here and how do we fix it? Best Practice Journal. 2014:62. http://bpac.org.nz/BPJ/2014/July/oxycodone.aspx.
26. Papaleontiou M, Henderson CR Jr, Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2010 Jul;58(7):1353–69. doi: 10.1111/j.1532-5415.2010.02920.x. Epub 2010 Jun 1.
27. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. BMJ. 2015 Feb 13;350:h532. doi: 10.1136/bmj.h532.
28. The Australian Pain Society. Pain in Residential Aged Care Facilities Management Strategies. August 2005. http://www.apsoc.org.au/PDF/Publications/Pain_in_Residential_Aged_Care_Facilities_Management_Strategies.pdf
29. Medsafe. New Zealand Data Sheet. Fentanyl Sandoz. Fentanyl transdermal patch. http://www.medsafe.govt.nz/profs/datasheet/f/fentanylsandozpatch.pdf.
30. Doris MK, Sandilands EA. Life-threatening opioid toxicity from a fentanyl patch applied to eczematous skin. BMJ Case Rep. 2015 Apr 29;2015. pii: bcr2014208945. doi: 10.1136/bcr-2014-208945.
31. Mulley AG. Improving productivity in the NHS. BMJ. 2010 Jul 27;341:c3965. doi: 10.1136/bmj.c3965.
32. Pers. Comm. Nicolls B. Clinical Director, Nelson Marlborough District Health Board. July 2016.
33. Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists audit of fellows 2016.
34. Health Quality & Safety Commission. The Find My Patients tool is accessible via the link on the lower right hand side of the relevant Atlas page.

Follow-up of cancer in New Zealand: time to review the model of care

Christopher GCA Jackson

Cancer is the number one cause of death in New Zealand and is a major cause of morbidity. Over the last decade the number of new registrations has increased by over 20%.[1] This increase is mainly due to population growth and aging rather than an increased incidence. Now, 6 out of 10 people newly diagnosed with cancer will be over the age of 60, and 25% of those newly diagnosed with colorectal cancer are aged over 80.[2] Our patients are getting older, more complex, and there are more treatment options than ever.

Screening programmes deliver an even greater number of new cancer diagnoses and there are a proliferation of possible treatment modalities. Today, more people are cured of cancer than ever before. With this comes an increasing number of survivors undergoing surveillance for recurrence and experiencing complications of late effects of treatment.

Political directives are in place to deliver better, sooner, more convenient cancer care closer to home, in a sparsely populated country. Accompanying this is a greater requirement for reporting and compliance, and with good reason.

How then will health systems cope with the increasing burden of providing comprehensive multidisciplinary care for people affected by cancer, in an era where we have more patients, with greater comorbidity, more treatment options, and higher expectations?

In this issue of *The Journal*, Kane et al.[3] report their findings of semi-structured interviews and focus groups with general practitioners reflecting on their role in management of patients with cancer, and their perceptions of areas for improvement in the chronic care model of cancer care. They identified gaps in knowledge, communication with secondary care providers, lack of role clarity and barriers to patients accessing general practice as being areas for improvement. The general practitioners interviewed for this article indicate a strong desire to be more involved in the long-term management of patients with cancer.

It is abundantly clear that the present model of cancer care in secondary and tertiary institutions is not sustainable. Many changes are already underway but more will be needed. It is equally clear that primary care is a central part of the future of New Zealand's cancer services. With an increasing role for general practice in cancer care, we need to take the issues highlighted in this report very seriously.

An area of cancer care that is common to primary and secondary care and demonstrates many of the issues raised by Kane et al. is that of follow-up after definitive treatment. Every year there are more than 3,000 people diagnosed with each of prostate, colorectal and breast cancer, the majority of whom are cured and undergo follow-up—many for five years or more. It is likely that there are more than 100,000 hospital outpatient appointments each year around the country associated with follow-up after curative treatment for cancer. Secondary care providers need to dispassionately evaluate what value is genuinely added by follow-up, and if continued hospital-based involvement is in a patient's best interests.

Models of nurse-specialist led care already exist in some places, although are predominantly based in tertiary centres. A model of general practice led, or shared care, could result in patients being cared for closer to home by a practitioner more familiar with their overall health needs

ISSN 1175-8716

and better placed to manage the competing demands of multiple coexisting health problems.

The purpose of follow-up is multi-factorial. Many patients diagnosed with cancer consider that earlier diagnosis may have been helpful for their condition. Following treatment, they reason that follow-up will result in earlier detection and a better outcome. Many will have positive relationships with their treating specialists and will enjoy ongoing contact. Surveillance for second primary cancers is undertaken, and measures for early detection of relapse are performed. With endocrine-responsive breast cancer, adherence to endocrine therapy is monitored and management of side-effects is initiated and monitored.

For colorectal cancer, follow-up is undertaken with history, physical examination, intermittent endoscopic evaluation, CT scanning and serum carcinoembryonic antigen. Some specialist units have already shifted follow-up from consultant-led to nurse-led, and have published reports highlighting the success of this model.[4] An Australian randomised trial of general-practice led compared to surgeon-led follow-up demonstrated that patient satisfaction, anxiety and quality of life were not different between groups, although there was a difference noted in the investigative procedures followed.[5]

Similarly for breast cancer, randomised trials show little difference in outcome between hospital-led and general practice-led care, and patients appear to find both satisfactory.[6] Among others, Cancer Australia is evaluating the effectiveness of "shared care" between hospital and general practice and offers a possible model for other tumour streams to follow.

The traditional model of specialist-led care is already being successfully challenged and with many benefits.

What conditions do we need to meet to ensure that we undertake appropriate follow-up, whatever the model of care?

Firstly, the care must be evidence based. Despite the intuitive appeal of follow-up, there is a surprising paucity of evidence for its effectiveness outside of a relatively limited range of conditions, such as colorectal cancer. Intensive follow-up for conditions that are incurable at relapse may do little other than introduce lead-time bias to our cancer statistics. Where there is evidence of no benefit for surveillance, we should stop. Instead, efforts and energy should be directed to areas where we can improve quantity or quality of life. Otherwise we will confuse activity with effectiveness.

Secondly, we must monitor our activity and our outcomes. Patients need assurance that what we are doing for them justifies the potential harm, is high quality and adds value to their care. Examples of this include a focus on the late effects of treatment such as cardiovascular morbidity following platinum based-chemotherapy, the increased incidence of diabetes following colorectal cancer diagnosis, or ameliorating the bone and metabolic effects of hormonal management of prostate cancer.

Programmes should be consistent across the country and have a focus on equity. Otherwise we will increase the already disturbing disparities in outcome that exist between Māori and non-Māori for most types of cancer. While the model of service provision may differ between communities (eg outreach buses or clinic based care), the substance of the activities must be comparable. To achieve this, expert groups with patient input should lead development, but to achieve consistency and implementation we will need a Ministry mandate. We already have many highly effective regional programmes, but are short of nationally consistent approaches for most.

Information technology systems will need to be utilised to ensure adequate recall and uptake. The systems will need to be sufficiently flexible to identify and recall patient groups when new evidence emerges that may result in benefit to them, such as when 10 years of hormonal treatment in breast cancer becomes warranted for particular sub-groups.

There must be minimal barriers to receiving care. If general practice is to take on some elements of care then funding should follow this. Also, care in a fee-for-service setting may create barriers to certain parts of our community. Although general practice-led care may in fact be more accessible to many than secondary care for geographical or other reasons, the question of access must be answered.

Potential harms must be identified and managed. For example, there is some evidence to suggest that specialist-led care may result in higher rates of adherence to adjuvant hormonal management in breast cancer[7] and this has led some to argue against devolving follow-up to nurse or primary care. However, with appropriate training, support and monitoring it is highly likely that similar rates of adherence could be attained by non-specialists.

Cancer specialists must also be quick to respond to those who are undertaking follow-up—whether it nurse or GP led. For example, if abnormalities on surveillance results are identified, such as a suspicious pulmonary nodule on routine imaging or an elevated serum tumour marker, then specialist evaluation is appropriate whether to offer advice or take over investigation and management. This must be done in a timely and streamlined manner.

The capacity in general practice is also not unlimited and cannot be expected to simply take over the current hospital delivered cancer surveillance. However general practice is well suited to the integrated management of people with multiple medical problems and balancing the competing needs of comorbid conditions. Cancer specialists by virtue of their training are experts in a more limited range of diseases and treatments. A patient undergoing cancer follow-up with multiple medical problems is likely to be better cared for in primary care than by an oncologist.

Integration of care, effective communication, joined-up information technology systems, collaboration and mutual respect will be the cornerstones of success. Collaboration is already well underway in many areas of New Zealand, but these excellent efforts will need to disseminated.

It is clear that the burden of cancer care is changing, and so we too must change. We cannot simply do more of what we are currently doing, otherwise our services will become obese and inefficient, congested and unresponsive, and will be overburdened and will implode. Follow-up for cancer is an area that can be reduced and rationalised to free up resource for more effective investments.

Cancer control has achieved great things where we have used evidence-based care and acted in a coordinated and thoughtful manner, sharing expertise and experience, and evaluated the outcomes of our efforts. We need to remember that very successful template as we look to design our model of care for the next 20 years.

Acknowledgements:
The author wishes to thank Dr Daniel Pettigrew and other colleagues in General Practice for their helpful comments on drafts of this editorial.

Author information:
Christopher GCA Jackson, Senior Lecturer in Medicine, University of Otago, Dunedin, New Zealand, Consultant Medical Oncologist, Southern District Health Board, Dunedin, New Zealand.

Corresponding author:
Christopher GCA Jackson, Senior Lecturer in Medicine, University of Otago, Dunedin, New Zealand, Consultant Medical Oncologist, Southern District Health Board, Dunedin, New Zealand.
christopher.jackson@southerndhb.govt.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6991

REFERENCES:

1. New Zealand Minsitry of Health. Cancer: Historical summary 1948–2012 Wellington, New Zealand 2015. Available from: http://www.health.govt.nz/publication/cancer-historical-summary-1948-2012.
2. New Zealand Minsitry of Health. Cancer: New registrations and deaths 2012. Wellington, New Zealand 2015. Available from: http://www.health.govt.nz/publication/cancer-new-registrations-and-deaths-2012.
3. Paul Kane, Marieke Jasperse, Richard Egan, Lynn McBain, Eileen McKinlay, Susan Pullon, Patries Herst. Continuity of cancer patient care in New Zealand; the general practitioner perspective. N Z Med J. 2016; 129:55–63. at https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6972
4. McFarlane K, Dixon L, Wakeman CJ, Robertson GM, Eglinton TW, Frizelle FA. The process and outcomes of a nurse-led colorectal cancer follow-up clinic. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2012;14(5):e245–9.
5. Wattchow DA, Weller DP, Esterman A, Pilotto LS, McGorm K, Hammett Z, et al. General practice vs surgical-based follow-up for patients with colon cancer: randomised controlled trial. Br J Cancer. 2006;94(8):1116–21.
6. Grunfeld E, Levine MN, Julian JA, Coyle D, Szechtman B, Mirsky D, et al. Randomized Trial of Long-Term Follow-Up for Early-Stage Breast Cancer: A Comparison of Family Physician Versus Specialist Care. Journal of Clinical Oncology. 2006;24(6):848–55.
7. Brito C, Portela MC, de Vasconcellos MT. Adherence to hormone therapy among women with breast cancer. BMC Cancer. 2014;14:397.

Pharmaceutical funding decisions must balance therapeutic innovation, opportunity costs and patient equity

Rajan Ragupathy, Michael Jameson

The complexity and pace of change in cancer medicine are both increasing rapidly. Early successes in areas of unmet need are widely reported, raising cancer patients' hopes of cure or prolonged survival. The resultant clamour for access to these drugs challenges politicians and government agencies to quickly fund these drugs, often faster than standard drug evaluation and prioritisation processes allow, and when other countries fund them, the public pressure for New Zealand to do so increases further. The Pharmaceutical Management Agency of New Zealand (PHARMAC) has the unenviable task of prioritising competing claims from different patient groups, often based on still-developing evidence of benefit.

In this edition of the NZMJ, Wonder and Fisher challenge PHARMAC's evaluation of newly developed agents for advanced melanoma, given the lack of other funded agents that prolong survival and the positive funding decisions made in Australia, Canada and the UK.[1] They acknowledge the huge price of these new medicines and we applaud their call for the sponsors to develop realistic pricing proposals. However, they also suggest that New Zealand adopt alternate pathways to achieve earlier drug access, such as managed entry or patient access schemes. While the article raises many thought-provoking points, it is focussed on funding therapies for melanoma and thus fails to address larger, more complex issues.

Arguably, the *raison d'etre* of PHARMAC—or any other Health Technology Assessment (HTA) agency—is the inescapable problem of opportunity costs: when you spend health dollars on one problem you cannot spend it on another. These are perhaps more starkly visible in New Zealand's drug funding decisions because PHARMAC has a strictly capped yearly budget.[2] However, the opportunity costs are not just in drug spending. PHARMAC has now announced that one of these immunotherapy drugs (nivolumab) will be funded from 1 July 2016 and another (pembrolizumab) from 1 September 2016. In this instance, the decision to fund immunotherapy for melanoma resulted in substantial unbudgeted costs to District Health Boards (frequent drug infusions, CT scans to monitor response, and management of patients and toxicities requiring more medical, nursing and pharmacy time); how this impacts on other health services is yet to be seen.

In the UK and Australia, where increased pharmaceutical costs can be met from regional healthcare spending or general government spending respectively, these opportunity costs may not be as immediately visible. This may allow decision makers more latitude to fund particular medicines.[2] However, analysis of decisions by the UK's National Institute of Care Excellence (NICE) and the Cancer Drugs Fund highlighted that many more Quality-Adjusted Life Years (QALYs) can be lost elsewhere in the health system.[3,4] These lost QALYs represent avoidable deaths and suffering for real patients. The Cancer Drugs Fund also illustrates that bypassing established pathways to fund particular medicines raises drug prices and lends

itself to funding of certain drugs for political expediency.[4] Funding the "squeaky wheel" or rescuing the group currently in the public eye disrupts attempts at patient equity. For example, these immune checkpoint inhibitors have substantial activity in lung cancer, especially those related to smoking, but it is unlikely that the public would be as impassioned about funding them for this indication as they were for melanoma, or trastuzumab (Herceptin®) for breast cancer.

While it is valid therefore to ask how many lives are being lost because PHARMAC declines to fund a particular medicine, it is also valid to ask how many lives are being saved elsewhere by that decision.[3–4] The percentage of gross domestic product spent on healthcare in New Zealand is low by OECD standards and has been falling in recent years, so it could be argued that the government ought to increase healthcare spending overall, and increase PHARMAC's budget.[5] However, it is likely that healthcare demand will always outstrip healthcare funding. In this context, PHARMAC lobbying the New Zealand Government for more funding may in fact do more harm than good in terms of opportunity costs. Similarly, framing the issue in terms of containing pharmaceutical expenditure versus saving lives may be a false dichotomy. A recent study commissioned by PHARMAC evaluated cancer medicines funded in Australia but not New Zealand in terms of clinically meaningful patient benefit—either improvement in progression-free survival or overall survival—using definitions from recent international research.[6–7] Only a few drugs met these definitions of benefit, meaning PHARMAC had avoided spending a great deal of money on relatively ineffective (or cost-ineffective) medicines which it could spend elsewhere. Crucially, PHARMAC had funded effective medicines for prostate and kidney cancers that Australia had not. These issues are, of course, much more complex, and PHARMAC is required to keep a broad view across all health, rather than just on one disease at a time.

There is also concern internationally that the prices of new medicines—not only for cancer, but also diseases such as hepatitis C—are unsustainable. Even where the medicines are clinically effective—and even meet cost-effectiveness thresholds under the right conditions—the total budgetary impact may be more than health systems as varied as those in Australia and the US can afford.[8,9] Even in the US—where comparative effectiveness and funding restrictions by public payers have been likened to 'death panels'—Medicare has begun trying to control escalating cancer drug costs.[10] Unless such efforts are successful and consistently applied, it is likely that rises in drug costs will exceed the ability of payers to increase pharmaceutical budgets. It is also worth noting that restricting or withdrawing access after a drug is in widespread use may generate substantial backlash, even if the initial promise for a particular indication is not borne out.[11] Providing alternate access pathways whereby a drug gains funding with lower certainty of benefit may lock the payer into continuing to pay for the drug or make it more difficult to negotiate more favourable pricing at a later date.

Given that new drug pricing is unlikely to drop substantially in the near future, and demand will increase as our population ages and new health benefits for these drugs are demonstrated, should we be changing the HTA system in New Zealand to match that in other countries? PHARMAC recognised the need to change and recently consulted widely on reviewing its decision criteria; its newly-announced Factors for Consideration incorporate these many complexities.[12] This new set of decision criteria is intended to ensure that the important decisions PHARMAC makes reflect our collective values. As it implements this new process it is vitally important that we, health professionals and consumer groups, help PHARMAC refine it further by continuing to engage with them, giving them a good perspective on the benefit of new medicines and challenging decisions we think are wrong. By doing so, we can advocate for those in need, while also ensuring that those who—for whatever reason—are less visible to the public gaze are not further disadvantaged in access to limited public health resources.

Disclaimer: The views in this editorial are the authors' own and are expressed in their capacity as health professionals and researchers. They do not necessarily represent the views of Waikato DHB or any other organisation the authors are affiliated with.

Competing interests:
The authors are employed by Waikato District Health Board (DHB), part of New Zealand's public health system. PHARMAC is the monopsony purchaser of pharmaceuticals, vaccines and selected medical devices used by the New Zealand public health system. The authors are involved in clinical trials and compassionate programmes for melanoma, lung cancer, Hepatitis C and other diseases as part of their employment at Waikato DHB. Waikato DHB receives payment from the sponsors of the clinical trials.

Author information:
Rajan Ragupathy, Clinical Trials and Research Pharmacist, Pharmacy Services, Waikato Hospital, Hamilton; Michael Jameson, Medical Oncologist, Regional Cancer Centre, Waikato Hospital, Hamilton. Associate Professor, Waikato Clinical Campus, Faculty of Medical and Health Sciences, University of Auckland, Hamilton.

Corresponding author:
Rajan Ragupathy, Pharmacy Services, Waikato Hospital, Hamilton, Pembroke Street, Private Bag 3200, Hamilton.
rajan.ragupathy@waikatodhb.health.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6992

REFERENCES:

1. Wonder M, Fisher R. Subsidised access to new melanoma drugs: in need of further innovation? N Z Med J. 2016; 129:37–54. at https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6971
2. Ragupathy R, Aaltonen K, Tordoff J et al. A 3-dimensional view of access to licensed and subsidized medicines under single-payer systems in the US, the UK, Australia and New Zealand. Pharmacoeconomics. 2012 Nov 1;30(11):1051–65.
3. Claxton K, Martin S, Soares M et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health Technol Assess 2015;19(14).
4. Claxton K. The UK's Cancer Drugs Fund does more harm than good. New Scientist 2015. [Online] [Last accessed 06 August 2016]. Available at: https://www.newscientist.com/article/dn26785-the-uks-cancer-drugs-fund-does-more-harm-than-good/
5. Keene L, Bagshaw P, Nicholls MG et al. Funding New Zealand's public healthcare system: time for an honest appraisal and public debate. N Z Med J. 2016 May 27;129(1435):10.
6. The Pharmaceutical Management Agency of New Zealand (PHARMAC). Do differences in funding cancer medicines in Australia and New Zealand impact on people's health?—A report of a study commissioned by PHARMAC. [Online]. [Last Accessed 06 August 2016]. Available at: https://www.pharmac.govt.nz/assets/cancer-comparisons-summary-2015-10-03.pdf
7. Ellis LM, Bernstein DS, Voest EE et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clinical Oncol. 2014 Apr 20;32(12):1277–80.
8. Ghinea N, Lipworth W. Affordable access to innovative cancer medicines—don't forget the prices. Med J Aust. 204 (6) 4 April 2016
9. Frakt AB. We Can't All Have It All: The Economic Limits of Pharmaceutical Innovation. JAMA. 2016 May 10;315(18):1936–7.
10. Mailankody S, Prasad V. Implications of proposed Medicare reforms to counteract high cancer drug prices. JAMA. 2016 May 5.
11. Vitry A, Nguyen T, Entwistle V, Roughead E. Regulatory withdrawal of medicines marketed with uncertain benefits: the bevacizumab case study. Journal Pharm Policy Pract. 2015 Oct 19;8(1):1.
12. The Pharmaceutical Management Agency of New Zealand (PHARMAC). How medicines are funded- factors for consideration. [Online] [Last Accessed 06 August 2016]. Available at: https://www.pharmac.govt.nz/medicines/how-medicines-are-funded/factors-for-consideration/

Methods of a national colorectal cancer cohort study: the PIPER Project

Melissa J Firth, Katrina J Sharples, Victoria A Hinder, Jerome Macapagal, Diana Sarfati, Sarah L Derrett, Andrew G Hill, Charis Brown, Papaarangi MJ Reid, Ross A Lawrenson, Carol Atmore, John P Keating, Mark Jeffery, Adrian H Secker, Charles De Groot, Christopher GCA Jackson, Michael PN Findlay

ABSTRACT

AIM: Colorectal cancer is one of the most common cancers, and second-leading cause of cancer-related death, in New Zealand. The PIPER (Presentations, Investigations, Pathways, Evaluation, Rx [treatment]) project was undertaken to compare presentation, investigations, management and outcomes by rurality, ethnicity and deprivation. This paper reports the methods of the project, a comparison of PIPER patient diagnoses to the New Zealand Cancer Registry (NZCR) data, and the characteristics of the PIPER cohort.

METHOD: National, retrospective cohort review of secondary care medical records (public and private) of all cases of ICD-10-AM C18-C20 on the NZCR in the calendar years 2007 and 2008 (main cohort) and an extended sample of Māori and Pacific cases, and non-Māori non-Pacific controls in 2006 and 2009 (extended cohort).

RESULTS: Of the 6,387 patients identified from the NZCR 5,610 (88%) were eligible for PIPER. Reasons for exclusion were non-adenocarcinoma histology (3%) and non-colorectal primary (2%). Data were collected on 3,695 patients with colon cancer, 1,385 with rectal cancer and 466 with cancer of the recto sigmoid junction.

CONCLUSIONS: The PIPER Project has generated comprehensive population level data detailing the diagnosis and management of colorectal adenocarcinoma in New Zealand. This will be used to assess the care provided to patients, and the impact of variations in care occurring between patient groups.

Colorectal cancer (CRC) is the second most common cancer in New Zealand (with 3,016 new cases in 2012) and the second-leading cause of cancer-related death.[1] Australia and New Zealand have similar incidence rates; the highest recorded worldwide.[2] Multiple studies, however, suggest survival post-CRC diagnosis is lower in New Zealand.[3–7] Differences in survival are likely due to both diagnostic and treatment factors.[3,7] Identification of these factors requires detailed investigation of the access to, and quality of, care for patients with CRC in New Zealand.

Professional guidelines relating to the optimal management of CRC exist, but there are no mandated minimum quality standards for delivery of CRC care in New Zealand. Previous attempts at comparing outcomes, for example via the Colorectal Surgical Society of Australia and New Zealand audit are limited by incomplete population coverage. A National Cancer Tumour Standards work programme is underway, but—at the time of writing—standards remain provisional.[8] Audits undertaken to date against these provisional standards are not uniform nationally, are not mandated, are not reported centrally, and results have not been published.

Disparities in survival post-CRC diagnosis are known to exist between groups of patients based on rurality, ethnicity and socioeconomic status.[9–14] Although CRC incidence is lower in rural areas and among Māori, once diagnosed, these groups are more likely to die of the disease compared to urban and non-Māori groups.[9–11] These disparities are not fully explained by

differences in stage at diagnosis. Some residual confounding is likely because stage at diagnosis is an imperfect measure of disease status. It is also possible, however, that variation in care post diagnosis is affecting survival outcomes. Reasons for poorer survival for Māori with colon cancer have been explored; several differences in quality of care indicators were found that were not explained by measured disease variables (such as stage at diagnosis) or patient characteristics.[11]

Pacific peoples also have substantially lower incidence rates of CRC, however estimates of survival are quite unstable due to small numbers; further research into the care received by Pacific patients, and their outcomes is needed.[12] Deprivation status and household income have also been suggested to adversely affect cancer outcomes in CRC patients in New Zealand,[13,14] over and above the influence of disease stage at diagnosis and ethnicity.[14]

Given the high incidence and within-population disparities in outcome, we hypothesised that health service factors relating to CRC treatment, as well as patient and disease characteristics, were likely to negatively impact on outcome. The objectives of the PIPER Project (Presentations, Investigations, Pathways, Evaluation, Rx [treatment]) were:

(i) to describe the patterns of presentation to secondary care, diagnosis, staging, treatment, follow-up and survival

(ii) to compare these patterns according to rurality, ethnicity and deprivation

(iii) to investigate the relationship between these factors and outcome (cause specific and overall survival).[15]

The PIPER Project is a national, retrospective cohort study including all patients diagnosed in New Zealand with colorectal adenocarcinoma in 2007 and 2008, along with an extended cohort (2006 and 2009) for analysing patterns of care for Māori and Pacific patients. The project is the largest of its kind conducted in New Zealand to date and utilises data collected directly from medical records, including from the private sector.

In this paper we report the methods of the PIPER Project, compare the CRC diagnoses recorded by PIPER to those on the New Zealand Cancer Registry (NZCR), and describe the characteristics of the patients included in the PIPER cohort.

Methods

Study population: All registrations for CRC (ICD-10-AM codes C18-C20) in 2006–2009 were provided by the NZCR[16] in a data set extracted on 17 May 2012. The NZCR is the central repository for all new cancer diagnoses (excluding non-melanoma skin cancers) that occur in New Zealand, as mandated by the Cancer Registry Act 1993.[16] In New Zealand, all patients are allocated a unique health system identifier, known as the National Health Index (NHI); this was used to link people across different health-related data sets such as the registry, the mortality collection and medical records.[17]

Two cohorts of patients were selected: (i) Main cohort: patients diagnosed between 1 January 2007 and 31 December 2008. This period was chosen to be recent enough to be relevant to current resource planning (given the relatively minor changes in management since that time) and provide sufficient follow-up time (6–7 years); (ii) Extended cohort: this comprised all participants in the main cohort as well as all Māori and Pacific patients diagnosed between 1 January 2006 and 31 Dec 2006, and 1 Jan 2009 and 31 Dec 2009, to provide greater numbers of Māori and Pacific patients for subsequent analyses. To obtain comparative data over the extended time frame we added a stratified random sample of non-Māori non-Pacific (nMnP) patients also diagnosed in 2006 and 2009. The stratification factors were year of diagnosis (2006, 2009) and cancer centre region (cancer services are delivered via six regions: Auckland, Waikato, MidCentral, Capital and Coast, Canterbury, and Southern District Health Boards); the number of nMnP patients selected matched the total numbers of eligible Māori and Pacific patients in each stratum.

We included all patients whose diagnosis of adenocarcinoma of the colon or rectum was confirmed by either histology, radiology or visualisation of tumour (during colonoscopy, sigmoidoscopy or surgery). Exclusion criteria were: date of diagnosis outside 2007–2008 for patients in the main

cohort, and outside 2006 and 2009 for the extended cohort; patients with recurrent disease (this included recurrent tumour at the site of a previous tumour, at the anastomosis following previous surgical resection of a CRC, or new metastatic disease on the background of a previous CRC tumour); patients who presented, were diagnosed, or received treatment for their primary CRC outside New Zealand; and patients who were not residents of New Zealand at the time of diagnosis. Cases were checked for eligibility by review of public and private secondary care clinical records. We defined date of diagnosis as the date of the first pathological report confirming CRC (where pathology was available). This date is often later than the date recorded on the NZCR, creating some shift in cohorts between NZCR diagnosis date and PIPER diagnosis date. The scope of the project did not include going back through NZCR late 2006 diagnoses to check if these would have fallen in the 2007 cohort as per the PIPER definition.

Data sources: Data were obtained from three main sources: i) retrospective review of patients' clinical records (from both public and private sectors) from the first presentation to hospital care resulting in the diagnosis of CRC until the time of case-review; ii) the national databases of hospital discharge diagnoses (National Minimum Dataset, NMDS) and mortality (Mortality Collection); iii) national data used to derive New Zealand Deprivation Index (a measure of deprivation based on regularly collected National census data)[18] and rurality for meshblocks of residence, and the GPS coordinates of meshblock centroids. A meshblock is a New Zealand-wide system of identifying geographical units, and is the smallest geographical unit for which Statistics New Zealand collects and provides statistical data.[19] National database data were merged with the clinical data using NHI numbers.

Demographic characteristics: Date of birth, gender and ethnicity were determined from NZCR data. Ethnicity fields on the NZCR are continually updated based on hospital and mortality data to improve accuracy[16] with a prioritisation process allowing for multiple ethnic affiliations to be recorded, with priority ordering to Māori followed by Pacific groups, Asian groups, other groups and New Zealand European.[20] Ethnicity data from hospitalisation events are self-determined from patients or their families using a standard question allowing multiple categories of ethnicity.[20] Data on all hospital discharge diagnoses were obtained from the NMDS from five years pre-diagnosis to estimate baseline comorbidity levels. Previously validated ICD-10 codes were used to identify these conditions.[21]

Rurality was assessed for each patient according to their residential address at the time of diagnosis. A Statistics New Zealand 2011 meshblock was assigned to each of the addresses using QAS Batch software by Experian™. This was then mapped to 2006 meshblocks, the closest to our main cohort. We used the Statistics New Zealand urban/rural profile classification system to obtain a rurality classification. This assigns meshblocks to one of three urban and four rural categories based on the dependence of the meshblock on a main urban area (assessed by comparing residential and employment addresses).[22] In our main analyses we grouped the seven categories into two categories, urban and rural, as recommended by the National Health Committee: rural = rural areas with moderate urban influence, rural areas with low urban influence, highly remote/rural areas and independent urban communities; non-rural = main urban areas, satellite urban communities and rural areas with high urban influence.[23] Centroid coordinates were also assigned to each meshblock to calculate a measure of travel distance to the diagnostic or treatment centre.

A deprivation score was assigned to each patient using the NZDep 2006 Index of Deprivation, which provides an area-based measure of deprivation for each meshblock (derived from New Zealand Census data) in deciles based on census variables such as financial benefit receipt, earning under an income threshold, housing tenure, and access to car or phone (1=lowest level of deprivation and 9=highest level of deprivation).[18] The NZDep score was assigned to each of the patients' addresses. Data presented in this paper uses the rurality category and the NZDep score of the address recorded for the patient at the time of diagnosis.

Key Performance indicators (KPIs) for measuring quality of care: PIPER's inves-

tigators and advisory group members consisted of individuals with expertise in colorectal surgery, medical oncology, radiation oncology, Māori health, Pacific health, general practice, rural health, patients' perspectives, biostatistics, health management, and clinical data collection. We identified a list of KPIs based on national and international guidelines.[24–28] A list of the data fields required to assess these KPIs was developed and piloted, with amendments based on availability and completeness of data in hospital notes. Data collected included patient demographics and co-morbidity, method of referral to secondary care, First Specialist Assessment (FSA), diagnosis, disease characteristics, cancer treatment, timelines, follow-up and outcome. A full list of data fields collected is provided in (Table 1).

The following fields were deemed unable to be collected during the pilot phase, due to a high proportion of missing data: baseline aspirin/ NSAID use; age of family member diagnosed with cancer (medical history); pre-chemotherapy height and weight; Eastern Cooperative Oncology Group (ECOG) performance status; planned duration of chemotherapy; response to chemotherapy; stage of disease as recorded by medical or radiation oncologist.

Outcomes: Data on disease outcomes were collected in the clinical record review (Table 1). Data on all hospital discharge diagnoses (adverse events) from 1 Jan 2001 (pre-CRC diagnosis) to post-CRC diagnosis until 10 April 2014 (date of extraction) were obtained from the National Minimum Dataset. Mortality data were obtained from the Mortality Collection, which provided mortality data to 28 Feb 2015 and coded cause of death until 31 Dec 2013.

Data collection: Clinical data were extracted from local hospital databases, patient electronic records and hard copy medical files. Data for patients treated in the private sector were collected from private clinicians' medical records following the clinician's written agreement. Data collection for each patient was carried out by regional data managers, trained in the use of PIPER's standardised data collection manual. Data managers reviewed potential cases for eligibility based on the DHB of domicile of the patient as recorded on the initial NZCR data set. If no information or no relevant (eg, cancer-related) information was found at the centre closest to the patient's domicile, a check against the national database of hospital admissions was undertaken to identify patients who may have been diagnosed or treated in regions other than their DHB of domicile as recorded by the NZCR. Data were extracted and either written onto a case report form and then entered into the project database, or entered directly into the project database. In each field the "Unknown" category refers to fields that were still unknown after all available information for the patient had been reviewed.

The PIPER Project database: A central Microsoft Access database was designed, developed and maintained by Cancer Trials New Zealand. This is housed on the University of Auckland secure server and is accessible only by secure log-on and password. Data managers at external sites accessed the database via remote sessions to the host server, which required individual user log on and password. Data sourced from national databases were also stored in a Microsoft Access database housed on the secure server. Data were anonymised for analysis.

Quality control: The database was developed using the fundamentals of good database design, including branch logic, limited field entry and dropdown lists to attain quality data entry. Reports were produced to ascertain completeness of data collection for individual patients. The following steps were taken to maintain consistent data extraction across the various centres: data managers underwent induction by the project manager; a data collection manual was developed which contained a definition for each data field and suggested documents to obtain the data from, listed in order of priority or relevance if more than one source was identified; the project manager made two visits to each site to conduct duplicate data extraction with review and feedback of any issues; queries on clinical data were reviewed by the project manager or clinical investigators and discussed at monthly data manager teleconferences. Checks were carried out across all sources of data to identify incongruities, including date order checks and

Table 1: Summary of the PIPER Project Data Fields.

Demographics	**Treatment**
Patient ID Date of Birth Gender Ethnicity	Not for active treatment Date of decision not for active treatment First treatment received Surgical referral Surgical FSA Surgical FSA date Primary resected Other cancer-related surgical procedure Surgical procedure Indication of surgery Date of surgery Date of discharge Length of stay Main surgical procedure Return to theatre Anastomotic leak 30 day mortality 90 day mortality Myocardial Infarction (MI) Pulmonary Embolism (PE) Completeness of excision Endoscopic excision only Multidisciplinary review Medical Oncology (MO) referral MO FSA MO FSA date Offered chemotherapy Chemotherapy regimen Chemotherapy start and stop dates Duration of chemotherapy Stopped chemotherapy early Reason for stopping chemotherapy Radiation Oncology (RO) referral RO FSA RO FSA date Offered radiotherapy Radiotherapy treatment regimen Radiotherapy start and stop dates Completeness of radiotherapy treatment Incomplete radiotherapy due to toxicity
Presentation	
Method of referral Date of referral Evidence of obstruction Date of First Specialist Assessment (FSA) FSA Department Emergency presentation to secondary care	
Staging	
Initial diagnosis method Date of initial diagnosis Site of primary tumour Tumour sidedness Synoptic pathology report Post-op T stage Post-op N stage Post-op M stage No. lymph nodes examined No. positive lymph nodes Lymphovascular invasion Tumour differentiation Distance of tumour to circumferential margin Mesorectal quality Computed Tomography (CT) of abdomen/pelvis CT chest Colonoscopy Completeness of pre-op colonoscopy Sigmoidoscopy Pre-operative stage Post-operative stage Stage at start of adjuvant therapy Completeness of staging	
Follow up	
Date of follow-up visit Department of follow-up visit	
Progressive Disease	**Outcome**
Site of first progressive disease Date of diagnosis of first progressive disease Method of diagnosis Treatment of progressive disease yes/no Surgical treatment detail Chemotherapy treatment detail Radiotherapy treatment Interventional radiology treatment detail	Reversal of stoma Diagnosis of metachronous tumour Diagnosis of new primary disease Date last seen For those who died: - cause of death - date of death

cross checks of related variables. Queries generated by these checks were forwarded to the regional data managers or to the project manager for resolution. Free text fields on the database were coded by an investigator or advisor with the appropriate expertise. Final cohort membership was determined based on the PIPER date of diagnosis post final data cleaning.

Statistical methods: Analyses are stratified by cancer site (colon vs rectal). The demographic and clinical characteristics of the cohort are described using appropriate numerical summary measures and graphs. Comparisons between groups (rurality, ethnicity and deprivation) in terms of presentation, staging, treatment and management (Table 1) are adjusted for: age, stage, co-morbidity and other prior factors (as appropriate), using generalised linear models.[29] Specific analyses are carried out for comparisons by ethnicity, using data for patients diagnosed in 2006–2009, using sampling weights to allow for the sampling of nMnP patients in the years 2006 and 2009. For each site and stage, where numbers permit, statistical models (including Cox regression and competing risk models) are used to explore the factors that may determine differences in patient outcome (cause-specific survival and overall survival) by rurality, ethnicity and social deprivation.

Sample size justification: Sample size calculations were done for the main PIPER cohort, years 2007 and 2008 (n=4,950), as some analyses are limited to this group. Of the 3,630 colon cancer patients and the 1,165 rectal cancer patients with known rurality in the main cohort, 26% lived in rural areas at diagnosis. To detect a difference in proportions meeting KPIs between urban and rural patients of 0.11 at the 0.05 level (2-sided) with a power of 80%, we would need 840 patients. Thus we have at least 80% power to detect differences in KPIs as small as 0.11 for the colon cancer group, the rectal cancer group, for stage II and III colon cancer patients (n=1,016 and 916 respectively), the group with non-metastatic rectal cancer (n=912) and the group with metastatic colorectal cancer (n=1,098). For evaluation of care for Māori and Pacific patients we use the extended PIPER cohort. The total number of Māori patients, with a known diagnosis, over the four years was 445. Of these, 308 had a diagnosis of colon cancer (including recto-sigmoid) and 137 rectal cancer. With these numbers we have 80% power to detect differences in proportions greater than 0.17 between Māori and nMnP at the 0.05 level in the overall comparisons and stage-specific comparisons. There were a total of 133 Pacific patients with a known diagnosis; 78 with colon cancer and 55 with rectal cancer. The smaller number of Pacific patients (even using total ethnicity rather than prioritsed ethnicity), means we have 80% power to detect differences greater than 0.3.

Project approval and conduct: Ethical approval for this project was granted by the Multi-Region Ethics Committee (reference number MEC/12/EXP/022). Approval was granted for data to be collected without individual patient consent. The project was overseen by the PIPER Study Management Group.

Results

There were 5,612 diagnoses of CRC registered on the NZCR during the years 2007 and 2008. In the extended cohort, there were an additional 244 Māori patients, 99 Pacific and 432 nMnP patients. This gave 6,387 potentially eligible cases for review. Of these 6,387 patients, 5,610 (88%) were determined to be eligible for the PIPER study. Exclusions included: non-adenocarcinoma morphology (n=172; 2.7%); no evidence of CRC found in the available clinical records (151; 2.4%); diagnosed outside study years (147; 2.3%); non-colorectal primary (120; 1.9%); no clinical records available on the patient (67; 1%); diagnosed or treated outside New Zealand (58; 0.9%); recurrent disease (47; 0.7%); not a New Zealand resident (10; 0.2%) and clinical diagnosis only (ie no pathology or radiology to confirm diagnosis (5; 0.1%)). Review of eligibility by patient variables demonstrated little variation by rurality and deprivation status, however Māori and Pacific patients had a greater proportion ineligible due to non-adenocarcinoma (6% for Māori and 7% for Pacific compared to 2% in nMnP).

Comparison of site of primary cancer collected for the PIPER project compared to that recorded on the NZCR showed reasonable consistency for colon cancer; of the 3,695 patients with colon cancer according to the PIPER notes review, 3,565

Table 2: Site of primary tumour as found in the PIPER Project compared to that recorded on the NZCR.

PIPER site of cancer										
NZCR site of cancer	Colon		Rectum		Recto-sigmoid		Unknown			
	N	%	N	%	N	%	N	%	Total	%
Colon	3,565	96.5	72	5.2	118	25.3	56	87.5	3,811	67.9
Rectum	54	1.5	1,226	88.5	140	30.0	6	9.4	1,426	25.4
Recto-sigmoid	76	2.1	87	6.3	208	44.6	2	3.1	373	6.6
Total	3,695	100.0	1,385	100.0	466	100.0	64	100.0	5,610	100.0

(97%) were classified as colon cancer on the NZCR (Table 2). Greater variability was seen with rectal cancer; of the 1,385 classified as rectal cancers in PIPER, only 1,226 (89%) were classified as rectal cancer on the NZCR. The remaining 11% of cases classified as rectal in PIPER were recorded on the registry as being located in the rectosigmoid (6%) or in the colon (5%). The discrepancy is due in part to differences in the source of information (PIPER used the operation note where this was available, as opposed to the pathology report which is used by the NZCR) and in part to the difficulty in classifying cancers near the rectosigmoid junction. Tumours classified as being located in the recto-sigmoid in PIPER showed the greatest variability with 208/466 (45%) also being classified as recto-sigmoid by the NZCR.

Characteristics of the PIPER patient cohort

The number of cases included for each year, based on date of diagnosis, by site of primary tumour and prioritised ethnicity is given in Table 3, illustrating the sampling for the extended cohort (years 2006 and 2009). Across the four years, the estimated percentages of patients whose tumour site was the colon, rectum and recto-sigmoid junction were 66%, 25% and 7% respectively. For 2%, the tumour site was unknown. These percentages are weighted back to the population according to the sampling weights. Table 4 presents the numbers and percentages of patients by demographic characteristics for colon, rectal and recto-sigmoid cancers (also weighted back to the population). Overall 5% of the CRC population were Māori and 1% Pacific, reflecting the lower CRC incidence among Māori and Pacific.

Discussion

The PIPER project has generated a data set of over 960,000 data points for 5,613 patients diagnosed with CRC in New Zealand. Cases were identified from the mandatory population-based NZCR. We observed a reasonable level of accuracy with respect to CRC diagnosis on the NZCR; 2% of those coded as ICD-10-AM codes C18-20 were found to have a non-colorectal primary on hand search of the medical record. For a further 2.4% we found no evidence of cancer in their medical records; however these cases included people diagnosed and managed conservatively outside the secondary care setting, or patients who were managed solely within the private sector but for whom no private sector records could be accessed. Secure storage, filing and access to retired practitioners' records in the private sector were found to vary greatly between individuals, and complicated data retrieval. We confirmed that the majority of cases of C18-C20 recorded on the NZCR are adenocarcinoma morphology (97%).

Further work is planned to compare the data held by the NZCR and the PIPER data. The classification of primary site as colon or rectum varied between the registry and the PIPER data set, particularly for rectal and recto-sigmoid cancers. This is likely to be due to differing definitions; in PIPER we classified site of primary disease by prioritisation from operation note, followed by pathological report for surgical specimen, followed by other pathological report (eg, biopsy post-colonoscopy), followed by colonoscopy report, and followed by other as written in medical record. The NZCR appears to use the first pathological diagnosis that would, for many cases, arise

Table 3: Numbers of patients with colorectal cancer included in the PIPER cohort by year of pathological diagnosis.

Year of diagnosis						
Site	**Prioritised Ethnicity**	**2006*** *N*	**2007** *N*	**2008** *N*	**2009*** *N*	**Total** *N*
Colon	Māori	64	60	60	72	256
	Pacific	21	9	18	18	66
	nonMāori - nonPacific	101	1,531	1,576	109	3,317
	Unknown	0	29	24	3	56
Rectum	Māori	34	39	22	42	137
	Pacific	12	10	13	20	55
	nonMāori - nonPacific	41	566	518	39	1,164
	Unknown	1	11	16	1	29
Recto-sigmoid	Māori	14	14	10	14	52
	Pacific	3	0	7	2	12
	nonMāori - nonPacific	12	178	189	14	393
	Unknown	0	6	2	1	9
Unknown	Māori	4	2	2	3	11
	Pacific	1	1	0	0	2
	nonMāori - nonPacific	0	18	16	12	46
	Unknown	0	3	0	2	5
All	Māori	116	115	94	131	456
	Pacific	37	20	38	40	135
	nonMāori - nonPacific	154	2,293	2,299	164	4,920
	Unknown	1	49	42	7	99
Total		308	2,477	2,473	352	5,610

*The cohort was extended to include patients diagnosed in 2006 and 2009 to provide more information on Māori and Pacific patients. All Māori and all Pacific patients were included, and a random sample of nonMāori-nonPacific patients.

from the colonoscopy pathology report. During data collection we noted regular variation between the site of disease as documented across multiple documents, eg, operation note versus discharge summary versus colonoscopy report; and between pathology report of endoscopic biopsy specimen and surgical specimen. For 1% of the study population, the site of primary disease was not able to be defined below the level of colorectal. This included patients for whom data were unable to be accessed, for example portions of the medical record (eg, volumes) were missing or access to private sector data were not approved by a private physician.

Data were collected from source documentation in both public and private medical records. While retrospective review presents challenges and limitations with respect to consistency and accuracy of data collection, we minimised the impact of this through: clear documentation of field definitions and source data; training, monitoring and regular meetings of project-specific data managers; and review of all available records and data sets for individual cases. Selection of the study cohort was considered to provide a balance between the age of the data and the ability to include a minimum of five-year follow-up for outcome assessment. There

Table 4: Demographic characteristics of the patients included in the PIPER cohort (so include patients in both the main and extension cohorts).

		Colon		Rectum		Recto-sig-moid		Un-known		Total	
		N	%†	N	%†	N	%†	N		N	%†
Gender	Female	1,944	52.28	521	33.92	194	34.64	31		2,690	46.63
	Male	1,751	47.72	864	66.08	272	65.36	33		2,920	53.37
Age at diagnosis	<40	66	1.24	29	1.98	11	1.50	0		106	1.42
	40–49	145	3.75	90	8.06	23	5.44	0		258	4.87
	50–59	368	10.84	226	16.21	66	10.60	13		673	12.45
	60–69	870	21.17	399	26.82	137	28.42	16		1,422	23.19
	70–79	1,261	36.39	399	31.49	145	35.48	15		1,820	34.89
	>=80	985	26.62	242	15.43	84	18.56	20		1,331	23.18
	Unknown Age	3		0		0		0		3	
Prioritised Ethnicity	Māori	256	3.87	137	5.62	52	7.28	11		456	4.60
	Pacific	66	1.00	55	2.26	12	1.68	2		135	1.36
	non Māori - nonPa-cific	3,317	95.13	1,164	92.13	393	91.04	46		4,920	94.04
	Unknown Ethnicity	56		29		9		5		99	
Rurality of residence at time of diagnosis	Urban	2,650	72.64	992	71.04	338	74.10	19		3,999	72.33
	Rural	954	27.36	357	28.96	120	25.90	9		1,440	27.67
	Unknown Rural	91		36		8		36		171	
New Zealand Deprivation Index of residence at time of diagnosis	1–2	714	22.25	262	15.58	83	19.92	3		1,062	20.36
	3–4	713	19.55	268	19.54	87	17.88	8		1,076	19.45
	5–6	801	19.69	278	22.92	105	19.86	6		1,190	20.52
	7–8	744	24.65	278	23.88	92	21.56	4		1,118	24.20
	9–10	612	13.87	256	18.08	88	20.77	7		963	15.47
	Unknown Dep	111		43		11		36		201	
Total	Total	3,695	100.0	1,385	100.0	466	100.0	64		5,610	100.0

†Percentages have been calculated weighted back to the population values using the sampling weights, to account for incomplete sampling of nMnP in 2006 and 2009. Percentages do not include unknowns.

have been limited changes to treatment practice of CRC in New Zealand in the interval between the cohort timeframe and the present day.

The data collected in PIPER will also allow us to investigate issues such as the group of data fields that were unable to be captured retrospectively from the medical records. We believe that this and on-going findings from the data set will highlight the need for a method of routine/prospective data collection across both the public and private sectors if we wish to continue to monitor quality of care provided to patients with CRC in New Zealand.

Conclusions

The PIPER Project has provided a population level, comprehensive data set detailing the diagnosis and management of CRC in New Zealand, a disease with significant disparities in outcome for patients in New Zealand. It provides a rich resource for studying the factors which may explain these disparities and further analyses of the collected data are currently underway.

Competing interests:

Melissa Firth reports grants from The Health Research Council of NZ & The Ministry of Health, grants from Genesis Oncology Trust, during the conduct of the study. Katrina Sharples, Victoria Hinder and Charis Brown report grants from Health Research Council of New Zealand, during the conduct of the study. Sarah Derrett reports other from Bowel Cancer New Zealand, outside the submitted work. Carol Atmore reports personal fees from PIPER project, University of Auckland, from null, during the conduct of the study. Jerome Macapagal and Michael Findlay report grants from The Health Research Council of NZ and The Ministry of Health, during the conduct of the study.

Acknowledgements:

This work was funded by a partnership grant (Findlay 11/764) from the Health Research Council of New Zealand and the Ministry of Health. The authors would like to sincerely thank Dr Wendy Stevens and Dr Dale Bramley for advice and support during project set-up, the regional Data Managers, the medical records staff across New Zealand hospitals and private practice staff, and the Ministry of Health Analytical Services team.

Author information:

Melissa J Firth, Project Manager, Discipline of Oncology, University of Auckland, Auckland; Katrina J Sharples, Associate Professor of Biostatistics, Department of Mathematics and Statistics and Department of Medicine, University of Otago, Dunedin; Victoria A Hinder, Research Fellow/Biostatistician, Discipline of Oncology, University of Auckland, Auckland; Jerome Macapagal, Database Development Officer, Discipline of Oncology, University of Auckland, Auckland; Diana Sarfati, Professor and Co-Head of Department, Department of Public Health, University of Otago, Wellington; Sarah L Derrett, Associate Professor, Public Health (Health Systems and Public Policy) and Director – Injury Prevention Research Unit, Department of Preventative and Social Medicine, University of Otago, Dunedin; Andrew G Hill, Consultant Colorectal Surgeon, Counties Manukau DHB and Professor, South Auckland Clinical School, University of Auckland, Auckland; Charis Brown, Senior Research Fellow, National Institute of Demographic and Economic Analysis, the University of Waikato, Waikato; Papaarangi M J Reid, Associate Professor and Tumuaki, Te Kupenga Hauora Māori, University of Auckland, Auckland; Ross A Lawrenson, Professor of Population Health, National Institute of Demographic and Economic Analysis, the University of Waikato, Waikato; Carol Atmore, Foxley Fellow, General Practice and Rural Health, University of Otago, Dunedin; John P Keating, Consultant Colorectal Surgeon, Capital and Coast District Health Board and Clinical Senior Lecturer, Wellington School of Medicine, University of Otago, Wellington; Mark Jeffery, Consultant Medical Oncologist, Canterbury District Health Board, Christchurch; Adrian H Secker, Consultant Colorectal Surgeon, Nelson-Marlborough District Health Board, Nelson; Charles De Groot, Consultant Radiation Oncologist and Clinical Director, Radiation Oncology, Waikato District Health Board, Waikato; Christopher G C A Jackson, Consultant Medical Oncologist, Southern District Health Board and Senior Lecturer, Dunedin School of Medicine, University of Otago, Dunedin; Michael P N Findlay, Consultant Medical Oncologist, Auckland DHB; Professor of Oncology, University of Auckland; Director Cancer Trials New Zealand, Auckland.

Corresponding author:

Melissa Firth, Cancer Trials New Zealand, Discipline of Oncology, Faculty Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland.
m.firth@auckland.ac.nz

URL:

https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6970

REFERENCES:

1. Ministry of Health. 2015. Cancer: New registrations and deaths 2012. Wellington: Ministry of Health.
2. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65(2):87–108.
3. Alafeishat L, Elwood M, Ioannides S. Cancer mortality and incidence trends comparing New Zealand and Australia for the period 2000-2007. N Z Med J. 2014; 127(1400):9–19.
4. Aye PS, Elwood JM, Stevanovic V. Comparison of cancer survival in New Zealand and Australia, 2006-2010. N Z Med J. 2014; 127(1407):14–26.
5. Skegg DC. Charting progress in the battle against cancer. N Z Med J. 2014; 127(1400):6–8.
6. Skegg DC, McCredie MR. Comparison of cancer mortality and incidence in New Zealand and Australia. N Z Med J. 2002; 115(1153):205–208.
7. Elwood JM, Aye PS, Tin S. Increasing disadvantages in cancer survival in New Zealand compared to Australia, between 2000–05 and 2006–10. PLoS One. 2016; 11(3):e0150734.
8. Ministry of Health, New Zealand. National tumour standards. Available online at http://www.health.govt.nz/our-work/diseases-and-conditions/cancer-programme/faster-cancer-treatment-programme/national-tumour-standards (Updated 16 April, 2015).
9. Robson B, Purdie G, Cormack, D. 2010. Unequal Impact II: Māori and Non-Māori Cancer Statistics by Deprivation and Rural–Urban Status, 2002–2006. Wellington: Ministry of Health.
10. Robson B, Purdie G, Cormack D. 2006. Unequal Impact: Māori and Non-Māori Cancer Statistics 1996–2001. Wellington: Ministry of Health.
11. Hill S, Sarfati D, Blakely T, et al. Ethnicity and management of colon cancer in New Zealand: do indigenous patients get a worse deal? Cancer. 2010; 116(13):3205–14.
12. Blakely T, Tobias M, Atkinson J, et al. Tracking Disparity: Trends in ethnic and socioeconomic inequalities in mortality, 1981–2004. Wellington: Ministry of Health.
13. Soeberg M, Blakely T, Sarfati D, et al. 2012. Cancer Trends: Trends in cancer survival by ethnic and socioeconomic group, New Zealand 1991–2004. Wellington: University of Otago and Ministry of Health.
14. Jeffreys M, Sarfati D, Stevanovic V, et al. Socioeconomic inequalities in cancer survival in New Zealand: The role of extent of disease at diagnosis. Cancer Epidemiol Biomarkers Prev. 2009; 18(3):915–921.
15. Cancer Trials New Zealand. The PIPER project: an internal examination of colorectal cancer management in New Zealand. Final report 7th august 2015. Available online at https://www.fmhs.auckland.ac.nz/en/sms/about/our-departments/oncology/cancer-trials-nz/trials-and-research-projects/open/piper-project.html (Updated August 2015).
16. Ministry of Health. New Zealand cancer registry (NZCR). Available online at http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/new-zealand-cancer-registry-nzcr (Updated 2014).
17. Ministry of Health, New Zealand. National health index. Available online at http://www.health.govt.nz/our-work/health-identity/national-health-index (Updated 10 May, 2012).
18. Salmond C, Crampton P, Atkinson J. New ZealandDep2006 index of deprivation user's manual. August 2007. Department of Public Health, University of Otago, Wellington. Available online at http://www.otago.ac.nz/wellington/otago020348.pdf
19. Statistics New Zealand. Meshblock definition. Available online at http://www.stats.govt.nz/methods/classifications-and-standards/classification-related-stats-standards/meshblock/definition.aspx (Updated 2015).
20. Ministry of Health. 2004. Ethnicity Data Protocols for the Health and Disability Sector. Wellington: Ministry of Health.
21. Sarfati D, Gurney J, Stanley J, et al. Cancer-specific administrative data-based comorbidity indices provided valid alternative to Charlson and National Cancer Institute Indices. J Clin Epidemiol. 2014; 67(5):586–595.
22. Bayley A, Goodyear R. New Zealand: An Urban/Rural profile. Wellington, New Zealand: The Product Development and Publishing Services Division of Statistics New Zealand. 2004. Available online: http://www.stats.govt.nz/browse_for_stats/Maps_and_geography/Geographic-areas/urban-rural-profile.aspx

23. The National Health Committee. Rural health, challenges of distance, opportunities for innovation. 2010. Wellington, New Zealand. Available online: http://www.rgpn.org.nz/Network/media/documents/pdfs/rural-health-challenges-opportunities.pdf

24. New Zealand Guidelines Group. Clinical practice guidelines for the management of early colorectal cancer Wellington: New Zealand Guidelines Group; 2011. Available online: https://www.health.govt.nz/system/files/documents/publications/early-management-colorectal-cancer-guideline.pdf

25. Van Cutsem E, Nordlinger B, Cervantes A, ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. Ann Oncol. 2010; 21 Suppl 5:v93–7.

26. Labianca R, Nordlinger B, Beretta GD et al. Primary colon cancer: ESMO clinical practice guidelines for diagnosis, adjuvant treatment and follow-up. Ann Oncol. 2010; 21 Suppl 5:v70–7.

27. Glimelius B, Pahlman L, Cervantes A, ESMO Guidelines Working Group. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21 Suppl 5:v82–6.

28. National Institute for Health and Care Excellence. Colorectal cancer: Diagnosis and management. Clinical guideline. United Kingdom: National Institute for Health and Care Excellence; 2011. Available online: https://www.nice.org.uk/Guidance/cg131

29. Lumley T, Kronmal R, Ma S. Relative risk regression in medical research: Models, contrasts, estimators, and algorithms. 2006; Working paper 293. Available online: http://biostats.bepress.com/uwbiostat/paper293/

Subsidised access to new melanoma drugs: in need of further innovation?

Michael Wonder, Rosalie Fisher

ABSTRACT

AIMS: Melanoma is the most serious of the three common forms of skin cancer. New Zealand and Australia have the highest melanoma incidence rate in the world. A number of new treatments for melanoma with different modes of action have recently become available. Our aim was to examine their availability and subsidized access in New Zealand and to compare their availability and access in Australia and England.

METHODS: We examined the clinical evidence base of the new treatments, their place in treatment guidelines and their consideration for reimbursement by PHARMAC in New Zealand, the PBAC in Australia and NICE in England.

RESULTS: The PBAC and NICE have recommended most treatments and their recommendations have been implemented promptly, using innovative access and pricing models. PHARMAC has rejected most of the new treatments and none has been funded. Pembrolizumab has been recommended with a low priority.

CONCLUSIONS: New Zealand should not be in the unenviable position whereby it has the highest incidence of a fatal disease yet is the last country in the Western world to fund effective treatments for it. We offer recommendations to all stakeholders to break the current access impasse.

Malignant melanoma is a cancer of the skin and is the most serious of the three common forms of skin cancer. Although melanoma is more often diagnosed in older people, it is increasingly affecting younger people.[1]

Metastatic melanoma is life-threatening and is associated with low survival rates;[2] approximately one out of every five people will survive for five years following a diagnosis with late-stage disease.[3] There are about 200,000 new cases of melanoma diagnosed worldwide each year.[4]

New Zealand and Australia have the highest melanoma incidence rate in the world; respectively, more than 4,000 and 11,000 new cases of melanoma are registered annually. Metastatic melanoma results in significant loss of life in both countries: more than 300 New Zealanders die of melanoma each year,[5] and in Australia in 2012 there were more than 1,500 deaths from melanoma.[6] Key strategies to prevent melanoma deaths are prevention, early detection and effective therapies for advanced disease.

For decades, the treatment options for patients with metastatic melanoma were few and of limited efficacy. The median overall survival of nine months had not changed in 30 years. A number of new treatments for patients with metastatic melanoma have become available in the past four years. They are all targeted treatments with new modes of action; they are more effective but also more costly, and are set to revolutionise the treatment of patients with metastatic melanoma.

Our objective was to examine the availability and subsidised access of these new medicines by melanoma patients in New Zealand and to compare their availability and access in Australia and England.

Epidemiology

Cutaneous malignant melanoma is a tumour of melanocytes in the basal layer of the epidermis. Risk factors for the development of melanoma include skin phototype, UV exposure, and genetic predisposition and thus it most common in Caucasian populations, such as those of

Australasia, North America, and Northern Europe.[7]

Melanoma is a particular health concern in Australia and New Zealand—countries with the highest global incidence of melanoma—and in the United Kingdom, where the incidence of melanoma has risen more rapidly over the last 30 years than those of the 10 most common cancers.[8]

In 2011, the age-standardised incidence rate (ASR) of cutaneous melanoma in Australia was 48 cases per 100,000 persons and from 2011 to 2013, the ASR was 37 per 100,000 in New Zealand.[6,9] In Australasia, melanoma is the fourth most common cancer (defined by the total number of cases), and in the UK, the fifth.

Importantly, in all three countries, melanoma disproportionately affects a younger group of patients; for example, it is the most common cancer to affect the 15–24 age group in Australia.[6] Consequently, mortality from melanoma results in greater loss of potential years than from other cancers in the US, an average of 20.4 years compared to 16.6 years per individual.[10]

Biology

Melanoma is staged according to the TNM classification, with stage groupings determined by thickness, ulceration and mitotic count and the presence of regional nodal metastases and metastatic disease.[11] Currently, the use of systemic treatments in melanoma is confined to patients with inoperable stage 3, or stage 4, melanoma.

Distinct sub-types of melanoma are now recognised, which differ by aetiology, clinico-pathological features and driver gene mutations. The observation that up to 50% of melanomas harbour a somatic mutation in the *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) gene was the foundation upon which a new drug class has been developed;[12] subsequently, a number of genotypes, correlating with site of melanoma origin and/or degree of UV exposure, were described among primary melanomas.[13,14]

In cutaneous melanomas, mutations resulting in aberrant signaling of the mitogen-activated protein kinase (MAPK) pathway such as *BRAF* and *NRAS* (neuroblastoma RAS viral (v-ras) oncogene homolog) mutations, are frequent. Mutations of codon 600 in the kinase domain of the BRAF gene account for 80% of mutations (most commonly V600E and V600K mutations) and all activate this important growth pathway. Currently, the tumoural BRAF status (mutant versus wild-type) is the only factor that influences systemic treatment type in advanced melanoma.

Another important biological feature of melanoma is that it is the most highly mutated of the haematological and solid organ malignancies.[15] It is postulated that the somatic mutation burden of melanoma results in a large number of antigens presented to the immune system and might account for the greater success of immunotherapies in this disease compared to other cancers.

The clinical course of metastatic melanoma is varied—the degree of immune control is widely speculated to account for the differences observed between patients—but it is inevitably fatal and, for many patients, leads to rapid deterioration and death.

Common sites of metastases are the skin, lymph nodes, lung, liver and brain and an individual's last months are typically highly morbid. The treatment intent remains one of palliation.

Current treatments

Up until 2011, the treatment options for patients with malignant melanoma were the alkylating agents dacarbazine (DTIC) and fotemustine and the antimicrotubule agent paclitaxel. Dacarbazine is indicated for the treatment of metastatic malignant melanoma, whereas fotemustine is indicated for disseminated melanoma including cerebral metastases.

Dacarbazine and fotemustine have been trialled extensively and have complete and partial response rates of around 10%. They do not prolong survival.[16,17]

Major improvements in the understanding of the biology of melanocytes and the drivers of their growth have led to the development of new agents with novel modes of action (Tables 1 and 2).

MAPK pathway inhibitors: BRAF and MEK inhibitors

The BRAF inhibitors vemurafenib and dabrafenib mesylate are selective inhibitors of mutant BRAF. In their phase III registration trials, both agents were compared to dacarbazine in previously untreated patients with advanced V600E mutated melanoma and both demonstrated marked superiority.[18,19] Vemurafenib and dabrafenib mesylate appear to have similar efficacy in these trials although they have not been compared directly (Table 2). Both treatments are oral and have acceptable toxicity profiles, although these differ somewhat. Owing to their high response rates, rapid onset of action and activity in the central nervous system,[20] the BRAF inhibitors are viewed as highly effective palliative treatments in the treatment of patients with advanced melanoma, including those with poor performance status. However, multiple mechanisms of resistance to these drugs are now described,[21] and long-term survivors treated with these drugs alone are in the minority.

Trametinib dimethyl sulphoxide is an oral, selective inhibitor of MEK1 and MEK2 (MAPK/ERK kinase 1 and 2). In a randomised phase III trial, trametinib dimethyl sulphoxide monotherapy was superior to dacarbazine or paclitaxel in untreated patients with BRAF V600E or V600K mutant melanoma but the treatment benefit in this population is modest compared to the BRAF inhibitors.[21]

There are now substantial data indicating that the MAPK pathway remains activated in patients with clinical resistance to the BRAF inhibitors.[22] Thus, combination BRAF and MEK inhibitor treatment was trialed in an attempt to lengthen the duration of control provided by BRAF inhibitors alone. Three phase III trials have established superiority of combination treatment over BRAF inhibitor monotherapy.[23,24,25] All trials were undertaken in the first-line setting; the first two studied the combination of dabrafenib mesylate and trametinib dimethyl sulphoxide, compared to dabrafenib mesylate or vemurafenib monotherapy,[23,24] and the third, combination vemurafenib with the MEK inhibitor cobimetinib against vemurafenib alone.[25] Each trial found a consistent and significant benefit in response rates and progression-free survival in favour of combination treatment. Overall survival data are not mature in the vemurafenib and cobimetinib trial but the others demonstrated a clear reduction in the risk of death with combination treatment. These findings, along with the observation that combination BRAF and MEK inhibition may be less toxic than BRAF inhibitor monotherapy,[23] have established combination treatment for BRAF mutant melanoma as the new standard of care.

Immune checkpoint inhibitors

Ipilimumab is a humanized monoclonal antibody targeting the cytotoxic T lymphocyte antigen-4 (CTLA-4) receptor, a negative co-stimulatory molecule expressed on effector and regulatory T cells.[26]

In two phase III trials evaluating pre-treated and treatment-naïve patients,[26,27] ipilimumab resulted in prolongation of overall survival compared to the gp100 vaccine or chemotherapy treatment, although response rates to this agent are low. Recently, data from the phase III trials have been analysed along with phase II data, finding a median overall survival of 11.5 months for patients with advanced melanoma treated with ipilimumab, but, more importantly, that the survival curves for these patients starts to plateau at three years, confirming that longer-term survival after this treatment is possible in responders.[28] Ipilimumab can cause serious immune-related side effects affecting the skin, gastro-intestinal tract, liver and endocrine glands.

Pembrolizumab and nivolumab inhibit a different immune checkpoint receptor, Programmed Death-1 (PD-1), whose interaction with ligands PD-L1 and PD-L2 found on tumour and antigen-presenting cells down-regulates T-cell activation. Nivolumab has been compared to chemotherapy as first-line treatment in patients with BRAF wild-type metastatic melanoma, offering significantly higher response and one-year survival rates.[29] Both nivolumab and pembrolizumab are superior to chemotherapy after failure of anti-CTLA-4 therapy.[30,31,32] Pembrolizumab and ipilimumab were directly compared as first-line treatments of advanced melanoma (KN-006 trial) and pembrolizumab was unequivocally more efficacious than ipilimumab,

as well as having an improved toxicity profile.[24] This important study has strongly influenced treatment guidelines and was highly relevant to the regulatory and reimbursement process for pembrolizumab in some countries.

The most impressive activity of immune checkpoint inhibitors in metastatic melanoma patients was observed in the phase III trial of combination nivolumab and ipilimumab, versus nivolumab or ipilimumab monotherapy.[33] The median progression-free survival in the combination arm was 11.5 months, compared to 6.9 months and 2.9 months in the nivolumab and ipilimumab arms respectively. This trial did not address the issue of combination versus sequential immunotherapy.

In summary, there are now more than 10 phase III randomised, controlled trials supporting the use of BRAF, MEK and immune checkpoint inhibitors to prolong life in patients with metastatic melanoma. These trials predominantly treatment regimens with the same mode of action, and the focus of much research and debate currently is the optimal sequencing of MAPK inhibitors and immunotherapies. Although randomised trial evidence comparing different sequences is not available, clinical practice is informed by data indicating that immune checkpoint inhibitors appear to be effective following kinase inhibitor therapy, and vice versa.[34,35] Additionally, the melanoma genotype, the clinical status of the patient and the registered indication for each agent are all factors in determining the order of systemic treatment. While combinations within the classes of kinase inhibitors and immune checkpoint inhibitors are effective and safe, use of BRAF and/or MEK inhibitors with immunotherapy remains experimental.

Further information on these new treatment options are provided in Table 1.

Treatment guidelines

Treatment guidelines from the US and Europe are the most relevant, as these incorporate the major drug developments in metastatic melanoma that have occurred since 2010. Australasian and British

Table 1: New treatments for patients with metastatic melanoma.

Medicine (generic name)	Ipilimumab	Vemurafenib	Dabrafenib mesylate	Trametinib dimethyl sulphoxide	Cobimetinib	Pembrolizumab	Nivolumab
Medicine (brand name)	Yervoy	Zelboraf	Tafinlar	Mekinist	Cotellic	Keytruda	Opdivo
Sponsor	Bristol-Myers Squibb (BMS)	Roche	GlaxoSmithKline (GSK)*	GlaxoSmithKline (GSK)*	Roche	Merck, Sharp & Dohme (MSD)	Bristol-Myers Squibb (BMS)
Mode of action	Checkpoint inhibitor	BRAF inhibitor	BRAF inhibitor	MEK inhibitor	MEK inhibitor	Programmed death 1 inhibitor	Programmed death 1 inhibitor
Route of administration	Parenteral	Oral	Oral	Oral	Oral	Parenteral	Parenteral
Date of approval (US)	25/03/2011	17/08/2011	29/05/2013	3/09/2013	10/11/2015	4/09/2014	22/12/2014
Date of approval (EU)	13/07/2011	17/02/2012	26/08/2013	30/06/2014	20/11/2015	17/07/2015	19/06/2015
Date of approval (Australia) (ARTG Start Date)	4/07/2011	10/05/2012	27/08/2013	14/02/2014	Not registered	16/04/2015	11/01/2016
Date of approval (New Zealand)	22/03/2012	16/02/2012	19/06/2014	26/03/2015	Not registered	3/09/2015	28/04/2016
Registered patient populations (New Zealand)	Advanced (unresectable or metastatic) melanoma, first-line	Advanced (unresectable or metastatic) melanoma, BRAF V600 mutation positive	Advanced (unresectable or metastatic) melanoma, BRAF V600 mutation positive	Advanced (unresectable or metastatic) melanoma, BRAF V600 mutation positive, monotherapy AND Advanced (unresectable or metastatic) melanoma, BRAF V600 mutation positive, combination (dabrafenib mesylate)	Not registered	Advanced (unresectable or metastatic) melanoma, monotherapy	Advanced (unresectable or metastatic) melanoma, monotherapy AND advanced (metastatic) melanoma, combination (ipilimumab)

* Current sponsor is Novartis

Table 2: Selected clinical trial data for newly approved treatments for metastatic melanoma.

Medicine (generic name)	Ipilimumab	Vemurafenib	Dabrafenib mesylate	Trametinib dimethyl sulphoxide	Cobimetinib	Pembrolizumab	Nivolumab
Trial design	Phase III; randomised	Phase III; randomised	Phase III; randomised	Phase III; randomised	Phase III; randomised (in combination with vemurafenib)	Phase III; randomised; first-line	Phase III; randomised; first-line
Patient population	1. Previously treated unresectable stage IIIC or stage IV melanoma 2. First-line treatment unresectable stage IIIC and stage IV melanoma	First-line treatment unresectable stage IIIC and stage IV BRAF mutant melanoma	First-line treatment unresectable stage IIIC and stage IV BRAF mutant melanoma	First-line monotherapy unresectable stage IIIC and stage IV BRAF mutant melanoma*	First-line treatment unresectable stage IIIC and stage IV BRAF mutant melanoma	First-line treatment unresectable stage IIIC and stage IV melanoma	First-line treatment BRAF-wild type melanoma
Comparator	1. gp100 peptide vaccine 2. Chemotherapy	Dacarbazine	Dacarbazine	Chemotherapy	Vemurafenib	Ipilimumab	Chemotherapy
Response rate (%)	1. 10.9 vs 1.5 2. 15.2 vs 10.3	48 vs 5	50 vs 7	22 vs 8	68 vs 45	33.7 vs 11.9	40 vs 13.9
Median PFS (months)	1. 2.86 vs 2.76 2. Not available	5.3 vs 1.6	5.1 vs 2.7	4.8 vs 1.5	9.9 vs 6.2	5.5 vs 2.8	5.1 vs 2.2
Median OS (months)	1. 10 vs 6.4 2. 11.2 vs 9.1	13.6 vs 9.7	Not available	Not available	22.3 vs 17.4	Not reached	Not reached vs 10.8
Toxicities	Immune-related skin, gastrointestinal, hepatic	Cutaneous including photosensitivity, fatigue, arthralgia	Cutaneous, pyrexia, fatigue, arthralgia	Cutaneous, diarrhea, fatigue, oedema	Fatigue, cutaneous, pyrexia, arthralgia, gastrointestinal	Fatigue, pruritus, rash, immune-related	Fatigue, pruritus, nausea, immune-related
Reference/s	1. Hodi 2010 2. Robert 2011	Chapman 2011	Hauschild 2012	Flaherty 2012	Larkin 2014	Robert 2015	Robert 2015

*Also studied in combination with dabrafenib mesylate in two randomised phase III trials

PFS = progression-free survival, OS = overall survival.

clinical practice guidelines advise the use of chemotherapy, palliative care or clinical trial participation for metastatic melanoma patients.[36,37] However, national standards for the treatment of patients with melanoma in New Zealand recommend the availability of BRAF and immune checkpoint inhibitor therapy for these patients.[38]

More specifically, the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines discuss the preferred sequence of drug therapy,[39,40] For patients who are rapidly deteriorating, both guidelines advocate pembrolizumab, nivolumab or BRAF and MEK inhibitors (the latter in those with BRAF mutant melanoma), owing to the higher response rates of these agents. Ipilimumab is reserved for those who are clinically stable or following kinase inhibitor treatment, where the treatment intent is long-term survival. For BRAF wild-type patients, pembrolizumab, nivolumab and ipilimumab are all accepted as first-line treatments but the ESMO Guidelines go further in stating that pembrolizumab is preferred due to its superior efficacy against ipilimumab and improved tolerability. It is worth noting that both guidelines support the use of kinase and immune checkpoint inhibitors in patients with brain metastases.

Prices

The prices of the current treatments in the US, England and Australia are provided in Table 3. They should be considered as indicative insofar as they are not expressed in the same currency and price level (eg, ex-manufacturer price). In many instances, the net reimbursed price is lower. Insofar as these medicines are expensive and beyond the purchasing capacity of most people with melanoma, reimbursement is essential to ensure patient access.

Reimbursement status (New Zealand)

The medicine reimbursement program in New Zealand, including the role of PHARMAC, is summarised in Table 4.

Dacarbazine has been listed in Section B of the New Zealand Pharmaceutical Schedule since 2005.[44]

Table 3: Prices of the new treatments for melanoma.[41,42,43]

Medicine	Ipilimumab	Vemurafenib	Dabrafenib mesylate	Trametinib dimethyl sulphoxide	Cobimetinib	Pembrolizumab	Nivolumab
US*	$7,200 (50 mg vial) (AWP)	$47 (240 mg tablet) (AWP)	$9,120 (120 capsules) (AWP)	$348 (2 mg tablet) (AWP)	~$6,000 (cycle) (WAC)	$2,158 (50 mg vial) (WAC)	$12,500/ month (AWP)
England**	£3,750 (50 mg vial)	£1,750 (56 x 240 mg tablets)	£933.33 (28 x 50 mg capsules)	Not available	£4275.67 (63 x 20 mg tablets)	£1,315 (50 mg vial)	£349 (40 mg vial), £1097 (100 mg vial)
Australia***	$48,159.70 (360 mg)	Not available	$5,888.32 (120 x 50 mg capsules)	$8,759.04 (30 x 2 mg tablets)	Not available	$11,426.36 (240 mg)	$7559.52 (360 mg)

* Price at launch; ** Price as stated in the British National Formulary; ***PBS list prices. AWP = average wholesale price, WAC = wholesale acquisition cost.

Vemurafenib

Roche lodged a submission with PHARMAC on 22 November 2011 for vemurafenib, seeking its listing in the New Zealand Pharmaceutical Schedule for patients with unresectable stage IIIC or stage IV melanoma positive for a BRAF V600 mutation.

The submission was considered by the PTAC in February 2012. "The Committee considered that overall vemurafenib was a very high cost treatment that provided only a small, short term, benefit."

The submission was referred to the Cancer Treatments Subcommittee (CaTSoP) who considered it the following month. "The Subcommittee recommended that vemurafenib should be funded for patients with unresectable stage IIIC or stage IV melanoma positive for BRAF V600 mutation. Because of the high cost of vemurafenib and the short-term evidence, members gave this recommendation a low priority. Members noted that if the price of vemurafenib were to significantly decrease, its priority rating may improve."

In the light of CaTSoP's recommendation, the submission was considered by the PTAC again in May 2012. "The Committee considered that there were few funded alternatives available and that vemurafenib improved the treatment of melanoma in this setting. Overall, the Committee considered that it would maintain its previous recommendation, that this application for vemurafenib should be declined because it only provided only a small benefit for a very high cost."

Roche is yet to lodge a resubmission.[44]

Ipilimumab

Bristol-Myers Squibb lodged a submission for ipilimumab on 21 May 2012 seeking a listing in the Schedule for patients with previously treated unresectable stage IIIC or IV melanoma.

The submission was considered by the PTAC in August that year. "The Committee noted that ipilimumab was a very expensive treatment, and considered that the non-specific immune activation related toxicity of ipilimumab was too hazardous to justify the uncertain incremental benefits at the price offered. The Committee recommended that the application be declined. The Committee further recommended that the application be considered by the Cancer Treatments Subcommittee."

The submission was considered by the CaTSoP in October 2012. "The Subcommittee considered that overall the evidence was relatively strong for ipilimumab providing a small increase in median overall survival. However, the evidence was very weak for any long-term benefit. Members considered that the evidence at this time indicated that the autoimmune effects of ipilimumab were too hazardous to justify the small, and uncertain, benefit at the price being offered. Therefore, the subcommittee recommended that the application be declined."

Table 4: Reimbursement/health technology assessment (HTA) agencies in New Zealand, Australia and England.[42,43,44]

Jurisdiction	New Zealand	Australia	England
Assessment agency	Pharmaceutical Management Agency (PHARMAC)	Pharmaceutical Benefits Advisory Committee (PBAC)	National Institute for Health and Care Excellence (NICE)
Technologies assessed	Medicines, vaccine, blood products, devices	Medicines, vaccines	Medicines, devices, procedures
Commencement of subsidised access	When listed in the New Zealand Pharmaceutical Schedule	When listed in the Schedule of Pharmaceutical Benefits	Within 90 days of the publication of a positive Final Appraisal Determination (FAD)
Submissions considered before local registration	Yes	Yes	Yes
Subsidised access possible before local registration	Yes	No	No
Early access scheme for emerging new medicines	No	Managed entry scheme	Patient access scheme

Bristol-Myers Squibb lodged a resubmission that was considered by the PTAC in February 2014. "The Committee recommended that the application be declined.

"The Committee further recommended that the application be referred to the Cancer Treatments Subcommittee for review once longer-term data from the randomised study had been provided.

"The Committee considered it likely that ipilimumab was associated with some long term survival advantage over best supportive care but remained uncertain of the magnitude of benefit."

Bristol-Myers Squibb is yet to provide the longer-term data to PHARMAC.[44] These data are now in the public domain.[28]

Dabrafenib mesylate

GlaxoSmithKline has lodged a submission for dabrafenib mesylate seeking its listing in the Schedule for patients with BRAF V600 mutation-positive stage III or stage IV malignant melanoma.

"The Committee recommended that the application for dabrafenib for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma be declined."

"The Committee considered given the high unmet need for effective treatments for metastatic melanoma it would be appropriate for one of vemurafenib, ipilimumab or dabrafenib to be funded. Members noted that all three treatments had been recommended for decline primarily due to their very poor cost effectiveness at the proposed prices. The Committee considered that all three offered some clinical benefit and recommended that PHARMAC run a competitive process to enable one of these treatments to be funded if reasonably cost effective."[44]

The sponsorship of dabrafenib mesylate was transferred to Novartis on 9 September 2015.[45]

Pembrolizumab

On 18 September 2015, the CaTSoP considered an application from MSD for the funding of pembrolizumab for the treatment of patients with metastatic or unresectable stage III or IV melanoma. The Subcommittee recommended that pembrolizumab should be funded for the treatment of metastatic or unresectable melanoma stage III or IV with low priority. The Subcommittee noted that the low

priority rating was influenced by the early evidence base, and the consequent uncertainty about its longer term benefits and potential risks, as well as its very high cost.

The PTAC considered the submission at its November 2015 meeting. The Committee recommended that pembrolizumab be funded for the treatment of metastatic or unresectable stage III or IV melanoma with a low priority.

At the November meeting, the Committee also noted that it may reconsider the funding of ipilimumab, including a review of the recently published long term follow-up data.[44]

Trametinib dimethyl sulphoxide, nivolumab

PHARMAC is yet to announce that it has received a funding application for these medicines (see footnote).[44]

Reimbursement status (Australia)

The Australian medicine reimbursement program, the Pharmaceutical Benefits Scheme, is summarised in Table 4.

The PBAC has established a process with the Medical Services Advisory Committee (MSAC) to enable the rapid assessment of co-dependent technologies.[46]

Dacarbazine is not listed on the PBS. Fotemustine was listed on the PBS on 1 April 2005 for patients with metastatic disease.[43]

Ipilimumab

The PBAC has considered multiple submissions to list ipilimumab on the PBS for the treatment of patients with stage III or stage IV malignant melanoma. The first two submissions (July 2011 & March 2012) were rejected due to concerns about the clinical place of ipilimumab in therapy and other reasons.

A third submission was considered in November 2012. The PBAC noted that the sponsor's expert advisory panel considered a requirement to use dacarbazine or fotemustine to be contrary to clinical judgment and would therefore be unlikely to be observed in practice.

The PBAC concluded that a requirement for patients to first try then fail ineffective and toxic first-line chemotherapy would not be clinically appropriate and requested that the PBS restriction be developed so as to permit the first-line use of ipilimumab.

The PBAC noted the high unmet clinical need for treatments for metastatic melanoma with proven survival advantage.

The PBAC noted that the cost effectiveness of ipilimumab is highly dependent on the duration of survival. Although concerned about the cost-effectiveness of ipilimumab if the claimed survival gain were not observed in practice, the Committee recommended the listing of ipilimumab for metastatic melanoma, subject to risk-share arrangements involving appropriate use, maintaining cost-effectiveness and managing financial risk.

Ipilimumab was listed in the Schedule of Pharmaceutical Benefits for patients with stage III or stage IV melanoma on 1 August 2013.[43]

Vemurafenib

The PBAC has considered two submissions to list vemurafenib on the PBS for use by patients with stage IIIC or stage IV melanoma positive for a BRAF V600 mutation. The first submission was deferred by the PBAC in July 2012 in order to obtain further information from the applicant and the MSAC on the following:

- Unacceptable cost effectiveness
- Negotiation of a risk-share agreement
- Further specification of the target patient population and the associated PBS restrictions
- Further revisions to the modeled economic evaluation and their effect on the ICER (applicant)
- Advice on the disease stage at which subsidised testing should occur, the total number of tests, the number of tests per patient reflecting the frequency of repeat testing, the costs of testing per patient treated with vemurafenib, and the cost of testing for resistance

The PBAC considered a resubmission for vemurafenib at its meeting in March 2013.

The PBAC deferred the resubmission in order for the Department of Health to consider an appropriate arrangement for data collection and to enable the Department to negotiate an appropriate price.

The PBAC made reference to the recent recommendation for ipilimumab and the submission for dabrafenib mesylate that was also considered for PBS listing at the March 2013 meeting. The PBAC intended to conclude that, on balance, vemurafenib and dabrafenib mesylate are clinically non-inferior to each other, and so should be cost-minimised against each other.

Roche is yet to lodge another submission so vemurafenib is not listed on the PBS.[43]

The interplay between the PBAC and the MSAC in relation to access to BRAF mutation testing is outlined in Figure 1.

Dabrafenib mesylate

The PBAC considered a submission to list dabrafenib on the PBS for the treatment of patients with BRAF V600 mutation positive stage IIIC or stage IV melanoma in March 2013. The submission was considered under the TGA/PBAC parallel process; under the TGA-PBAC parallel processes, a submission to the PBAC may be lodged at any time from the date of lodgement of a TGA registration dossier.

The PBAC deferred the submission in order to be informed of the TGA delegate's proposed registration and rationale, to enable the Department of Health to consider an appropriate arrangement for data collection and to negotiate an appropriate price.

A re-submission, that included a revised pricing proposal, was considered by the PBAC in July 2015. The PBAC recommended the PBS listing of dabrafenib mesylate that become effective on 1 December 2013 with a special pricing arrangement.[43]

Trametinib dimethyl sulphoxide

In March 2014, the PBAC considered a submission to listing trametinib dimethyl sulphoxide on the PBS for use in combination with dabrafenib mesylate by patients with BRAF V600 mutation positive stage III or stage IV melanoma.

The PBAC rejected the submission on the basis that the superior comparative effectiveness of trametinib dimethyl sulphoxide with dabrafenib mesylate over dabrafenib mesylate monotherapy had not

Figure 1: Access to BRAF testing.[47]

MSAC consideration of BRAF testing for vemurafenib and dabrafenib mesylate

2 August 2012

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of BRAF testing to help determine eligibility for proposed PBS-subsidised vemurafenib in unresectable stage IIIC or stage IV metastatic cutaneous melanoma, MSAC deferred the application until its responses to PBAC's requests for advice and further information from the applicant are considered by PBAC. If PBAC refers more matters to MSAC for advice, MSAC will reconsider these referrals.

If PBAC subsequently decides to recommend to the Minister that vemurafenib be listed on the PBS, MSAC will support an expedited process for its reconsideration to align its support for public funding of BRAF testing according to the circumstances recommended by PBAC.

5 April 2013

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of BRAF V600 mutation testing to help determine eligibility for proposed PBS-subsidised vemurafenib in unresectable stage III or stage 4 metastatic cutaneous melanoma, MSAC deferred the application until PBAC reconsiders the PBS listing of vemurafenib. MSAC noted that this might be associated with a PBAC reconsideration of dabrafenib, an alternative BRAF inhibitor.

1 August 2013

"After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of BRAF mutation testing to help determine eligibility for proposed PBS-subsidised dabrefenib in unresectable Stage III or Stage IV metastatic cutaneous melanoma, MSAC supports its public funding via a new MBS item, with an MBS fee of $230.95 and an item descriptor of:

A test of tumour tissue from a patient with unresectable stage III or stage IV metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to BRAF V600 mutation status for access to dabrafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC also reaffirmed its April 2013 advice that, as part of implementing coordinated MBS and PBS listing of these co-dependent health technologies, appropriate data be collected prospectively to be reviewed two years after listing."

Figure 2: PBAC's consideration of pembrolizumab.

The PBAC noted that, following lodgement of the submission on 5 November 2014, an extraordinary amount of important additional information was provided throughout the process of evaluation, including:

- 24 November 2014: trial data from KN-002 provided by the sponsor (20 slides)
- 28 January 2015: revised model and revised managed entry scheme (MES) proposal with the PSCR (16 pages)
- 13 February 2015 (after the ESC meeting): early results of KN-006 provided by the sponsor (38 pages) (KN-006 = randomised trial data directly comparing pembrolizumab with ipilimumab in ipilimumab naïve patients)
- 17 February 2015: TGA delegate's overview provided by the sponsor (96 pages)
- 25 February 2015: Attachment and PES Addendum to the ESC Advice to comment on the additional post-submission information (20 pages)
- 4 March 2015: further sensitivity analyses for the revised model and suggestions for the MES proposal with the pre-PBAC response (24 pages)
- 6 March 2015: additional information provided by the sponsor on proposed subsidised access to pembrolizumab for ipilimumab refractory patients via a funding arrangement from the sponsor (2 pages)

This was in addition to five meetings with the Department before the submission was lodged (3 December 2013, 13 May 2014, 27 August 2014, 28 August 2014, and 5 September 2014) and two post-submission meetings (10 December 2014 and 2 March 2015) between the sponsor and the Department.

The provision of extraordinarily large post-submission documents had placed an unreasonable pressure on the PBAC's supporting processes, and evaluation capacity, particularly just prior to the PBAC meeting. As a consequence, there was insufficient time to comprehensively evaluate all the material provided, and address relevant matters such as the open-label design, the potential for differences in drop-out rates between the trial arms, and the difference between the pembrolizumab dosage regimens in KN-006 and the dosage regimen requested for TGA approval and PBS subsidy. Also, since much of the material relating to KN-006 was accepted as being provided on a confidential basis, it would be redacted from the published version of the PBAC Outcomes document and of the Public Summary Document, unless permission is granted by the sponsor or it is published elsewhere between the time of the PBAC meeting and these PBAC-derived publications.

The ESC considered that the proposed managed entry scheme should be built around the ongoing phase III clinical trial (KN-006) with its stated co-primary endpoints of progression-free survival and overall survival.

The PBAC considered that the MES for pembrolizumab should be guided by the following.

- The initial price of pembrolizumab for PBS listing would be determined on the basis of the current cost per patient to the PBS of ipilimumab at its effective price. Rather than a direct price reduction, this would be achieved by setting the RSA expenditure caps for pembrolizumab with reference to the average cost of ipilimumab per patient using appropriate historical PBS dispensing data, and the revised utilisation estimates based on current ipilimumab utilisation via the PBS. These data indicated that approximately patients have commenced ipilimumab each year, with an average of induction doses per patient, with approximately ‘’% of these patients having undergone reinduction therapy with ipilimumab. The annual percentage increases in utilisation after the first year would be calculated as described in the submission (see table after paragraph 6.65 above). Any annual pembrolizumab expenditure beyond these caps should be rebated XXX% to the Commonwealth to generate the reduced effective price to apply from initial listing until such time as it might change at the end of the MES.
- The review of new evidence should be provided as soon as possible (and expected to be within two years) after maximal follow-up of the KN-006 trial, noting that the final analysis of overall survival for this trial is expected to report in the second quarter of 2016.
- The clinical evaluation for KN-006 should formally report both progression free survival (PFS) and overall survival (OS) using the standard graphics of Kaplan-Meier curves, and with standard reporting of results.
- The economic evaluation based on KN-006 should directly use the Kaplan-Meier curves observed based on individual patient data from the trial to estimate incremental PFS and incremental OS up to the median duration of follow-up across the two arms compared in the clinical evaluation, and then apply extrapolation modelling for both arms for PFS and OS curves from this time point, ie no statistical adjustments should be used to account for differential use of post-progression therapies.

been established. The PBAC also noted the higher rate of adverse events with combination therapy compared with dabrafenib mesylate monotherapy.

In November 2014, the PBAC considered a resubmission for trametinib dimethyl sulphoxide that included a Managed Entry Scheme (MES) proposal. A MES provides a mechanism to address the uncertainty over the size of the additional clinical benefit of new medicine while providing early access to those patients for whom there is a high clinical need.

The PBAC recommended the listing of trametinib dimethyl sulphoxide for use in combination with dabrafenib mesylate for the treatment of patients with BRAF V600 mutation positive stage III or stage IV malignant melanoma. Trametinib dimethyl sulphoxide was listed on the PBS under a MES on 1 August 2015.

Information about the benefits of trametinib dimethyl sulphoxide in clinical practice will be collected, analysed and presented to the PBAC for consideration in the near future. Prescribers and patients must be aware that trametinib dimethyl sulphoxide does not prove as beneficial in clinical practice as appeared in the clinical data presented to the PBAC, it may subsequently have its restriction modified or be removed from the PBS by the Commonwealth, or at the request of the sponsor.[43]

Pembrolizumab

The PBAC considered a submission to list pembrolizumab on the PBS for the treatment of patients with stage IIIC or stage IV melanoma in March 2015. The submission was considered under the TGA/PBAC parallel process; the main indication sought was for first-line use by ipilimumab naïve patients.

The PBAC's consideration of this submission is discussed in Figure 2.

The PBAC recommended the listing of pembrolizumab as for use as monotherapy by patients with stage III or stage IV melanoma, with an initial risk share arrangement to achieve the same cost per patient to the PBS as is currently the case for ipilimumab, to thus give a reduced effective price of pembrolizumab.

The PBAC recommended that the listing should be limited to patients who have not been exposed to ipilimumab, noting that the sponsor has undertaken to subsidise ongoing access to pembrolizumab for patients who are refractory to ipilimumab.

The PBAC supported the sponsor's request that, for patients with a BRAF mutation, the PBS listing of pembrolizumab should follow progression after treatment with dabrafenib mesylate (combined with trametinib dimethyl sulphoxide after trametinib dimethyl sulphoxide is listed).

Pembrolizumab was listed on the PBS under a MES on 1 September 2015.[43]

Nivolumab

The PBAC considered a submission to list nivolumab on the PBS for use by patients with stage III or stage IV melanoma in July 2015. The PBAC rejected the submission because it failed to include a comparison with pembrolizumab.[43]

Reimbursement (England)

The medicine reimbursement program in England, including the role of NICE, is summarised in Table 4.

In March 2014, the Medicines & Healthcare products Regulatory Agency (MHRA) announced it was launching an Early Access to Medicines Scheme (EAMS), saying it would allow earlier access to potentially lifesaving medicines for patients with severe or life-threatening conditions.

For a new medicine to qualify for the EAMS, it must be granted a promising innovative medicine designation based on early (phase I and/or II) clinical data and satisfy additional criteria including the severity of the condition the medicine is intended to treat and the level of improvement over previously authorised treatments.[48]

The MHRA has approved two medicines for melanoma under the EAMS: pembrolizumab and nivolumab.[49]

NICE has assessed the following new treatments for patients with melanoma:[42]

- Vemurafenib—recommended as an option for treating BRAF V600 mutation positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme (December 2012).

- Ipilimumab—recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme (July 2014).
- Dabrafenib mesylate—recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation positive melanoma only if the company provides dabrafenib mesylate with the discount agreed in the patient access scheme. (October 2014).
- Pembrolizumab—recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only after the disease has progressed with ipilimumab and, for BRAF V600 mutation positive disease, a BRAF or MEK inhibitor and when the company provides pembrolizumab with the discount agreed in the patient access scheme (October 2015). Because pembrolizumab was made available in the NHS through the early access to medicines scheme, NHS England has indicated that this guidance will be implemented 30 days after final publication. In November 2015 pembrolizumab was recommended as an option for the treatment of adults with advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, only when the company provides pembrolizumab with the discount agreed in the patient access scheme.
- Trametinib dimethyl sulphoxide—recommended for use in combination with dabrafenib mesylate for the treatment of patients with advanced unresectable or metastatic BRAF V600 mutation positive melanoma in June 2016.
- Nivolumab—recommended for use for the treatment of patients with advanced, unresectable or metastatic melanoma in February 2016..

Table 5 summarises the current reimbursement status of the new treatments for patients with melanoma.

Discussion

Significant advances have occurred in the drug treatment of patients with metastatic melanoma since 2010. The development of the BRAF and MEK inhibitors, and immune checkpoint inhibitors, offer unprecedented clinical benefits to patients with advanced disease. Important advantages of these novel drugs are their ability to treat sites of disease previously viewed as refractory to systemic therapy, and manageable toxicity profiles. As a result, there has been accelerated regulatory approval of some of these agents. However, all of these treatments are high-cost, and the reimbursement process fundamentally drives access to them.

Timely access to at least one agent in each class of drug is critical in New Zealand, Australia and England, where metastatic melanoma is a major public health concern. When confronted by the evidence surrounding the funding process in the three countries, the differences are stark. The reimbursement/HTA agencies in Australia and England, recognising the unmet need of melanoma patients and acknowledging the importance of equitable geographical access, have taken innovative and extraordinary measures to make at least one drug from each novel class available in a timely manner. In contrast, New Zealand's agency, PHARMAC, has rejected multiple applications to fund any of these drugs over a four-year period, and there are no signs to indicate that any of them will be listed in the New Zealand Pharmaceutical Schedule anytime soon. It is difficult to understand, let alone accept, such inertia with the melanoma statistics of this nation.

The recommendation by a technical advisory committee (PTAC) that PHARMAC run a competitive tender to fund one of ipilimumab, vemurafenib and dabrafenib mesylate, is unusual; we are not aware of the PBAC or any of the NICE Appraisal Committees having provided similar tactical advice to their corresponding bureaucracies. Furthermore, the PTAC recommendation that PHARMAC run a competitive tender to fund medicines that have different modes of action undermines the basic science and makes one start to question whether the primary focus of the Committee is science (pharmacology) or finance (money).

Table 5: Summary of the reimbursement status of the new treatments for patients with melanoma.

Medicine (generic name)	Ipilimumab	Vemurafenib	Dabrafenib mesylate	Trametinib dimethyl sulphoxide	Pembrolizumab	Nivolumab
Submission considered by PTAC	Yes	Yes	Yes	No	No	No
Date/s of consideration	August 2012, February 2014	February 2012, May 2013	November 2014	Not considered	Not considered	Not considered
Outcome/s	Rejection, Rejection	Rejection, Rejection	Rejection	No outcome	No outcome	No outcome
Date of listing/ implementation	Not listed	Not listed	Not listed	Not listed	Not listed	Not listed
Submission considered by PBAC	Yes	Yes	Yes	Yes	Yes	Yes
Date/s of consideration	July 2011, March 2012, November 2012	July 2013, March 2013	March 2013, July 2013	March 2014, November 2014	March 2015	July 2015, November 2015
Outcome/s	Rejection, Rejection, Recommendation	Deferral, Deferral	Deferral, Recommendation	Rejection, Recommendation	Recommended	Rejection, recommended
Date of listing/ implementation	1 August 2013	Not listed	1 December 2013	1 August 2015	1 September 2015	1 May 2016
Submission considered by NICE Appraisal Committee	Yes	Yes	Yes	Yes	Yes	Yes
Date/s of consideration	September 2011, November 2011, February 2012, September 2012	May 2012, July 2012, September 2012	Not available	March 2016, May 2016	July 2015, August 2015	November 2015
Outcome/s	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended
Date of listing/ implementation	March 2013	March 2013	January 2015	September 2016	November 2015	March 2016

These new medicines are expensive but they are also effective. We are not calling for their immediate reimbursement without a thorough and fair assessment of their value (eg, cost effectiveness). The PBAC rejected most of the initial submissions for these medicines. Nonetheless, we urge the Government and/or PHARMAC to find solutions to the current unacceptable access stalemate. New Zealanders with melanoma deserve better than this; we suspect that patients are suffering to the point of dying due as a result. It is nigh on impossible to obtain empirical data to prove this; whilst it is (somewhat) easy for PHARMAC to calculate how much money it has saved, it is much harder to determine how many lives have been lost as a consequence.

New Zealand should not be in the unenviable position whereby it has the highest incidence of a fatal disease yet it is the last country in the Western world to fund effective treatments for it.

We note the recent PHARMAC report on access to new cancer medicines with the associated claim that New Zealanders are getting access to the best cancer medicines available.[50] The findings from this study are

in stark contrast to other studies that have found New Zealanders have poorer access to new medicines in general.[51,52] Notwithstanding our concerns about many aspects of the PHARMAC analysis, it has scant reference to the new medicines for melanoma.

We describe a number of examples of the momentum in Australia and England to reimburse new systemic treatments for patients with metastatic melanoma in a timely manner. Both countries have introduced schemes that allow early access to promising therapies for patients with life-threatening diseases, while managing the risks associated with evolving clinical trial data and real-world experience. A central principle of the MES in Australia is the ongoing evaluation of promising new medicines with the commitment to providing patients with the most efficacious and safest treatments at a given time; in other words, the reimbursement process will attempt to keep in step with the latest evidence. It is our strong view that New Zealand should look to adopt a similar scheme.

Another example of the commitment to a high standard of care for melanoma patients is the harmonization of the processes for the reimbursement of a medicine and its corresponding diagnostic test, demonstrated by Australia's PBAC and MSAC assessment of dabrafenib mesylate and BRAF mutation analysis. To our knowledge, no such procedure exists in New Zealand and is a further weakness that may lead to sub-standard and inequitable care for melanoma patients.

What is/are the causes of the inertia?

- PHARMAC is yet to receive funding applications for these medicines from their respective sponsors. This seems unlikely as submissions for most of the new medicines have already been considered by PTAC. PHARMAC is yet to publish all of the funding applications that were considered by the PTAC in August and November 2015.
- There is no funding. The listing of these medicines in the New Zealand Pharmaceutical Schedule will come at a cost to the fixed PHARMAC budget. It is unclear if PHARMAC has the budget to list some/all of these medicines. Likewise, it is unclear if PHARMAC has asked the Government for extra funds if the current PHARMAC budget precludes their listing.
- The clinical benefits of the new treatments are lacking or are uncertain. Notwithstanding the concerns of the PTAC and others about the benefits and harms of the new treatments over the long term, this has not prevented their reimbursement in Australia and England (and elsewhere). Their inclusion in authoritative clinical guidelines suggests that other experts in the field are of the view that their clinical benefits outweigh their risks.
- Poor access to co-dependent technologies; whilst this may be an issue for dabrafenib mesylate and vemurafenib, it isn't for ipilimumab, trametinib dimethyl sulphoxide and pembrolizumab.
- Proposed unit prices are 'unacceptable' to PTAC/PHARMAC. This is an issue but we have limited information to evaluate this. Other HTA agencies have also expressed concerns about their high unit costs but this has not prevented their reimbursement.

In the light of the above, we offer the following recommendations to all stakeholders:

- PHARMAC invite/encourage all relevant sponsors to lodge funding applications, regardless of whether they have been approved by Medsafe
- Medsafe consider expediting its assessment/approval process for certain new medicines
- PTAC uphold the underlying science in funding applications
- Government explore options for the subsidized access to necessary co-dependent technologies. This may well be an additional role for PHARMAC.
- PHARMAC consider funding some of these new medicines before their registration by Medsafe. While there is no legislative impediment to this, there may be a budgetary one.
- PHARMAC ask the Government for additional monies to fund some/all of these new medicines if PHARMAC's fixed budget for the current financial year has been exhausted/fully committed.

- PHARMAC consider the adoption of new access models such as the new MES in Australia and the patient access scheme in England
- The sponsors of the medicines concerned prepare and submit funding applications that include realistic pricing/funding proposals. PHARMAC should consider these applications as soon as possible.

PHARMAC has done an excellent job over many years in containing pharmaceutical expenditure in New Zealand. The agency has been very successful in focusing the public discussion on the country's medicine reimbursement program to fiscal matters. Discussions on the value of new medicines and the health forgone have gained little attention. It is high time to shift the focus of the discussion from cost to value. Likewise, it is time to shift the current mindset of PHARMAC from being a defender of the public purse to a pragmatic problem solver.

Authors' footnote 19 July 2016:

This manuscript was submitted for publication on 16 December 2015 and accepted for publication on 4 May 2016. We note the subsequent events:

- On 28 April 2016, Medsafe approved nivolumab for use as monotherapy for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma and in combination with ipilimumab for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).
- On 4 May 2016, PHARMAC announced that it proposed to list nivolumab on the New Zealand Pharmaceutical Schedule, as monotherapy for advanced melanoma patients.
- On 9 May 2016, PHARMAC published a CaTSoP minute on nivolumab. The Subcommittee considered an application from Bristol-Myers Squibb on 22 April 2016 for the listing of nivolumab as monotherapy and in combination with ipilimumab for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma. CaTSoP recommended the listing of nivolumab for the former patient population (medium/high priority) and deferred it for the latter patient population.
- On 18 May 2016, PHARMAC published a PTAC minute on nivolumab. On 5-6 May 2016, the PTAC considered a funding application for nivolumab for use and monotherapy and in combination with ipilimumab. The PTAC recommended the listing of nivolumab as monotherapy (medium priority) but rejected its listing for use in combination.
- On 9 June 2016, following a consultation period, PHARMAC announced the decision to fund nivolumab from 1 July 2016, for patients meeting the special authority criteria.
- The proposed special authority criteria were amended, including provision for nivolumab to be combined with ipilimumab (noting that ipilimumab remains unfunded).
- On 29 June 2016, PHARMAC commenced consultation on a proposal to fund pembrolizumab from 1 September 2016
- PHARMAC has confirmed that funding applications for pembrolizumab, BRAF and MEK inhibitors remain under consideration. PHARMAC is yet to publish details on the funding applications that were considered by the PTAC in February and May 2016. It is unclear if PHARMAC has received additional funding applications for these medicines.

The decision to fund nivolumab and the consultation on the funding of pembrolizumab must be viewed as significant advances, but does not influence our concluding remarks.

Competing interests:
Mr. Wonder reports a grant from Medicines New Zealand to conduct of the study and personal fees for various consulting projects with the pharmaceutical industry outside the submitted work. Medicines New Zealand had no influence in the content of the manuscript. Dr. Fisher reports personal fees from Advisory board—MSD New Zealand, outside the submitted work.

Author information:
Michael Wonder, Wonder Drug Consulting Pty Ltd, Cronulla, Australia; Rosalie Fisher, Auckland DBH Oncology Services Auckland City Hospital, New Zealand.

Corresponding author:
Michael Wonder, Wonder Drug Consulting Pty Ltd, PO Box 470, Cronulla, Australia.
wonderdrug@optusnet.com.au

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6971

REFERENCES:

1. National Institute for Health and Care Excellence. NICE Guidance. Conditions and Diseases. Cancer. Skin Cancer. Melanoma: assessment and management. [NG14]. July 2015. Available at http://www.nice.org.uk/guidance/ng14 [Accessed 1 December 2015].
2. A Snapshot of Melanoma. National Cancer Institute. Available at: http://www.cancer.gov/research/progress/snapshots/melanoma Accessed August 26, 2015.
3. Melanoma Skin Cancer. American Cancer Society. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003120-pdf.pdf [Accessed August 26, 2015].
4. World Health Organization. International Agency for Research on Cancer. Globocan 2012: estimated cancer incidence, mortality and prevalence in 2012. Available at http://globocan.iarc.fr/Default.aspx [Accessed 30 November 2015].
5. Melanoma New Zealand. About melanoma. Statistics. Available at http://www.melanoma.org.nz/melanoma/overview/ [Accessed 1 December 2015].
6. Australian Government. Australian Institute of Health and Welfare. Melanoma skin cancer. Available at http://www.aihw.gov.au/cancer/melanoma/ [Accessed 1 December 2015].
7. MacKie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. Ann Oncol. 2009;20 Suppl 6:vi1-7
8. Cancer Research UK. Cancer Statistics. Statistics by cancer type. Skin cancer statistics. Skin cancer incidence statistics. Skin cancer incidence overt time. Available at http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer/incidence#heading-Two [Accessed 1 December 2015].
9. New Zealand Ministry of Health. Publications. Cancer: Selected Sites 2009, 2010, 2011. Available at http://www.health.govt.nz/publication/cancer-selected-sites-2009-2010-2011 [Accessed 1 December 2015].
10. Ekwueme DU, Guy GP Jr, Li C, et al. The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-United States, 2000 to 2006. J Am Acad Dermatol. 2011;65(5 Suppl 1):S133–43.
11. Balch CM, Gershenwald JE, Soong S, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–6206.
12. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417(6892):949–54.
13. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005;353(20):2135–47.
14. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11 in uveal melanoma. N Engl J Med. 2010;363(23): 2191–9.
15. Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-asso-

ciated genes. Nature. 2013;499(7457):214–8.

16. Serrone L, Zeuli M, Sega FM, Cognetti F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J Exp Clin Cancer Res. 2000;19(1):21–34.
17. Crosby T, Fish R, Coles B, Mason MD. Cochrane Database Syst Rev. 2000;(2):CD001215.
18. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–16.
19. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358–65.
20. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(11):1087–95.
21. Flaherty KT, Robert C, Hersey P, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367(2):107–14.
22. Sullivan RJ, Flaherty K. Resistance to BRAF-targeted therapy in melanoma. Eur J Cancer 2013;49(6):1297–304.
23. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877–88.
24. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521–32.
25. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867–76.
26. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.
27. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364(26):2517–26.
28. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015;33(17):1889–94.
29. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372(4):320–30.
30. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375–84.
31. Dummer R, Daud A, Puzanov I, et al. A randomized controlled comparison of pembrolizumab and chemotherapy in patients with ipilimumab-refractory melanoma. J Transl Med 2015, 13(Suppl 1):O5.
32. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16(8):908–18.
33. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23–34.
34. Larkin J, Lao CD, Urba WJ, et al. Efficacy and safety of nivolumab in patients with BRAF V600 mutant and BRAF wild-type advanced melanoma: a pooled analysis of 4 clinical trials. JAMA Oncol. 2015;1(4):433–40.
35. Dummer R, Hauschild A, Lindenblatt N, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v126–32.
36. Cancer Council of Australia. Health Professionals. Clinical Guidelines. Skin Cancer. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand, November 2008. Available at http://www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/ClinicalPracticeGuidelines-ManagementofMelanoma.pdf [Accessed 30 November 2015].
37. Marsden JR, Newton-Bishop JA, Burrows L, et al. Revised U.K. guidelines for the management of cutaneous melanoma

2010. Br J Dermatol. 2010;163 (2): 238–256.

38. New Zealand Ministry of Health. National Tumour Standards. Standards of Service for Melanoma Patients in New Zealand. Available at http://www.health.govt.nz/our-work/diseases-and-conditions/cancer-programme/faster-cancer-treatment-programme/national-tumour-standards [Accessed 30 November 2015].

39. National Comprehensive Cancer Network (NCCN). NCCN Guidelines. Melanoma. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#melanoma [Accessed 9 December 2015].

40. Dummer R, Hauschild A, Lindenblatt N, et al. Cutaneous Melanoma: ESMO Clinical Practice Guidelines. Ann Oncol. 2015;26 (suppl 5): v126–v132.

41. MAESTrO database. Available at www.maestro-database.com [Accessed 9 December 2015].

42. National Institute for Health and Care Excellence. http://www.nice.org.uk [Accessed 9 December 2015].

43. Australian Government. Department of Health. Pharmaceutical Benefits Scheme. Available at www.pbs.gov.au [Accessed 9 December 2015].

44. PHARMAC. Available at http://www.pharmac.health.nz [Accessed 9 December 2015].

45. New Zealand Medicines and Medical Devices Safety Authority. Available at http://www.medsafe.govt.nz [Accessed 9 December 2015].

46. Australian Government. Department of Health. Health Technology Assessment. Transition Arrangements for Co-dependent Technologies in 2012. Available at http://www.health.gov.au/internet/hta/publishing.nsf/Content/co-1 [Accessed 30 November 2015].

47. Australian Government. Department of Health. Medicare Benefits Advisory Committee. Available at http://www.msac.gov.au [Accessed 9 December 2015].

48. UK Government. Medicines, medical devices and blood regulation and safety guidance. Apply for the early access to medicines scheme (EAMS). Available at https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams [Accessed 30 November 2015].

49. Regulatory Affairs Professionals Society. Regulatory Focus. News. Cancer Drugs First to Take Advantage of UK Early Access Scheme. Available at http://www.raps.org/Regulatory-Focus/News/2015/06/03/22616/Cancer-Drugs-First-to-Take-Advantage-of-UK-Early-Access-Scheme/#sthash.HjPnmbu5.dpuf [Accessed 30 November 2015].

50. PHARMAC. News. NZers getting access to best cancer medicines. Available at http://www.pharmac.health.nz/news/media-cancer-comparisons/ [Accessed 9 December 2015].

51. Wonder M, Milne R. Access to new medicines in New Zealand compared to Australia. N Z Med J. 2011;124(1346):12–28.

52. Ragupathy R, Aaltonen K, Tordoff J, Norris P, Reith D. A 3-dimensional view of access to licensed and subsidized medicines under single-payer systems in the US, the UK, Australia and New Zealand. Pharmacoeconomics. 2012;30(11):1051–65.

Continuity of cancer patient care in New Zealand; the general practitioner perspective

Paul Kane, Marieke Jasperse, Richard Egan, Lynn McBain, Eileen McKinlay, Susan Pullon, Patries Herst

ABSTRACT

AIM: As cancer treatments become more effective, increasing numbers of cancer patients seek long-term support from general practice. This study aimed to canvass the perspective of GPs on issues around continuity of care for these patients.

METHODS: In this qualitative study purposive sampling was used to invite a range of New Zealand GPs from urban and rural communities in the Greater Wellington and Otago/Southland areas to participate. A total of 34 GPs took part in three semi-structured individual interviews and six focus groups.

RESULTS: Six main themes emerged; the participating GPs noted they wanted more involvement in their patients' cancer journeys but were not always clear of their place in relation to cancer specialists and other health care providers. They saw cancer as a chronic condition to be managed long term. They mentioned the breast cancer and palliative care models as examples to be followed. Poor communication and barriers for patients in accessing GP care were seen as areas for improvement.

CONCLUSION: Participating GPs felt that the current cancer care pathway could be improved with a better understanding of their own role and through improved communication with patients, cancer specialists and other health professionals.

Due to improvements in the prevention and treatment of heart disease, stroke and infectious diseases, New Zealand (NZ), like the rest of the developed world, is confronted with an aging population. This together with new cancer screening programmes and increased public awareness, has contributed to an increase in cancer diagnoses worldwide.[1,2] With more effective treatment options for an increasing number of patients with cancer, the number of those who will need ongoing medical care is on the rise.[1,2]

The cancer journey of patients and their families is a complex one. After diagnosis, patients undergo a range of treatments accompanied by various tests and scans. In addition, most patients experience a multitude of cancer-related and treatment-related side effects. During their journey patients are initially under the care of surgeons and/or medical and radiation oncologists (cancer specialists). While in hospital, many patients are cared for by multidisciplinary teams (MDTs) consisting of: surgeons, medical and radiation oncologists, oncology nurses, radiation therapists, dieticians and physiotherapists.[3] MDTs discuss patient progress on treatment and management of side effects seeking joint decisions.[4]

Patients may continue to regularly consult their GP about pre-existing conditions during this time as well as for continued support of their side effects when their treatment is completed, whether in remission or not. Patients whose cancer recurs will often re-enter the hospital system to receive further treatment.[5]

Continuity of care is defined as care that a patient "experiences over time, as coherent and linked, and is the result of good information flow, good interpersonal skills and a good combination of care".[6]

ISSN 1175-8716

(page 1) In an ideal world the transitions between surgeons, medical oncologists, radiation oncologists, other healthcare professionals and general practice care should be seamless. However, when "continuity of care" is compromised, patients become unsure of who to go to for support and ongoing care while during and after they have completed specialist hospital care. Lack of continuity of care and the importance of implementing strategies to facilitate this was addressed in Aubin et al.[6] In New Zealand, the disjointed transition between tertiary, secondary and primary care was highlighted by a recent evaluation of a supportive care service provided by the Cancer Society of New Zealand (CSNZ) and there was some evidence that the role of GPs in the care of patients with cancer is not always clear.[7] The New Zealand Ministry of Health made the provision of supportive continuity of care for cancer patients a priority in its latest guidelines.[5,8]

As more cancer patients rely on their general practice for continued support and care, the lack of systems to provide continuity of care will be highlighted impacting on patients, their families and general practice services. The main objective of the current study was therefore to explore with New Zealand GPs their perceptions of current care pathways and identify issues around continuity of care for cancer patients.

Design

In this qualitative study, data collection and analysis for this research was guided by constructivist grounded theory principles.[9] Firstly that understanding the issue at hand did not necessarily mean discovering a clear and unbiased truth, rather a perspective could be constructed from the data. Second, that data is analysed in a structured fashion usually with several iterations, driven by the perspective of both researchers and participants. Data were collected in three semi-structured individual interviews and six focus groups totalling 34 GPs. Semi-structured interviews and focus groups were conducted by authors one, two and three.

Table 1: Potential questions for semi-structured interviews or to guide focus group discussion.

No.	Potential questions
1	How many patients with a new cancer diagnosis do you see in a year?
2	How much contact did you have with those patients over the course of their cancer journey?
3	What do their visits to you involve? Advice? Counselling? Repeat prescriptions?
4	What was your experience of the lines of communication between you and the specialist team responsible for their cancer treatment?
5	Do you feel well enough informed about current treatments to advise your patients with a new or ongoing cancer diagnosis?
6	Do you feel well informed about the kinds of services provided by the DHB and NGOs for cancer patients?
7	How well supported by those organisations do you feel in your role as a GP?
8	If you have issues with any of the above, can you describe any remedies which you feel would be useful to you in your role?
9	If you have positive experiences can you explain these and how those might be further improved or expanded on?
10	Can you highlight issues around provision of care affecting particular groups within your patient base? For example, relating to Māori patients, younger or older patients, patients from varying socio-economic backgrounds?
11	Is there anything specific to your practice you feel impacts on the question we are attempting to address? For example, as rural practice or as a Māori Primary Care provider?

Purposive sampling was used to recruit participants. A diverse range of general practices in the Greater Wellington, Otago and Southland regions were identified (eg rural and urban, low and high SES). General practitioners at those practices were invited to participate by an introductory letter. This was followed up by a phone call to confirm participation and arrange a suitable time and venue for the interview or focus group. Only one of the general practices approached declined to participate because of time constraints. The interviews took place in the GPs' workplace. Each interview or focus group was audio recorded and transcribed. Field notes were made to accompany the audio record. Coding of the transcripts was done on a line by line basis for analysis, with organisation of transcripts supported by NVIVO software (QSR International Pty Ltd, version 9). A system of peer coding was utilised; author two coded all transcripts, authors one and three coded sample transcripts. Email communication and face to face meetings supported code development and provided a way to resolve any differences before agreeing on the final code headings used. Sequential coding and analysis was conducted prior to the next interview or focus group taking place. The entire team met twice over the course of the study period. This permitted discussion of emerging themes and adjustments in the interview schedule allowing emerging themes to be explored with subsequent participants. Ideally data collection and analysis continues until saturation is achieved and no new themes emerge.[10] In this study we believe saturation was achieved with respect to the major themes reported. A summary of findings was made available for participants if they wished to provide feedback. Māori consultation was undertaken utilising the University of Otago/Ngati Tahu committee process. Ethical approval for the study was obtained from the Ministry of Health Multi-Region Ethics Committee (MEC/12/EXP/037). The project was part funded by the National Support Services Manager's Office of the Cancer Society of New Zealand.

Table 2: Participant demographics and work experience.

Number (percentage) of participants	**n (%)**
Total number of participants	34 (100%)
Location	
North Island	19 (56%)
South Island	15 (44%)
Gender	
Male	21 (62%)
Female	13 (38%)
Ethnicity	
New Zealand European/Pakeha	19 (56%)
Other	14 (41%)
British	2 (14%)
Dutch	2 (14%)
German	1 (7%)
Israeli	1 (7%)
South African	1 (7%)
American	1 (7%)
Canadian	1 (7%)
Chinese	3 (21%)
Sri Lankan	2 (14%)
Age	
25–34 years	3 (9%)
35–44 years	7 (21%)
45–54 years	13 (38%)
55–64 years	8 (24%)
65–69 years	3 (9%)
Work experience in New Zealand	
0–10 years	11 (32%)
11–20 years	8 (24%)
21–30 years	6 (17%)
31–40 years	6 (17%)
Undisclosed	3 (9%)
Overseas experience	19 (56%)

Results

The following section describes the participant characteristics and the six

main themes that were developed from individual interview and focus group data: lack of involvement with cancer patients, uncertainty in the role of GPs in continuity of care, cancer as a chronic condition, poor communication with specialists, existing models of good practice, and barriers for patients accessing GPs.

Participant Characteristics

Data were collected from a total of 34 GPs practicing in a range of settings (urban and rural) across New Zealand to explore their current involvement with cancer patients under their care. Participant demographics and work experience are shown in Table 1. More than half of the participants were male and the overall age range was 25–69 years (Mode = 45–54 years). Approximately half of the participants identified as New Zealand European, with the remainder identifying with other ethnicities. With respect to work experience, the years of working in New Zealand as a GP ranged from 1.5–38 years (Median = 16.35) and just over half the participants had also practiced overseas.

Involvement with cancer patients

Participants reported that typically an individual GP will engage with approximately 10–20 newly diagnosed cancer patients a year. The extent of their involvement with this group was subject to considerable variation ranging from patients who "dropped off the radar" to patients who had regular consultations. When asked about the reasons for such a wide variation, participants suggested that this could depend on the presence of pre-existing conditions, the individual's diagnosis treatment and prognosis, quality of their relationship with the patient and the patient's emotional dependence on the GP.

'Some patients, you see them quite regularly but some patients literally disappear and you don't see them again ...' (F1, GP1)

Role for GPs in continuity of care

All participants believed they have a significant role to play when it comes to the ongoing supportive care of their cancer patients. GPs explained they did not perceive a role in making decisions about specialised treatment, but rather in explaining what this treatment would involve and how it might affect their patients. In addition to clarifying information given by the cancer specialist, they would address the psychosocial needs of the patient and their family, as well as managing side effects and pre-existing conditions.

'I really wouldn't have any input into the actual therapy and treatment ... it would be mainly to see how they're coping, and if they've got other conditions, to make sure that those are looked after.' (I1, GP1)

'I quite like to see them in parallel with the consultants so that they still come to me and we can talk about what the consultant said and what the treatment involves and how they are managing that and the sort of effects of that on them ... Then they have the usual general practice needs of everyone else which need to be managed alongside that ...' (F3, GP3)

Cancer as a chronic condition

Participants saw cancer as a chronic condition in the light of increased numbers of patients who have successfully completed cancer treatment. They described their involvement in supportive care of these patients as being similar to their involvement in the management of those with chronic conditions such as heart disease, asthma and diabetes.

'... take heart failure, it's a highly complicated thing and yet we deal with the vast majority of people with heart failure and it's got tricky drugs and its on-going and its chronic and so I'm not suggesting that we can take over from oncology, of course not, we can't. They are highly specialised

drugs and treatment but there's a lot of lower end stuff that I would be able to manage like yearly reviews or six monthly reviews with specialists guidelines like a lot of other chronic illness, models of care for chronic illness ... cancer's chronic now.' (F6, GP3)

Communication with cancer specialists

GPs expressed a strong desire to be better informed about cancer diagnosis, prognosis and ongoing management. Suggestions included specific guidance from cancer specialists and/or continued professional development (CPD) initiatives. The GPs emphasized the importance of clear communication from cancer specialists and clarity of expectations and responsibilities.

'... then we can look up in their last letter and it says ... "This is how we manage it in our department" and ... we are able to treat them then ...' (F2, GP1)

Participants discussed how their interaction with cancer specialists is often (but not always) characterised by miscommunication, issues with timeliness and dissatisfaction with the content of the communication.

'The letters from the hospital are often frustratingly slow ... to explain about this "Oh I've got to see somebody else and I don't know why I'm going?", well I don't know either and I can't allay their fears or I can't explain anything to them because I just don't know.'

*'I think the letters are far too complicated and long and they're clinical summaries for themselves.' (F3,*GP1)

Some GPs commented that they would appreciate it if cancer specialists informed them of the rationale behind the suggested treatment, management of common side effects, prognosis and requirements for follow up.

A coordinated IT infrastructure was considered extremely effective in situations where this had already been implemented. Some participants reported systems where GP practices can electronically access DHB records as soon as they are created. There was also recognition that some cancer specialists communicated very well with their general practitioner colleagues.

'A nice example today ... I just read the first letter from the oncologist and he was put on this chemotherapy and he could have this this this side effect, and this and this is the treatment ... and I knew exactly what to do!' (F5, GP1)

Shared care approach

Participants expressed a desire for a cross sectorial approach to cancer care, particularly in the case of elderly patients living in isolation, which if realised may go some way to managing the increasing burden of care associated with New Zealand's aging population.

'Certainly if the [cancer] specialists could regard the GPs as being part of the team and if we have a role to play maybe at monitoring certain aspects, that relieve them at the clinic, if they ask us to monitor this patient every month for a couple of months and look out for this, that, or the other and then we'll see them again at six months ... I'm sure there's a willingness and a recognition from my GP colleagues that this is what we do.'

Existing models of good practice: coordinated care

Across the range of focus groups and interviews the GPs were very positive about two models of care both of which included the involvement of a range of disciplines. In the first, the coordinated approach of the breast cancer team was regarded as something the oncology speciality in general could aim to replicate.

'The breast service is really good.' (F5, GP6)

'A good example would be ... a chronic care nurse who acts as that patient's contact person, establishes a relationship with the patient, liaises amongst various health professionals to ease them along, reminds them about things depending on the need and may even go to appointment with the person for some of the ... less capable patients. It's something that works really well ...' (F4, GP3)

In the second, GPs also spoke highly of their engagement with their local palliative care hospices and discussed how effective the shared care/partnership model was and how it could facilitate ongoing continuity of care for cancer patients who were terminally ill. They mentioned how effective it is to have 24/7 access to nursing contacts and

care in alleviating anxiety for the patient and family but also for themselves as GPs.

'The hospice runs a partnership programme ... and the patients are told if you have any questions these are the numbers to call, ok so 24/7 service, you call this nurse you call this number and you'll get the appropriate advice ...' (F2, GP1)

Barriers for patients accessing their GPs

The general practice service provision model in New Zealand was frequently mentioned as a barrier to good service. Patient co-payment for GP services was seen as a significant obstacle to accessing care. GPs felt that patients had concerns about their ability to advise on and provide support for highly specialised treatments and management. They perceived that some patients preferred to engage with the specialist as a more desirable option medically or financially.

'... the hard thing is always money.... patients may think I'm with the specialist now so I'll stick to the specialist because it's cheaper for me, I don't pay for him every time and he gives me my scripts and I get them for free.' (I3, GP)

In contrast to this, geography and infrastructure often hindered access to specialist services and GPs therefore were an easier option in those situations.

'I think it is difficult travel wise ... we're in _____ so it's easier for them to come and see us than to travel all the way into _____' (F2, GP2)

GPs felt that that patients and cancer specialists were unclear as to their role in regards to supportive cancer care. GPs felt that patients found difficult to engage with the GP about their cancer if the specialists had not initiated that involvement.

'I've found patients in my notes who've had no follow up because there was a breakdown in communication at that level ... and they slip under the radar because they haven't been referred back to us.' (FG1, GP1)

'The patient pathway, a clear knowledge of where they stand in the pathway whether they're primarily looked after by their GP or by the hospital, that would be more worthwhile.' (F3, GP1)

Discussion

This study sought the opinions of a range of GPs in the Greater Wellington, Otago and Southland regions on issues around continuity of care of cancer patients. Overall, their opinion was that there were gaps in the continuity of care of these patients in their own practice.

With increasing numbers of those with cancer, general practice services have an increasingly important part to play in their ongoing support. The current lack of continuity of care between cancer specialists and general practitioners results in a disjointed cancer trajectory for patients[11] resulting in unmet medical and psychosocial needs.[6,11–15]

Similar to the Survey of Physicians' Attitudes Regarding the Care of Cancer Survivors study it seems that New Zealand GPs also vary in how they see their role in providing ongoing support for those with cancer.[16] Many of the issues identified by the participants in the current New Zealand study could be collectively described as "lack of role clarity". All participating New Zealand GPs (n=34) saw themselves uniquely placed to play a role in the supportive care of patients with cancer and their families, because of their long standing relationship and involvement with the health care of different family members. Participants were invested in enhancing and increasing their involvement in ongoing supportive care. Most of the participating GPs already had a significant level of engagement with their patients with cancer and were concerned when for a few this did not happen. Lack of involvement in the supportive care of some patients was often due to the GPs not knowing what was going on with their patients.

A Norwegian study exploring the involvement of GPs in the follow up of cancer patients identified several factors that may contribute to the level of engagement of cancer patients with their GPs.[17] Different patients have different needs: some patients want a lot of information about their disease and treatments, others do not. Some Norwegian patients sought out their GPs because they had a long standing trusting relationship with them and their GPs had provided care for

pre-existing conditions, side effects and psychosocial problems. Others mentioned that seeing a GP was better than different cancer doctors at the out-patient clinics. Reasons for not visiting the GP included financial constraints, lack of accessibility and a perceived lack of knowledge of cancer, cancer treatments and side effects.[12,17,18] The GPs in this study reported that their level of involvement and the need for information differed between individual patients. They mentioned that their familiarity with the medical history of the patient and their family would make them particularly suitable to give ongoing medical and psychosocial support.

The provision of timely and useful information to GPs about patient treatment, anticipated side effects and their management was seen by GPs as a very important component in knowing what to expect and what to tell their patients. However, many GPs spoke of a lack of adequate communication, with letters from cancer specialists being too late to be of any use and/or did not provide the required information to inform the patient. This aligns with some of the perceptions shared by patients who took part in the evaluation of the Cancer Society's Living Well Programme.[7] Patients described themselves seeking information about treatment and side effects from their GP because they did not receive it (nor heard it) from their cancer specialist. Other similar studies also identified an unmet need for treatment and side effect information.[12–14]

Most authors in the field have suggested that shared care by the GP, cancer specialists and home services is likely to facilitate continuity of care for those with cancer. In support of this, the GPs in the current study described some of the shared breast cancer care programs as being excellent with a coordinating nurse ensuring continuity of patient care. However, this approach will only be successful if there is clarity about the roles and responsibilities of GPs, oncology specialists, coordinating nurses and patients, and if there is good communication and coordination between the different health care providers.[6,14,18,19]

The study was conducted just prior to central funding for cancer coordinator nurses coming on stream. The New Zealand Ministry of Health evaluation of that measure concluded in June 2016. This study provides useful additional information when considering the effectiveness of the coordinator role.

Limitations

While this study targeted and successfully attracted participation across a spectrum of general practitioners in two different areas of New Zealand, the absence of a perspective from GPs of Māori or Pacific Island (PI) ethnicity stands out. These communities, and Māori in particular, have a disproportionate burden in terms of cancer incidence.[20] The research team did make contact with and agreed participation with a PHO which employs GPs from and provides services to a large Māori and PI community. Unfortunately, with the time and resources available to the team and the workload of the PHO this did not come to fruition. Other primary care disciplines or patients were not interviewed.

The research team included general practice, radiation therapy, psychology, health promotion and research backgrounds and the majority have been involved in provision of cancer care. Author two was involved in the majority of the data collection and provided a consistent perspective in terms of data analysis. All participants had opportunity to feedback to the analysis.

Conclusion

The growing numbers of those affected by cancer expect the best possible care and a seamless transition between hospital care and general practice care. This New Zealand study showed that the participating GPs generally believed that the continuity of cancer care can be improved. They noted that improving role clarity would result in better communication between cancer specialists, general practitioners, other health care professionals and patients. Such improvements would result in better continuity of care and thus improve the journey of patients with cancer. These results are likely not unique to New Zealand and may also help inform improvements in international cancer care.

Competing interests:
Nil.

Acknowledgements:
This study was conducted with support from the National Office of the Cancer Society of New Zealand.

Author information:
Paul Kane, Department of Radiation Therapy, University of Otago, Wellington; Marieke Jasperse, Department of Primary Care and General Practice, University of Otago, Wellington; Richard Egan, Preventive & Social Med, University of Otago, Dunedin; Lynn McBain, Department of Primary Care and General Practice, University of Otago, Wellington; Eileen McKinlay, Department of Primary Care and General Practice, University of Otago, Wellington; Susan Pullon, Department of Primary Care and General Practice, University of Otago, Wellington; Patries Herst, Department of Radiation Therapy, University of Otago, New Zealand.

Corresponding author:
Paul Kane, Department of Radiation Therapy, University of Otago, Wellington, New Zealand.
paul.kane@otago.ac.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6972

REFERENCES:

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–1403. doi:10.1016/j.ejca.2012.12.027.
2. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer facts and Figures 2013 Annual Report. CA Cancer J Clin. 2014;64:25–271. doi:10.3322/caac.21235.
3. Fleissig A, Jenkins V, Catt S, Fallowfi L. Multidisciplinary teams in cancer care: are they effective in the UK? Lancet Oncol. 2006;7(November):935–943.
4. Ruhstaller T, Roe H, Thurlimann B, Nicoll JJ. The multidisciplinary meeting: An indispensable aid to communication between different specialities. Eur J Cancer. 2006;42(15):2459–2462. doi:10.1016/j.ejca.2006.03.034.
5. Ministry of Health New Zealand. Faster Cancer Treatment Programme: Cancer Care Coordination.; 2014.
6. Aubin M, Giguère A, Martin M, et al. Interventions to improve continuity of care in the follow-up of patients with cancer (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. Cochrane Database Syst Rev. 2012;(7):Art. No.: CD007672.
7. Kane P, Jasperse M, Boland P, Herst P. A pathway to empowerment: evaluating a cancer education and support programme in New Zealand. Eur J Cancer Care (Engl). 2014;23(5):668-674. doi:10.1111/ecc.12188.
8. Ministry of Health New Zealand. Guidance for Improving Supportive Care for Adults with Cancer in New Zealand.; 2010.
9. Charmaz K. Constructing Grounded Theory: A Practical Guide through Qualitative Analysis. London: Sage Publications Ltd; 2006.
10. Liamputtong P. Qualitative Research Methods. Vol 3rd ed. Melbourne: Oxford University Press Australia and New Zealand; 2009.
11. Klabunde CN, Han PKJ, Earle CC, et al. Physician Roles in the Cancer-Related Follow-Up Care of Cancer Survivors. Fam Med. 2013;45(7):463–474.
12. Khan NF, Evans J, Rose PW. A qualitative study of unmet needs and interactions with primary care among cancer survivors. Br J Cancer. 2011;105 Suppl (S1):S46–S51. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3251949&tool=pmcentrez&rendertype=abstract Accessed April 18, 2012.
13. Shea-Budgell MA, Kotaras X, Myhill KP, Hagen NA. Information needs and sources of information for patients during cancer follow-up. Curr Oncol. 2014;21:165–173.
14. Hoekstra RA, Heins MJ, Korevaar JC. Health care needs of cancer survivors in general practice: a systematic review. BMC Fam Pract. 2014;15(1):94. doi:10.1186/1471–2296–15–94.
15. Søndergaard EG, Grøne BH, Wulff CN, Larsen PV, Søndergaard J. A survey

of cancer patients' unmet information and coordination needs in handovers--a cross-sectional study. BMC Res Notes. 2013;6:378. doi:10.1186/1756–0500–6–378.

16. Blanch-Hartigan D, Forsythe LP, Alfano CM, et al. Provision and discussion of survivorship care plans among cancer survivors: results of a nationally representative survey of oncologists and primary care physicians. J Clin Oncol. 2014;32(15):1578–1585. doi:10.1200/JCO.2013.51.7540.

17. Anvik T, Holtedahl KA, Mikalsen H. "When patients have cancer, they stop seeing me"--the role of the general practitioner in early follow-up of patients with cancer--a qualitative study. BMC Fam Pract. 2006;7:19. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1435903&tool=pmcentrez&rendertype=abstract Accessed April 29, 2012.

18. Lewis RA, Neal RD, Hendry M, et al. Patients 'and healthcare professionals' views of cancer follow-up: systematic review. 2009;(July).

19. McCabe MS, Partridge AH, Grunfeld E, Hudson MM. Risk-based health care, the cancer survivor, the oncologist, and the primary care physician. Semin Oncol. 2013;40(6):804–812. doi:doi: 10.1053/j.seminoncol.2013.09.004.

20. Hill S, Sarfati D, Robson B, Blakely T. Indigenous inequalities in cancer: What role for health care? ANZ J Surg. 2013;83(1-2):36–41. doi:10.1111/ans.12041.

The incidence of Orofacial Cleft in live births in New Zealand

John MD Thompson, Peter R Stone, Megan Sanders, Harriette van der Zee, Barry Borman, Peter V Fowler

ABSTRACT

AIM: To determine the incidence of orofacial cleft at birth in New Zealand over 10 years from January 2000.

METHODS: Comparison of data collected from cleft units and data held on the national minimum dataset.

RESULTS: The overall incidence of OFC in New Zealand over a 10 year period was found to be 1.79 per 1,000 live births, higher than the norm for Western society. The major reason for this increased rate was an increased rate for the Māori 2.37 per 1,000 live births, specifically related to a Cleft Palate alone rate over twice that of the European (1.54 vs 0.73 per 1,000 live births). The rate for Pacific was half way between (1.04 per 1,000 live births). The rate of Cleft Lip alone was significantly lower in both Māori and Pacific populations. Different sex ratios were also seen in relation to Cleft Lip and Cleft Lip and Palate for Māori and Pacific compared to those normally reported.

CONCLUSIONS: Māori have an increased incidence of Orofacial Cleft due to one of the highest rates of Cleft Palate alone in the world. Further aetiological studies involving genetic and environmental factors are required to elicit the reasons for this increased incidence.

The rate of orofacial cleft (OFC) in Western society is commonly quoted to be around 1 in 700 live births (1.4 per 1,000 live births). A study across 30 European registries has shown this to vary both within and between countries; with a reported mean of 1.52 per 1,000 live births 95%CI (1.49, 1.55) but a range from 0.63 in Valles, Spain to a high of 2.62 in Finland.[1] By these estimates we would expect 82–94 children are born in New Zealand each year with an orofacial cleft assuming 54,000–62,000 births per year

Studies of the incidence of OFC in New Zealand to date have been limited to a few local studies. Howie and Phillips reported an incidence of 2 per 1,000 live births between 1964 and 1967, which accounted for 6.4% of congenital malformations at National Women's Hospital, the main maternity hospital in Auckland during that period.[2] They found an increased rate of an isolated cleft palate (CP) amongst Māori; however they found no case of isolated cleft lip (CL) amongst Māori. These results were confirmed in a Northland study in the 1970s[3] and another Auckland-based study by Chapman covering the period 1960–76.[4] More recently, local data have been published from Christchurch from 1960 to 2000[5] and from 2000 to 2009,[6] based on clinic records; however the estimates from these studies reflect a mostly European population.

Data reported from official New Zealand sources have been published in the annual reports of the International Clearing-house for Birth Defects Surveillance and Research,[7] and show a rate of non-syndromic OFC of 1.55/1,000 live births over the five years from 2005 to 2009.

OFC has also been shown to be more frequent in Asian populations.[8–10] These increased rates among Asian groups appear to have continued even after they have emigrated to new countries in Western societies,[11] New Zealand has a fast-growing Asian population (Asian births 1991: 3.0%, 2006: 8.8%, 2013: 11.2%), with a younger demographic than the general population (NZ census data).[12] This implies that there is a potential for an increase in the number of OFC cases to be seen in New Zealand.

The aims of this study were to compare data over a 10-year period, obtained from two national sources and in doing so to describe the incidence in New Zealand over the 10-year period. The data sources compared were those from the five surgical cleft treatment centres in New Zealand, responsible for treatment of all cleft in New Zealand and the National Minimum Dataset (NMDS) that contains International Classification of Disease (ICD) coding of all hospital discharges in New Zealand.

Methods

Data was obtained for all cases of OFC that required surgical repair (Cleft lip alone (CL), Cleft Palate alone (CP) and Cleft lip and palate (CLP)). Syndromic cases were included, as the study was investigating the incidence at birth—at which time the presence of a syndrome is often not known (some may not be diagnosed for many years). Cases of submucosal cleft requiring repair are included, however incidental findings of bifid uvula, which required no referral to the service and hence no repair, are not.

Data were collected from two sources:

1. All five units that care for cleft lip and palate in New Zealand were asked to identify all new cases born over the 10-year period from 1 January 2000 to 31 December 2009 and whose treatment was being carried out by the unit. These records were kept by the cleft co-ordinators, who were all appointed post 2000 and data from earlier in the audit was established from appointment records. Data obtained included cleft type, sex, ethnicity, date of birth and National Health Index.
2. The National Minimum Dataset, which contained all discharges from public hospitals in New Zealand (treatment for OFC is funded by the public health system in NZ), was interrogated for all discharges with ICD9 coding 749 in any diagnosis field (up to 25), (cleft palate and cleft lip) and all its subcategories, over the 10-year period from 1 January 2000 to 31 December 2009. Data obtained included sex, ethnicity, date of birth, National Health Index and ICD coding (25 fields).

Where discrepancies existed between the cases identified by the cleft units and the coding in the National discharge dataset, the following steps were used to clarify each discrepant case:

1. If a case was identified on the NMDS but had not been identified by the cleft centre audit, the case notes of the child were reviewed at the hospital of birth to clarify if the child was born with a cleft. When it was clarified that the child did have a cleft, this was then additionally checked with the corresponding cleft team.
2. For cases identified by the cleft centre audit but not the NMDS, the national health index (NHI) of those cases was interrogated in the NMDS to determine what discharge coding had been ascribed.

We used the NMDS to define ethnicity, as that is the source used for the denominator (being the total number of live births) and in other New Zealand official statistics. Ethnicity was assigned using the standard prioritisation method, the method prioritises in the following order (1) Māori, (2) Pacific peoples (Tokelaean, Fijian, Nuiean, Tongan, Cook Island Māori, Samoan, Other Pacific Islander), (3) Asian (South East Asian, Indian, Chinese, Other Asian), (4) Various other ethnicities (Latin American/Hispanic, African, Middle Eastern, Other) and finally (5) European (Other European, Other European (not further defined), NZ European).[13] We used the data from the cleft units to determine the type of cleft with confirmation from the clinical notes and type of operation(s) carried out.

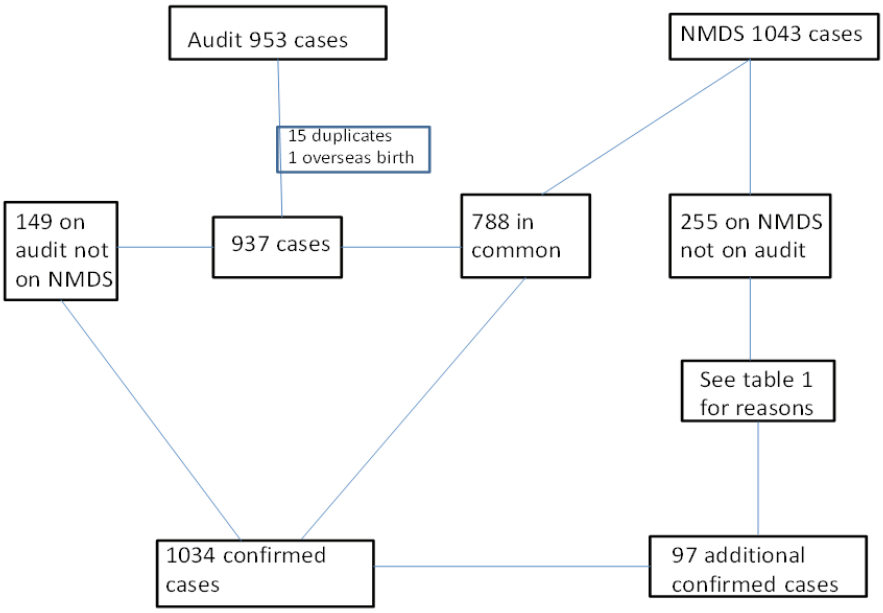
Statistical analysis

Comparison of rates of cleft by ethnicity and sex were compared by testing differences in proportions. Odds ratios were estimated to ascertain ethnic and sex stratified risks using the logistic regression procedure in SAS v9.3 (SAS Institute, Cary, N.C.).

Results

The national cleft unit audit identified 937 cases over the 10-year period (after the removal of duplicate observations, where treatment had occurred in more than one

Figure 1: Flowchart of identification of audit and NMDS identified oro-facial cleft cases.



centre), while 1,043 cases were identified with ICD coding in the NMDS. There were 255 cases identified on the NMDS but not identified by the cleft unit audit, and 149 identified in the cleft unit audit but not on the NMDS, leaving 788 identified by both sources (Figure 1).

Examination of the clinical notes of the 255 cases that had not been identified from the cleft unit audit revealed information that could be placed into 10 different categories. The main categories were (1) coded as having had cleft surgery but not identified by the cleft unit audit (25.9%); (2) bifid uvula identified at Ear Nose and Throat (ENT) surgery and no further referral (presumably as not considered to be of clinical significance) (20.4%); (3) no evidence of a cleft was found in the clinical notes (14.1%); and (4) died at or soon after birth (12.2%). The full list of categorisation is shown in table 1a.

Of those cases not identified on the clinical audit but coded as having cleft surgery (n=66), cross-checking was then carried out with the cleft unit that should have been responsible for each patient. This resulted in confirmation of a cleft in all but three cases (who are not known to any unit and the authors believe are likely to have been miscoded). The classification of these 66 cases is shown in Table 1b. The

Table 1a: Categorisation of cleft cases notified by the National Minimum Dataset not on the original cleft unit audit.

‡Coded as surgical repair of cleft - but not on audit	66 (25.9%)
Cleft/Bifid uvula - probably NOS and not referred	52 (20.4%)
No mention of cleft in clinical notes	36 (14.1%)
†Died or seriously ill child - not likely to have surgery	31 (12.2%)
Overseas birth	25 (9.8%)
Cleft queried but NOS on examination at cleft clinic	20 (7.8%)
Sub mucosal cleft NOS and no referral made	8 (3.1%)
Cleft diagnosed then diagnosis changed	7 (2.8%)
Coded under different NHI	7 (2.8%)
†Procedure carried out outside audit period but have cleft	3 (1.2%)

† Included in final dataset

‡ Include in final dataset except 3 cases excluded as per table 1b

Table 1b: Categorisation of cleft cases coded as surgical repair on the National Minimum Dataset (n=66).

Missed by audit	38
Contracted patient, not on any units books	16
Repaired but not in a non-cleft unit hospital	2
Now overseas	2
Lost to follow up	3
Deceased never seen	2
†Not a cleft	3

†Excluded from final dataset

main category was confirmation of the case (n=38) and was mostly related to those who diagnosed at a later age with a submucosal cleft palate (SMCP); these had been kept on a separate database in one unit and had not been included in the supplied audit data. A number (n=16) of patients had been seen by a surgeon from one of the cleft units under private contract at out-patient clinics in regional centres, with the surgery carried out at the cleft unit, with follow up back at the regional centre. Upon retirement of the surgeon these cases should have reverted back to a regional unit, but none of the units considered these patients to be under their care and hence had not included them in their audit data.

Of the 149 cases identified by the cleft unit audit but not on the initial NMDS data, all were included as they were known to have had surgery relating to a cleft. Re-interrogation of the discharge dataset found 124 of these cases had surgical coding for cleft lip or palate. A re-interrogation of the dataset was carried out using ICD10 coding. Further investigations at the Ministry of Health revealed a discrepancy in the Ministry of Health mapping of ICD9 and ICD10 coding. Seven had coding relating to the cleft but not coded as having a cleft as follows: Q87.0 (n=4, Congenital malformation syndromes predominantly affecting facial appearance), L90.5 (n=1,Scar conditions and fibrosis of skin), Q38.0 (n=1, Congenital malformations of lips, not elsewhere classified), Z42.0 (n=1, Follow-up care involving plastic surgery of head and neck).

A further case had coding Q210 Ventricular septal defect amongst other cardiac codes, but no coding for the cleft as no surgery had taken place for the cleft. Another six cases

Table 2: Total number of cleft cases/births by year and ethnicity.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	**Total**	**Rate/ 1,000 live births**
Māori	26	34	28	31	26	27	23	36	26	32	289	2.37
	10,980	10,968	10,565	11,310	11,723	12,193	12821	13,707	13,902	13,653	121,822	
Pacific	8	7	9	15	6	8	14	9	10	14	100	1.65
	5,611	5,672	5,622	5,809	5,779	5,765	6,078	6,632	6,853	6,891	60,712	
European/ Other	70	57	56	66	72	65	63	60	64	72	645	1.63
	39,408	38,204	37,700	38,264	38,607	38,886	39,734	41,847	41,641	40,981	395,272	
Total	104	98	93	112	104	100	100	105	100	118	1034	1.79
	55,999	54,844	53,887	55,383	56,109	56,844	58,633	62,186	62,396	61,525	577,806	
Rate	1.86	1.79	1.73	2.02	1.85	1.76	1.71	1.69	1.60	1.92	1.79	

Table 3: Number and rate (per 1000 live births) of orofacial cleft by type, sex and ethnicity.

	Cleft Palate				**Cleft Lip**				**Cleft Lip and Palate**			
	Male	Female	Total	Rate	Male	Female	Total	Rate	Male	Female	Total	Rate
Māori	80 (1.27)	108 (1.82)	188	1.54	20 (0.32)	18 (0.30)	38	0.31	31 (0.49)	32 (0.54)	63	0.52
Pacific	26 (0.83)	37 (1.25)	63	1.04	8 (0.26)	3 (0.10)	11	0.18	13 (0.42)	13 (0.44)	26	0.43
Euro/ Other	122 (0.60)	167 (0.86)	289	0.73	106 (0.52)	51 (0.26)	157	0.40	142 (0.70)	57 (0.30)	199	0.50
Total	228	312	540	0.93	134	72	206	0.36	186	102	288	0.50
Rate	0.77	1.11	0.93		0.45	0.26	0.36		0.63	0.36	0.50	

had no cleft coding and on further investigation were determined to have SMCP which was yet to be operated on. We received no data back for nine cases and two NHIs sent were in an invalid format.

Thus the cross validation of data sources has resulted in a total of 1,034 cases (937 confirmed cases from the cleft audit, and 97 additional cases identified from the NMDS (31 cases whom had died without referral to a cleft unit, 63 cases coded as surgical repair but not on audit, and three cases whom were born in the audit period, but not having had primary surgery and therefore not being included in the audit data) of cleft lip and palate over the 10 year period. This resulted in a rate of 1.79/1,000 live births (Table 2). The table also shows that there are distinct differences in the overall rate of OFC by ethnicity with the Māori rate being statistically significantly higher at 2.37/1,000 live births vs 1.65/1,000 live births for Pacific and 1.63/1,000 live births for Non Māori/Non Pacific populations.

This difference in rates of OFC is highlighted by the difference in rates of CP alone (Table 3), the rate in Māori being twice that of the Non Māori/Non Pacific rate (1.54 vs 0.73/1,000 live births) with the Pacific rate intermediate (1.04/1,000 live births). The rates of CL with or without CP were 0.83, 0.61, and 0.90/1,000 live births for Māori, Pacific and Non Māori/ Non Pacific respectively. Of note is that the Pacific rate of CL alone was 0.18 compared to 0.31 and 0.40 for Māori and Non Māori/ Non Pacific respectively. Rates of CLP were 0.43 for Māori while Pacific and Non Māori/Non Pacific rates were 0.52 and 0.50 respectively. The relatively small numbers of cases in these ethnic-specific groups meant a lack of power to detect statistically significant differences.

A further issue is that there are differences in risk associated with sex within ethnic groups (table 4). For CP alone there is a similarly and statistically increased risk in both male (OR=2.12) and female (OR=2.11) for Māori compared to Non Māori/Non Pacific. The risks for Pacific male (OR=1.39) and female (1.45) are intermediate with the male:female ratio preserved.

Table 4: Odds ratios associated with Male vs Female and Ethnic group by cleft type.

	Cleft Palate Male	**Female**	**Cleft Lip Male**	**Female**	**Cleft Lip and Palate Male**	**Female**
Māori	2.12 (1.60, 2.81)	2.11 (1.66, 2.69)	0.61 (0.38, 0.98)	1.15 (0.67, 1.97)	0.70 (0.48, 1.04)	1.83 (1.19, 2.82)
Pacific	1.39 (0.91, 2.12)	1.45 (1.01, 2.06)	0.49 (0.24, 1.01)	0.38 (0.12, 1.23)	0.60 (0.34, 1.05)	1.49 (0.81, 2.72)
Euro/Other	Ref	Ref	Ref	Ref	Ref	Ref
Male vs Female	0.69 (0.59, 0.82)	Ref	1.77 (1.33, 2.36)	Ref	1.73 (1.36, 2.21)	Ref
Ethnicity*Sex interaction	P=0.99		P=0.19		P=0.0017	

For CL alone, the risk for males is significantly lower in Māori males compared to the Non Māori/Non Pacific group but no difference is seen in females. For Pacific, the differences in sex are similar but do not reach statistical significance, however, the numbers in these groups are relatively small.

Of particular note are the differences associated with CLP. Both Māori and Pacific males show decreased risks of borderline significance compared to Non-Māori/Non Pacific. Female Māori show a significantly increased risk compared to Non Māori/Non Pacific. The risk for Pacific females is elevated but not of statistical significance. An interaction term of ethnicity by sex was statistically significant (p=0.0017). Calculating the ethnic specific risks of male vs female for CLP gives odds ratios of (Māori 0.91 95% CI=0.56, 1.50, Pacific 0.95 95%CI=0.44, 2.05, and Non Māori/Non Pacific of 2.38 95% CI=1.75, 3.23).

Discussion

This is the first nationwide study of the incidence of OFC in New Zealand. It provides data over a 10-year period, showing a national incidence of 1.79/1,000 live births (1 in 559) that is relatively high in terms of the quoted international incidence. The overall rate is statistically significantly higher in Māori compared to Non Māori: 2.37/1,000 (1 in 422) vs 1.63/1,000 (1 in 612), however even the non-Māori rate is high in terms of international comparisons.

This study also provides the first information on the rates of cleft lip and palate amongst the Pacific population. Whilst the population is somewhat smaller and the yearly estimates of incidence vary, the overall incidence of OFC over the 10-year period is almost identical to that of the Non Māori/Non Pacific group.

The increased rate amongst Māori is almost exclusively due to the increased rate of cleft palate alone in this population. The increased rate has been suggested in earlier audits carried out over 30 years ago.[2–4] This nationwide study clarifies these findings. The rate of cleft palate alone is in fact twice that of Non Māori/Non Pacific, with Pacific falling midway between the two. This difference in rate suggests a genetic component is involved either directly or perhaps through interactions with environmental factors. There have been a number of genes related to cleft lip and palate however, to date, these genes account only for a small proportion of cases, mostly related to syndromic related clefts. Whilst the rate of CP alone is higher in Māori and Pacific populations, the internationally recognised predominance of female CP is preserved across ethnicities.

Contrary to earlier reports, there are cases of cleft lip alone in Māori, though the rate is lower in Māori males compared to that of the Non Māori/Non Pacific population, but not different for Māori females. The rate for the Pacific population is half of that for the Non Māori/Non Pacific group; the risk is decreased for both males and females, however small numbers mean a lack of power to show statistically significant effects. The predominant male effect is evident in the Non Māori groups, while not statistically significantly different, the rates are similar for Māori male and female and appears to be due to a decreased rate in Māori male. It has been proposed that the audit be repeated in five-year cycles and, with increased data over time, the sex and ethnic patterns in CL will become clearer.

The most notable sex effect is that for CLP where the expected male predominance exists for the Non Māori/Non Pacific population but there is no sex differential in rates for Māori or Pacific. We do not know of any other population in the world where this male predominance does not exist for CLP. The data suggest that this is a combination of a slightly lower rate of CLP in Māori and Pacific males than expected and a slightly higher than expected rate amongst females.

Data for live births are only published for Māori, Pacific and other ethnic populations, thus we were not directly able to assess the impact of the growing Asian population. The overall rate of OFC has not increased over time, thus suggesting that over the period 2000–2009 there has been little impact from the increasing Asian birth rate.

Data provided to the international clearinghouse for birth defects that uses information from the NMDS excludes cases that are also coded as being part of a syndrome. The published rates equate to 547 cases of cleft palate alone compared to

540 from this study. The difference is greater in the cases of cleft lip with or without cleft palate where the reported numbers to the international clearing house are 359 compared to 494 in this study. The reasons for these discrepancies are not entirely clear; though the clearing house data exclude those with a syndrome, it would normally be expected that many of these would likely have only palate involvement. Our data do not currently allow reliable identification of those who have a cleft as part of a syndrome, and this should be a goal for the future. Non syndromic OFC rates do, however, pose some difficulties, as some cases may not be identified and confirmed as syndromic until later in childhood.

The study also raises an issue about how clinical coding is carried out. In the New Zealand setting, ICD coding is carried out at hospital level by non-clinically trained coders. In this instance, the data would suggest significant over-coding of OFC, due to lack of depth of knowledge and/or misinterpretation of clinical notes. We do not believe there is likely to be an issue of undercoding. Cases were identified by the audit and missed on the initial NMDS download, mainly due to a discrepancy in ICD9 and ICD10 codings at Ministry of Health level. All primary repair in NZ is carried out in the public health system and if any cases were operated on in the private system, they would still require referral back to the cleft units for provision of other services such as orthodontic and speech language therapy, so would be expected to be known by one of the units.

Furthermore,there are more general implications of the coding of clinical data. This study has shown substantial differences in the numbers of cases coded for what should be a relatively clearcut diagnosis. Thus, the implications for reported rates of other common diseases with less categorical diagnoses could be significant.

In conclusion, this study has clarified the incidence of orofacial clefts in New Zealand and confirmed a high rate of CP alone in the Māori population and unexpected male:female ratios of CLP for Māori and Pacific populations. This dataset is providing a base for ongoing studies on the epidemiology, genetics, quality of life, burden of care and treatment outcome studies.

Competing interests:
Nil.

Acknowledgements:
We thank the cleft units for providing data of all the cases they have seen over the last 10 years, particularly Susan Reay and Lynne Walker. We also thank the regional paediatricians/obstetricians across the 20 District Health Boards who took the time to check clinical notes for evidence of a cleft lip and/or cleft palate in the notes. Assoc Prof Thompson is supported in part by Cure Kids.

Author information:
John MD Thompson, Department of Paediatrics: Child & Youth Health, Department of Obstetrics & Gynaecology, University of Auckland, Auckland; Peter R Stone, Department of Obstetrics & Gynaecology, University of Auckland, Auckland; Megan Sanders, Auckland Regional Centre for Plastic Reconstructive & Hand Surgery and New Zealand National Burns Centre, Middlemore Hospital, New Zealand; Hariette van der Zee, Oral health unit, Canterbury District Health Board, New Zealand; Barry Borman, Centre for Public Health Research, University of Massey, Wellington; Peter V Fowler, Department of Paediatrics: Child & Youth Health, University of Auckland, Oral health unit, Canterbury District Health Board, New Zealand.

Corresponding author:
John MD Thompson, Department of Paediatrics: Child & Youth Health, University of Auckland, Private Bag 92019, Auckland.
j.thompson@auckland.ac.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6973

REFERENCES:

1. Calzolari E, Rubini M, Neville AJ, Bianchi F. EUORCAT and Orofacial clefts: The epidemiology of Orofacial clefts in 30 European regions. European Surveillance of Congenital Anomalies 2002.
2. Howie RN, Phillips LI. Congenital malformations in the newborn: a survey at the National Women's Hospital, 1964–67. N Z Med J. Feb 1970;71(453):65–71.
3. Hanify JA, Metcalf P, Nobbs CL, Worsley KJ. Congenital malformations in the newborn in Northland: 1966-1977. N Z Med J. Sep 24 1980;92(668):245–248.
4. Chapman CJ. Ethnic differences in the incidence of cleft lip and/or cleft palate in Auckland, 1960-1976. N Z Med J. May 11 1983;96(731):327–329.
5. Fowler P, Esson I. Non-syndromal oro-facial clefts in the Canterbury/West Coast region, 1960-2000. N Z Dent J. Sep 2005;101(3):72–74.
6. Smit R, Fowler PV. Non-syndromal orofacial clefts in the Canterbury/West Coast region during the 2000-2009 period. The New Zealand dental journal. Dec 2010;106(4):129–131.
7. The International Centre on Birth Defects - ICBDSR Centre. 2011 Annual report with data for 2009. Roma, Italy 2011.
8. Cooper ME, Ratay JS, Marazita ML. Asian oral-facial cleft birth prevalence. Cleft Palate Craniofac J. Sep 2006;43(5):580–589.
9. Dai L, Zhu J, Zhou GX, Wang YP, Miao L. [The monitoring of cleft lip with or without cleft palate in China: 1996–2000]. Zhonghua Kou Qiang Yi Xue Za Zhi. Nov 2003;38(6):438–440.
10. Natsume N, Kawai T, Kohama G, et al. Incidence of cleft lip or palate in 303,738 Japanese babies born between 1994 and 1995. Br J Oral Maxillofac Surg. Dec 2000;38(6):605–607.
11. Forrester MB, Merz RD. Rates for specific birth defects among offspring of Japanese mothers, Hawaii, 1986–2002. Congenit Anom (Kyoto). Jun 2006;46(2):76–80.
12. Statistics New Zealand. NZ census data. 2015; http://www.stats.govt.nz/Census.aspx. Accessed 8/1, 2016.
13. Ministry of Health. Ethnicity Data Protocols for the Health and Disability Sector. Wellington 2004.

Productivity losses associated with Fetal Alcohol Spectrum Disorder in New Zealand

Brian Easton, Larry Burd, Jürgen Rehm, Svetlana Popova

ABSTRACT

AIM: To estimate the productivity losses due to morbidity and premature mortality of individuals with Fetal Alcohol Spectrum Disorder (FASD) in New Zealand (NZ).

METHODS: A demographic approach with a counterfactual scenario in which nobody in NZ is born with FASD was used. Estimates were calculated using (Census Year) 2013 data for the NZ population, the labour force, unemployment rate and average weekly wage, all of which were obtained from Statistics NZ.

In order to estimate the number of FASD cases in 2013 and the related morbidity, the prevalence of FASD, obtained from the available epidemiological literature, was applied to the general population of NZ. Assumptions made on the level of impairment that would affect the ability of individuals with FASD to participate in the workforce or would reduce their productivity were based on data obtained from the current epidemiological literature.

RESULTS: In 2013, approximately 0.03% of the NZ workforce experienced a loss of productivity due to FASD-attributable morbidity and premature mortality, which translated to aggregate losses ranging from $NZ49 million to $NZ200 million – that is, 0.03% to 0.09% of the annual gross domestic product in NZ.

These costs represent estimates for lost productivity attributable to FASD and do not include additional costs incurred by governmental and private entities including social costs, such as both higher costs and or less effective spending by the education, health and justice systems.

CONCLUSION: The estimated productivity losses associated with FASD further reinforces that effective FASD prevention as a primary public health strategy may be of significant value.

Across the world, alcohol is the fifth leading contributor to disability and mortality, accounting for over 5% of worldwide mortality and nearly 4% of disability-adjusted life years.[1] Furthermore, alcohol consumption often results in harm both to the drinker as well as to individuals associated with the drinker. One example of such harm is that caused by the consumption of alcohol during pregnancy. Prenatal alcohol exposure is an established cause of Fetal Alcohol Spectrum Disorder (FASD). A safe level of alcohol exposure during pregnancy has yet to be identified, nevertheless it is widely accepted that heavy drinking confers the greatest risk of FASD.[2,3] Prenatal alcohol exposure results in a highly variable expression of adverse outcomes. As a result, the term FASD encompasses a group of disorders where alcohol exposure can affect any organ system.[3]

FASD is comprised of four categorical disorders: Fetal Alcohol Syndrome (FAS), Partial FAS (pFAS), Alcohol-Related Neurodevelopmental Disorder (ARND) and Alcohol-Related Birth Defects (ARBD).[3,4] The FASD phenotype is variably expressed, and comorbidities are common.[3,5–10] These are highly variable disorders, with age and development dependent upon changes in phenotype.[11,12] However, FASD is considered a 'hidden' disability and a complex diagnosis.[13] Damage to the central nervous system is a unifying concept for nearly all of the FASD diagnoses.[4,12,14,15]

Although no research has confirmed the prevalence of FASD in New Zealand, it is generally assumed that the prevalence is approximately 1% of live births, an assumption that is based on multiple prevalence studies in other countries (acknowledging, however, that there may be variations in the patterns of alcohol consumption during pregnancy in different countries/cultures).[16–18] More recent prevalence studies have reported prevalence rates well above 1% of live births in some locations across the world using a screening protocol for school-age children (ie, active case ascertainment).[19] Also, and unsurprisingly, high-risk populations with higher drinking rates have an increased likelihood of having alcohol-exposed pregnancies.[20,21] The FASD rates are well above prevalence rates for Autism Spectrum Disorder or Down syndrome.[22]

The prevalence of FASD is currently unknown in both the general population and, in some high-risk communities of New Zealand. Therefore, for the purpose of this study, the most commonly cited rough estimates of the prevalence of FAS (1 per 1,000)[17] and FASD (9 per 1,000)[18] among the general population in Canada were used. Since the exact prevalence of FAS/FASD is unknown, it was assumed that the prevalence was constant across all birth cohorts.

In a recent review of mortality in individuals with FASD, the two leading causes of death were malformations of the central nervous system and congenital cardiac abnormalities.[23] The three other leading causes of death were sepsis, kidney malformations and cancer. This study also revealed that over half of the reported deaths (54%) occurred in the first year of life.[23] Other studies have demonstrated that FASD is associated with a vast number and wide range of health and behavioural problems including increased premature mortality rates compared to the general population.[3,5–9,24] Additionally, the phenotype for FASD is highly variable and as affected people age, the rates of comorbidity tend to increase, which ultimately increases both complexity and severity of the phenotype.[6]

Because of difficulties "fitting into" mainstream life, the attempted suicide rate for persons with FASD has been reported to be higher (22%) than the rate for the general US adult population (3%) and persons with intellectual disabilities (8%).[25]

Thus, since FASD begins in the prenatal period, the disorders cause a large burden of lifelong duration on society. The costs change across age groups and only recently have costs incurred by adolescents and adults been considered. The costs in this age group are incurred primarily through the health care system, mental health and substance abuse treatment services, the criminal justice system, and the long-term care of individuals with intellectual and physical disabilities.[2,3,26–38]

A significant portion of the societal economic burden from FASD results from lost productivity and decreased participation in the workforce (the labour force less those who are unemployed) including those losses resulting from early mortality. Surprisingly, given the significance, the existing cost estimates of FASD have neglected to examine the productivity losses caused by reduced participation in the workforce.[27,30,39-41]

FASD has not yet emerged as a public health priority in New Zealand, although the Ministry of Health is paying more attention to it.[42] Canada has already placed importance on this issue.[17,26,31–38,43,44] The Canadian approach is due in part to their recognition of the costs associated with FASD-affected individuals' need for specialized the care and services, but also due to their increased awareness of costs may potentially be reduced by implementing effective prevention programs.[40] Such prevention efforts need to focus on reducing the number of affected individuals, the severity of the resulting impairments, and the premature mortality due to prenatal alcohol exposure.[6,8,26] These efforts could be accomplished by eliminating prenatal alcohol exposure or, at the very least, by reducing the number of women who drink heavily during pregnancy.

The purpose of this study was to estimate the productivity losses of individuals with FASD due to morbidity and premature mortality, as one aspect of the total costs of FASD in New Zealand.

Method

The counterfactual scenario

All cost estimates involve a counterfactual scenario, which compares the actual state of affairs with an alternative one, the costs reflecting the economic differences between them valued at appropriate prices.

This report adopts a counterfactual scenario in which no individual in the population was born with FASD. It uses the "demographic" method,[45] and focuses only on the impact of market production (the productivity loss) resulting from the morbidity and premature mortality of individuals with FASD.

This counterfactual scenario was chosen because it is readily understandable and because it and its consequential estimation method involve fewer—often contentious—assumptions. It avoids some issues that make the estimation of social costs challenging, such as dealing with inflation, economic change and time discounting. It produces an estimate for a particular year (2013) as a result of effects earlier in time, instead of an estimate of the effects in a particular year. A consequence of this particular counterfactual scenario is that the total will vary through time as a result of economic and population changes, and the scenario takes into consideration such variables as business cycle (unemployment) and price changes (inflation). However in the medium-term these will not change the order of magnitude.

An alternative to the "demographic" approach is the "human capital" approach, which would be more applicable if the alternative scenario involved a phasing-out of FASD (eg, if an effective prevention program was introduced over time). Whereas the counterfactual scenario used here assumes an effective program was introduced many decades ago; the estimate represents the long-term equilibrium. It may be taken as an indication of the eventual long-term productivity gains from effective prevention.

There are two different concepts used in this paper: "labour force" and "workforce". "Labour force" refers to the number of individuals actually working or willing to work. "Workforce" refers to the number of individuals actually working and does not account for those who are willing to work. The difference between the "labour force" and the "workforce" is the unemployed labour force. Therefore, "workforce" constitutes the employed labour force (for more information please see http://www.yourarticlelibrary.com/difference/difference-between-labour-force-and-workforce/40438/).

Population estimates of individuals with FASD

New Zealand data on population of the labour force, unemployment rate, and the average weekly wage were obtained from Statistics New Zealand for the most recent available year (i.e., 2013).[46]

For the purpose of this analysis, three groups of individuals with: 1) Fetal Alcohol Syndrome (FAS; the most recognisable form of FASD); 2) other-FASD (pFAS, ARND and ARBD); and 3) FASD overall (FAS, pFAS, ARND, and ARBD) were analysed separately. In order to estimate the number of individuals with FAS and other-FASD, the most commonly cited prevalence of FAS (0.1%)[17] and FASD (0.9%)[18] in North America was applied to the general population of New Zealand in 2013.

It is possible that those with FASD are more likely to be unemployed; however, because such no estimate exists, we have assumed the proportion of individuals with FASD that are unemployed is the same as that of the general population.

All cost figures are presented in New Zealand dollars for the 2013 year.

Severity levels of intellectual impairment attributable to FASD

As described below and in Easton et al.[47] population estimates of individuals with FASD can be stratified by the severity of intellectual impairment attributable to FASD, so as to account for its effect on both the level of participation in the workforce and productivity of individuals with FASD. Disabilities attributed to birth defects, vision or hearing problems or any other physical disabilities were not included.

Individuals with FAS and other-FASD will have multiple areas of brain impairment when measured on standardised tests. For the purposes of this study, the domain of intellectual impairment will represent the relevant impairment. Individuals with FASD can be classified into four groups according to their level of impairment.[48]

1. *Broad cognitive impairment* (does not meet criteria for intellectual disability). The term minimal brain dysfunction (MBD) has also been used previously to describe this population, and includes individuals with learning disabilities, speech and language disorders, attention deficit hyperactivity disorder, and other similar disorders.
2. *Mild intellectual disability*. Previously known as mild mental retardation, this category includes individuals with an Intelligence Quotient (IQ) and adaptive behaviour scores between 50 and 75. Individuals within this category can often acquire academic skills up to the 6th grade level, can become fairly self-sufficient and in some cases live independently with episodic or ongoing community and social supports.
3. *Moderate intellectual disability*. This category includes individuals who have an IQ and adaptive behaviour score of 35–49. They can typically carry out work and self-care tasks with ongoing supervision at moderate levels. They typically acquire communication skills in childhood and are able to live and function successfully within the community in a staffed and supervised environment such as a group home.
4. *Severe intellectual disability*. This category includes individuals with an IQ and adaptive behaviour score below 35. Such individuals may master very basic self-care skills and some communication skills. Their intellectual disability is often accompanied by neurological disorders, and they most commonly require continuous supervision, assistance and high levels of structure.

It was assumed that 100% of individuals with FAS are impaired and only about 25% of individuals with other-FASD are impaired. Such individuals would be expected to have different levels of reduction in productivity due to their intellectual impairment. The distribution of levels of mental impairment severity among individuals with other-FASD was assumed to be the same as that for individuals with FAS (50% with broad cognitive impairment, 33% with mild intellectual disability, 12% with moderate intellectual disability, and 5% with severe intellectual disability).

The percent reduction in productivity of individuals with FAS and other-FASD was adapted from Harwood and colleagues[48] and modified based on the expert opinion of Drs. Larry Burd and Albert Chudley (personal communication).

Mortality

As described above, individuals with FASD have a higher mortality rate. The effects can be measured by using cause-of-death data combined with pooled prevalence estimates of the major disease conditions associated with FASD, as obtained from a recent meta-analysis conducted by Popova and colleagues.[10] For a detailed methodology on estimation productivity losses due to premature mortality of individuals with FASD, please see Easton et al.[49]

However, it is unnecessary to add a separate assessment for the purposes of this paper. If FASD rates at birth are the ones assumed (ie one percent of the cohort), then the rates in the labour force will be lower (because of the higher mortality rate). The counterfactual scenario requires the addition to the labour force of those individuals with FASD who die from premature mortality relative to those without FASD. Subject to a very small effect, this is equivalent to assuming that the rate of FASD for the labour force is the same as the rate for the birth cohort. Ignoring this small difference means the estimates provided here are slightly on the conservative side.

Results

Population estimates of individuals with FASD

Using data on the general population in New Zealand (4.43 million in 2013) and assuming a prevalence of 0.1% for FAS and 0.9% for other-FASD, the number of individuals with FASD was estimated as follows: 4,400 individuals with FAS and 39,900 with other-FASD, for a combined total of 44,300 individuals with FASD in New Zealand in 2013 (Table 1).

Table 1: Model parameters for the calculation of productivity losses due to FASD-attributable morbidity and premature mortality in New Zealand 2013.

Parameters	Number of individuals	Source
Total population in New Zealand	4.43 Million	[46]
Population participating in labour force (54. 4%)	2.41 Million	[46]
Population with FAS (0.1% of the total population)	4,400	[17]
Population with other-FASD (0.9% of the total popu-lation)	39,900	[18]
Population with FASD (1% of the total population)	44,300	
Population with FAS participating in labour force (54.4% of the total population with FAS)	2,400	
Population with other-FASD participating in labour force (54.4% of the total population with other-FASD)	21,700	
Population with FASD participating in labour force (54.2% of the total population with FASD)	24,100	
Compromised productivity of the workforce with FAS (100% of the pop-ulation with FAS participating in labour force)	2,400	Expert opinion (personal communication)
Compromised productivity of the workforce with other-FASD (25% of the population with other-FASD participating in labour force)	5,400	Expert opinion (personal communication)
Compromised productivity of the workforce with FASD (sum of pop-ulation with FAS and other-FASD participating in labour force with compromised productivity)	7,800	

FAS: Fetal Alcohol Syndrome

FASD: Fetal AlcoholSpectrum Disorder

Statistics New Zealand from Infoshare (http://www.stats.govt.nz/infoshare/).[46]

Approximately 54.4% (2.41 million) of New Zealand's general population participated in the paid labour force in 2013[46]. By applying this percentage to the number of individuals with FASD, it was estimated that about 24,100 individuals with FASD were in the New Zealand labour force in 2013 (or 0.03% of the total labour force). Based on the assumption that all individuals with FAS and 25% of individuals with other-FASD have some level of intellectual impairment, it was estimated that 7,800 individuals with FASD who are in the workforce (the labour force less the unemployed) have decreased productivity (Table 2).

Productivity losses of individuals with FASD due to morbidity

It was assumed that the magnitude of productivity losses for individuals with FASD was directly related to their level of intellectual impairment. Table 2 presents the proportions of individuals with FASD by the levels of intellectual impairment, as well as the lower and upper boundary for their percent of reduction in productivity by categorical level of impairment. In order to estimate a weighted average of the lower (24%) and the upper (50%) boundaries, the percent of reductions in productivity were combined across severity levels and weighted by the number of individuals in each respective group (Table 2).

Since 6.2% of the labour force was unemployed[46], the estimated loss of productivity by the effective workforce was applied to only 93.8% of those with FASD who were assumed to be in the labour force (the workforce equals the labour force minus those unemployed).

Estimating the effect of the counterfactual scenario of no FASD in New Zealand

If there were no cases of FASD in New Zealand (the counterfactual scenario), then the effective workforce would increase by

Table 2: Percentage and number of individuals with FAS and other-FASD by level of intellectual impairment and their percentage of reduction in productivity in New Zealand in 2013.

Impairment Category	Percentage of individuals with FAS and other-FASD[a,b]	Estimated number of individuals with FAS and other-FASD in New Zealand	Percentage reduction in productivity of individuals with FAS and other-FASD Lower Boundary[c]	Percentage reduction in productivity of individuals with FAS other-FASD Upper Boundary[d]
Broad cognitive impairment	50%	3,900	10%	40%
Mild intellectual impairment	33%	2,575	25%	50%
Moderate intellectual impairment	12%	935	50%	70%
Severe intellectual impairment	5%	390	100%	100%
Total		7,800		
Weighted Average			24.25%	49.9%

FAS: Fetal Alcohol Syndrome

FASD: Fetal Alcohol Spectrum Disorder

[a]Estimated based on expert opinion (Larry Burd and Albert Chudley)

[b]Based on the assumption that 100% of individuals with FAS are intellectually impaired and only about 25% of individuals with other-FASD are intellectually impaired (Albert Chudley, expert opinion)

[c]Based on Harwood et al.[48]

[d]Estimated based on expert opinion (Larry Burd and Albert Chudley)

Table 3: Model of potential increases in income using a counterfactual scenario (no one is born with FASD) in New Zealand 2013.

	Lower Boundary	Upper Boundary
Equivalent number of productivity-compromised individuals with FASD in labour force	1,880	3,840
Equivalent number of productivity-compromised individuals with FASD in workforce (ie allowing for unemployment)	1,760	3,600
Average annual wage in relevant population of NZ	$28,000	$55,660
Loss of annual income per person with FASD in labour force	$2,270	$9,230
Loss of annual income per productivity-compromised person with FASD in labour force	$6,990	$28,410
Productivity losses due to FASD-attributable morbidity and premature mortality (additional economy-wide income)	**$49 Million**	**$200 Million**

FASD: Fetal Alcohol Spectrum Disorder

Notes: Statistics New Zealand from Infoshare (http://www.stats.govt.nz/infoshare/).[46]

Numbers are rounded.

Lower boundary based on weighted average reduction in productivity of 24%; upper boundary based on weighted average reduction in productivity of 50%. Lower boundary assumes all workers are working for minimum wage rather than halfway between it and the average wage.

the equivalent of 1,760 to 3,600 full time workers (derived by applying a weighted average of reduction in productivity—24% [lower estimate] and 50% [upper estimate]; see Table 2) to the number of individuals with FASD with compromised productivity within the workforce—ie the labour force minus the unemployed (about 7,800 people; Table 1). The additional worker effect represents a boost of between 0.08% and 0.16% to the New Zealand workforce of 2.26 million individuals in 2013, if, as the counterfactual scenario posits, there were no cases of FASD in New Zealand (Table 3).

Estimated value of the productivity losses of individuals with FASD due to morbidity

Estimates of productivity losses resulting from decreased labour force participation can then be converted into dollar value by multiplying the effective reduction in the number of participating workers with FASD by their marginal dollar product. The standard assumption is that a worker's marginal product is comparable to the average wage.[45]

The average weekly wage (ordinary plus overtime) in New Zealand was $1,066, which is equivalent to $55,660 per year. However, it could be argued that the average worker with FASD comes from a more socially-deprived background, and as a result, have a lower average wage than a typical member of the labour force. In order to provide the most conservative estimate, it was assumed that, as a conservative estimate, the actual wages for a person from a background that gives rise to FASD is the minimum wage of $28,000 (in 2013). This amounts to an average annual reduction of $2,270 to $9,230 for each worker with FASD (including those that are unemployed). This represents 7.8% to 16.2% of the wages they would earn if they did not have FASD. When this wage is applied to the difference in the effective workforce, the estimated national income of New Zealand would increase between $49 million and $200 million, if New Zealand had no cases of FASD.

Discussion

Conservatively, around 0.03% of the New Zealand workforce experiences a loss of productivity due to FASD-attributable morbidity and premature mortality. This markedly reduces their remuneration and, consequently has a dampening effect on the overall New Zealand economy. The immediate effect of FASD-attributable morbidity and premature mortality is confined to a small proportion of the population; the estimated aggregate loss ranged from $49 million to $200 million in New Zealand in 2013.

These estimates of productivity losses due to morbidity and premature mortality attributable to FASD are, by design, equally conservative and probably underestimated in terms of the total social costs of FASD. However, there is some level of confidence that the estimates of the aggregate productivity losses due to FASD are within a plausible range. The reported estimates do not include the additional productivity losses of those caring for individuals with FASD who are, as a result, unable to work in the paid labour force due to their caregiving or from inefficient or otherwise unnecessary expenditure in the education, health or justice systems. Without such cost pressures resulting from FASD, these resources could be diverted to other areas of private and public spending in order to benefit New Zealand as a whole.

Policy makers could utilize the estimates of productivity losses due to FASD-attributable morbidity and premature mortality in order to evaluate the potential benefits of FASD prevention programs. There are several studies from Canada and the Unites States that have reported on cost-effectiveness/cost-comparisons of a number of preventive strategies, namely: i) prevention of unintended pregnancy and alcohol use during pregnancy, ii) early interventions for children and adults with FASD, iii) early and cost-effective approaches to diagnosing FASD, and iv) prevention of secondary disabilities.[50–53] For example, a study by Thanh et al.[52] (2013) investigated the break-even effectiveness

of the Alberta FASD Service Networks in reducing secondary disabilities including the productivity cost of unemployment, shelter cost of homelessness, educational cost of school disruption, criminal justice cost of crime and medical cost of mental health problems. The total costs for the service network were derived from the actual spending of the service networks and estimated to be $6.12 million Canadian dollars annually including costs for diagnostic services, support services, prevention services and operational costs. The study found that the benefits of the service network would range from $8.87 million to $17.73 million Canadian dollars annually. Accordingly, the return for every Canadian dollar invested in the service network would range from $1.45 to $2.90.

A cost-effective prevention effort to eliminate FASD in New Zealand would produce, over the long term, an economic benefit from productivity gains alone. Such benefits would not, of course, accrue immediately, because the newly born do not immediately enter the workforce. Additionally, targeted prevention efforts need to include reducing the severity of the resulting impairments of those born with FASD, as well as the premature mortality due to prenatal alcohol exposure.

In terms of the productivity losses alone, New Zealand could ultimately spend up to $190,000 per day (i.e., $49 million per year) or more on an effective prevention program to prevent new cases of FASD. However the benefit to cost ratio would be considerably higher than one, because of reduced (or more effective) spending in other parts of the economy such as health care, special education, and corrections.[43,44,49,54-58]

There are several limitations of the current study. Firstly, the prevalence of FASD in New Zealand is currently unknown, either among the general population, special populations (eg, children in care, criminal justice population), and/or other specific communities. Therefore, the prevalence commonly reported for Canada was used, which may not be accurate. Secondly, it was assumed that the prevalence of FASD is the same across all socio-economic groups in New Zealand, which is also not known and may not be correct. Thirdly, the prevalence of FASD by age group is also currently unavailable and therefore, it was not possible to calculate productivity losses by age group. Fourthly, due to the lack of data, it was assumed that the proportion of individuals with FASD that are unemployed is the same as that of the general population. Lastly, only intellectual impairment attributable to FASD was accounted for in this study. Other disabilities attributed to birth defects, vision or hearing problems, or any other physical disabilities were not included in the estimated costs.

Despite these limitations, the results of this study have confirmed that FASD is a significant burden to New Zealand. However, it must be noted that this cost study did not estimate potential savings, since the estimates include both avoidable and unavoidable costs. Also, this study should not be confused with a cost-benefit or cost-effectiveness analysis. However, the estimates of the burden and costs associated with FASD presented here can contribute to a meaningful cost-effectiveness analyses and, eventually, cost-benefit analyses of FASD policies and programs.

The scope and accuracy of the cost figures presented in this study are contingent on the current data availability. As more data become available, this study has the potential to be expanded.

Competing interests:
Nil.

Acknowledgements:
This work was supported by a grant from Alcohol Healthwatch, New Zealand. We would like to thank Sally Casswell, Christine Rogan and Anna Sarnocinska-Hart. We have availed ourselves of the expertise of Professor Albert Chudley of the Department of Paediatrics and Child Health and Biochemistry and Medical Genetics of the University of Manitoba, Canada.

Funding:
The majority of funding came from a Health Workforce New Zealand Innovations Grant. Additional funding for research was provided by the Auckland Medical Research Foundation, the University of Auckland School of Medicine Foundation and the Joint Anaesthesia Faculty Auckland. Corporate sponsorship of consumable surgical items was obtained from Kimberly-Clark, Smith & Nephew, NZ Blood, Covidien, Baxter, and DSTC. OBEX and Zimmer loaned equipment for the study days.

Author information:
Brian Easton, Honorary Research Fellow, Centre for Social and Health Outcomes Research and Evaluation (SHORE), Massey University, Auckland, New Zealand. Honorary Fellow, Department of Public, Health, Wellington School of Medicine, University of Otago, Wellington, New Zealand; Larry Burd, Professor, Director, North Dakota Fetal Alcohol Syndrome Center UND Medical School, Grand Forks, North Dakota, US; Jürgen Rehm, Director, Social and Epidemiological Research Department, Centre for Addiction and Mental Health (CAMH), Toronto, Canada. Senior Scientist, Campbell Family Mental Health Research Institute, CAMH, Toronto, Canada. Professor and Chair, Addiction Policy, Dalla Lana School of Public Health, University of Toronto (UofT), Toronto, Canada. Professor, Dept. of Psychiatry, Faculty of Medicine, UofT, Toronto, Canada. Head, PAHO/WHO Collaborating Centre for Mental Health and Addiction, Head, Epidemiological Research Unit, Technische Universität Dresden, Klinische Psychologie & Psychotherapie, Dresden, Germany. Faculty member, Graduate Department of Community Health and Institute of Medical Science, UofT, Toronto, Canada; Svetlana Popova, Senior Scientist, Social and Epidemiological Research, Centre for Addiction and Mental Health, Toronto, Canada. Associate Professor, Epidemiology Division, Dalla Lana School of Public Health, University of Toronto (UofT), Toronto, Canada. Associate Professor, Factor-Inwentash Faculty of Social Work, (UofT), Toronto, Canada. Graduate Faculty Associate Member, Institute of Medical Science, (UofT), Toronto, Canada.

Corresponding author:
Brian Easton, 18 Talavera Tce, Kelburn, Wellington, 6012, New Zealand.
eastonbh@paradise.net.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6974

REFERENCES:

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224–2260. (Errata published 2013, in Lancet 381(9874), 1276; Lancet 381(9867), 628).
2. Abel EL. Fetal alcohol abuse syndrome. New York: Plenum Press; 1998.
3. Stratton K, Howe C, Battaglia F. Fetal Alcohol Syndrome: diagnosis, epidemiology, prevention, and treatment. Washington DC: National Academy Press; 1996.
4. Chudley AE, Conry J, Cook JL, et al. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. Can Med Assoc J. 2005;172:S1–S21.
5. Astley SJ, Clarren SK. Diagnostic guide for fetal alcohol syndrome and related conditions: the 4-Digit Diagnostic Code. 2nd ed. Seattle: University of Washington Publication Services; 1999.
6. Burd L, Klug MG, Martsolf J. Increased sibling mortal-

ity in children with fetal alcohol syndrome. Addict Biol. 2004;9:179–186.

7. Burd L, Klug MG, Bueling R, et al. Mortality rates in subjects with fetal alcohol spectrum disorders and their siblings. Birth Defects Res A Clin Mol Teratol. 2008;82:217–223.
8. Habbick BF, Nanson JL, Snyder RE, Casey RE. Mortality in fetal alcohol syndrome. Can J Public Health. 1997;88:181–83.
9. Iyasu S, Randall LL, Welty TK, et al. Risk factors for sudden infant death syndrome among northern plains Indians. The JAMA. 2002;288:2717–2723.
10. Popova S, Lange S, Shield K, Mihic A, Chudley A E, Mukherjee RAS, Bekmuradov D, Rehm J. Co-morbidity of Fetal Alcohol Spectrum Disorder: A systematic literature review and meta-analysis. The Lancet, 2016; 387: 978-8. DOI: http://dx.doi.org/10.1016/S0140-6736(15)01345-8. Available from http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)01345-8/abstract
11. Burd L, Cotsonas-Hassler TM, Martsolf JT, Kerbesian J. Recognition and management of fetal alcohol syndrome. Neurotoxicol Teratol. 2003a;25:681–688.
12. Paintner A, Williams AD, Burd L. Fetal alcohol spectrum disorders —Implications for child neurology, Part 2: Diagnosis and management. J Child Neurol. 2012;27:355–362.
13. Chasnoff IJ, Wells AM, King L. Misdiagnosis and missed diagnoses in foster and adopted children with prenatal alcohol exposure. Pediatrics. 2015;135:264–270.
14. Burd L, Carlson C, Kerbeshian J. Mental health disorders comorbid with fetal alcohol spectrum disorders. In Sher L, Kandel I, Merrick J, editors. Alcohol-related cognitive disorders: research and clinical perspectives. New York: Nova Science Publishers; 2009. p. 111–123.
15. Burd L, Fast DK, Conry, J, Williams A. Fetal alcohol spectrum disorders as a marker for increased risk of involvement with correction systems. J Psychiatry Law. 2010;38:559–583.
16. May PA, Gossage JP, Kalberg WO, et al. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev Disabil Res Rev. 2009;15:176–192.
17. Public Health Agency of Canada (PHAC). Fetal alcohol spectrum disorder (FASD): A framework for action. 2003.
18. Roberts G, Nanson J. Best practices. Fetal alcohol syndrome/fetal alcohol effects and the effects of other substance use during pregnancy. Ottawa Canada: Canada's Drug Strategy Division, Health Canada; 2000.
19. May PA, Baete, A, Russo J, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics. 2014;134:855–866.
20. Barry KL, Caetano R, Chang G, et al. Reducing Alcohol-Exposed Pregnancies: A Report of the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect. U. S. Department of Health and Human Services. 2009. Available from http://www.cdc.gov/ncbddd/fasd/documents/redalcohpreg.pdf
21. Nelson DE, Naimi TS, Brewer RD, et al. Metropolitan-area estimates of binge drinking in the United States. Am J Public Health. 2004;94:663–671.
22. Substance Abuse and Mental Health Services Administration (SAMHSA), Fetal Alcohol Spectrum Disorders Center for Excellence. Fact Sheet: The Language of Fetal Alcohol Spectrum Disorders, 2004. Available from: http://www.fasdcenter.samhsa.gov/documents/WYNKLanguageFASD2.pdf
23. Thompson A, Hackman D, Burd L. Mortality in Fetal Alcohol Spectrum Disorders. J Pediatr. 2014;4:21–33.
24. Lemoine P, Harousseau H, Borteryu JP, Menuet JC. Les enfants de parents alcooliques: Anomalies observee a propos de 127 cas [The children of alcoholic parents: Anomalies observed in 127 cases]. Quest Med. 1968;21:476–82.
25. Dubovsky D, Whitney N. Modifying approaches to improve outcomes for women in treatment who have fetal alcohol spectrum disorder. Paper presented at the 4th National Conference on Women, Addiction and Recovery, Chicago, I. 2010.
26. Conry J, Fast DK. Fetal alcohol syndrome and the criminal justice system. Vancouver: British Columbia Fetal Alcohol Syndrome Resource Society and the Law Foundation of British Columbia. 2000.
27. Credé S, Sinanovic E, Adnams C, London L. The utilization of health care services by children with Foetal Alcohol Syndrome in the Western Cape, South Africa. Drug Alcohol Depend. 2011;115:175–182.

28. Harwood H. Updating estimates of the economic costs of alcohol abuse in the United States: Estimates, update methods, and data. Report prepared by the Lewin Group for the National Institute on Alcohol Abuse and Alcoholism. Based on estimated, analyses, and data reported in H Harwood, D Fountain and G Livermore, the Economic costs of alcohol and drug abuse in the United States, 1992. Report prepared for the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services. (NIH Publication No. 98-4327). Rockville MD: National Institutes of Health. 2000 Available from: http://pubs.niaaa.nih.gov/publications/economic-2000/alcoholcost.PDF.

29. Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders [ICCFASD]. Consensus statement on recognizing Alcohol-Related Neurodevelopmental Disorder (ARND) in primary health care of children. Rockville (MD): ICCFASD; 2011.

30. Lupton C, Burd L, Harwood R. Cost of fetal alcohol spectrum disorders. Am J Med Genet C Semin Med Genet. 2004;127C(1): 42–50.

31. Popova S, Lange S, Mihic A, et al. Prevalence of Fetal Alcohol Spectrum Disorder in correctional systems: A systematic literature review. Can J Public Health. 2011a;102:336–340.

32. Popova S, Lange S, Burd L, Rehm J. Health care burden and cost associated with Fetal Alcohol Syndrome: Based on official Canadian data. PloS ONE, 2012a;7: e43024. doi:10.1371/journal.pone.0043024

33. Popova S, Lange S, Burd L, et al. Cost of Fetal Alcohol Spectrum Disorder diagnosis in Canada. PLoS ONE. 2013a;8:e60434. doi: 10.1371/journal.pone.0060434

34. Popova S, Lange S, Burd L, et al. Cost of specialized addiction treatment of clients with Fetal Alcohol Spectrum Disorder in Canada. BMC Public Health. 2013b;13:570. DOI: 10.1186/1471-2458-13-570

35. Popova S, Lange S, Burd L, Rehm J. Canadian children and youth in care: The cost of Fetal Alcohol Spectrum Disorder. Child Youth Care Forum. 2014a;43:83-96. doi: 10.1007/s10566-013-9226-x

36. Popova S, Lange S, Burd L, et al. Cost of speech-language interventions for children and youth with Fetal Alcohol Spectrum Disorder in Canada. International Journal of Speech-Language Pathology. 2014b [Epub ahead of print] doi: 10.3109/17549507.2013.862858

37. Popova S, Lange S, Burd L, Rehm, J. Cost attributable to FASD in the Canadian correctional system. Int J Law Psychiatry. 2015. doi:10.1016/j.ijlp.2015.03.010. Available from: http://www.sciencedirect.com/science/article/pii/S0160252715000497

38. Public Health Agency of Canada (PHAC). Assessment and diagnosis of FASD among adults: A national and international systematic review 2011.

39. Abel EL, Sokol RJ. A revised conservative estimate of the incidence of FAS and its economic impact. Alcohol Clin Exp Res. 1991;15(3) :514–524.

40. Klug MG, Burd L. Fetal alcohol syndrome prevention: Annual and cumulative cost savings. Neurotoxicol Teratol. 2003;25763–765.

41. Rice D, Kelman S, Miller L. The Economic costs of alcohol and drug abuse and mental illness: 1985 Rockville MD: U.S. Department of Health and Human Services; 1990.

42. Ministry of Health. Taking Action on Fetal Alcohol Spectrum Disorder (FASD): A discussion document. Wellington, New Zealand: Ministry of Health; 2015.

43. Chudley AE, Kilgour AR, Cranston M, Edwards M. Challenges of diagnosis in fetal alcohol syndrome and fetal alcohol spectrum disorder in the adult. Am J Med Genet C Semin Med Genet. 2007;145C:261–272.

44. Thanh N, Jonsson E. Costs of fetal alcohol spectrum disorder in Alberta, Canada. Can J Clin Pharmacol. 2009;16:e80–e90.

45. Single E, Collins D, Easton B, et al. International guidelines for estimating the costs of substance abuse. 2nd ed. Geneva, Switzerland: World Health Organization; 2003.

46. Statistics New Zealand. Infoshare. Available from http://www.stats.govt.nz/infoshare

47. Easton B, Burd L, Sarnocinska-Hart A, et al. Productivity losses because of morbidity attributable to Fetal Alcohol Spectrum Disorder in Canada: A demographic approach. J Stud Alcohol Drugs. 2014;75:1011–7.

48. Harwood HJ, Napolitano DM, Kristiansen PL. Economic costs to Society of Alcohol and

Drug Abuse and Mental Illness: 1980. Rockville (MD): Alcohol Drug Abuse and Mental Health Administration; 1984.

49. Easton B, Burd L, Sarnocinska-Hart A, et al. The cost of lost productivity due to fetal alcohol spectrum disorder-related premature mortality. J Popul Ther Clin Pharmacol. 2015;22:e3–8.

50. Gifford AE, Farkas KJ, Jackson L, et al. Assessment of benefits of a universal screen for maternal alcohol use during pregnancy. Birth Defects Res A Clin Mol Teratol. 2010;88:838–46.

51. Hopkins RB, Paradis J, Roshankar T, et al. Universal or targeted screening for fetal alcohol exposure: A cost-effectiveness analysis. J Stud Alcohol Drugs. 2008;69:510–9.

52. Thanh NX, Jonsson E, Moffatt J, et al. An economic evaluation of the Parent-Child Assistance Program for preventing Fetal Alcohol Spectrum Disorder in Alberta, Canada. Adm Policy Ment Health. 2015; 42: 10–18.

53. Thanh NX, Moffatt J, Jacobs P, et al. Potential impacts of the Alberta fetal alcohol spectrum disorder service networks on secondary disabilities: a cost-benefit analysis. J Popul Ther Clin Pharmacol. 2013;20:e193–200.

54. Popova S, Stade B, Lange S, et al. Economic impact of fetal alcohol syndrome and fetal alcohol spectrum disorders: A systematic literature review. Alcohol Alcohol. 2011b;46:490–497.

55. Popova S, Stade B, Lange S, Rehm J. A model for estimating the economic impact of fetal alcohol spectrum disorder. J Popul Ther Clin Pharmacol, 2012b;19:e51–e65.

56. Stade B, Ungar W, Stevens B, et al. The burden of prenatal exposure to alcohol: Measurement of cost. Journal of Fetal Alcohol Syndrome International. 2006;4:1–14.

57. Stade B, Ali A, Bennett D, et al. The burden of prenatal exposure to alcohol: Revised measurement of cost, 2007. Can J Clin Pharmacol. 2009;16:e90–e102.

58. Popova S, Lange S, Burd L, Rehm J. Economic burden of Fetal Alcohol Spectrum Disorder in Canada in 2013. Alcohol Alcohol. 2015 [Epub ahead of print].

Lack of housing, hospital treatment and premature mortality: a cohort study of people in Counties Manukau district

Simon Thornley, Roger Marshall

ABSTRACT

AIM: We considered risk factors for mortality in people admitted to Counties Manukau inpatient facilities, who were also identified by medical staff to have insufficient housing.

METHOD: A cohort study of people aged 15 to 75 years admitted to Counties Manukau inpatient facilities were selected between 2002 and 2014, with ICD-10 codes for insufficient housing. Diagnostic records identified people with substance use and other clinical conditions. Mortality records were used to track survival.

RESULTS: During the study period, 1,182 individuals were identified, 126 (10.7%) of whom died during a median follow-up of 5.7 years. Median survival of the cohort was 63.5 years (95% confidence interval (CI): 58.7 to 69.9) which is about 20 years less than the general population. Of the cohort, the strongest associations with premature mortality were among people with cannabis-related disorders (adjusted hazard ratio [aHR] 2.15; 95% CI: 1.10 to 4.22), diabetes (aHR 1.75; 95% CI: 1.05 to 2.93) and Maaori, compared to European and other ethnic groups, except Asian and Pacific (aHR 1.80; 95% CI: 1.14 to 2.85).

CONCLUSION: This population has high mortality. Within this group, Māori and people diagnosed with substance use and diabetes are at even higher risk of premature death.

Attention has recently focused on the effect of housing on health. Improving warmth and reducing damp inside houses, reducing fall-related hazards and overcrowding are important interventions that are likely to influence the health of residents.[1] But the absence of a home is itself an issue that is likely to affect health.[2] The definition of "homelessness" in published research has a wide scope, from the most restrictive definition of 'sleeping rough' to more inclusive versions that include being a temporary resident in a permanent private dwelling.[3] People living in camping grounds, shelters and temporary commercial accommodation, such as boarding houses, are also often included in the definition.[3] With this more inclusive definition, an estimate of the prevalence of homelessness is less than 1% in New Zealand.[3]

Studies from the US[2] and Sweden[4] highlight the high prevalence of alcohol-related harm, drug addiction, severe mental illness and increased mortality risk in homeless populations. The extent to which lack of housing is a cause, or an effect, of these conditions is difficult to estimate, yet published research clearly indicates that homelessness and these conditions co-exist. Provision of shelter is often managed by the state (in the form of social services) or by privately run charities. Since it is likely that lack of housing adversely affects these conditions, and that homelessness is likely to complicate the recovery from medical disorders, we conducted a study, using healthcare data, to describe the population who attended Counties Manukau inpatient services and who were identified as having inadequate housing. This study estimates the burden and risk factors associated with mortality among this group.

Methods

This study was carried out with a cohort of people with inadequate housing, aged 15 to 75 years, who were admitted (a presentation to hospital lasting three hours or more) to Counties Manukau inpatient facilities in South Auckland, between January 2002 and December 2014 for any condition, including psychiatric, emergency department presentations and elective surgery. "Inadequate housing" was identified by ICD-10 additional codes *Z59x (***Table 1***)*, which indicate a degree of insufficient housing. These codes encompass a range of issues that include housing-related and economic hardship, which affect their diagnosis. The National Minimum Dataset was used to identify subjects. Text searches of all diagnosis codes for the index admission were used to identify people who smoked tobacco or cannabis, had diabetes, alcohol-related conditions, psychotic disorders, depression, suicidality, obesity or cancer. These variables were chosen since other studies had identified these conditions as common among homeless populations. The service from which the patient was discharged was also included: mental health crisis (inpatient), adult medicine or paediatrics; emergency medicine; intensive care; surgical, gynaecological and dental; maternity or neonates; other mental health and geriatrics specialties. Discharge diagnosis data was then linked with national mortality records using an encrypted unique identifier derived from the National Health Index (NHI).

The statistical analysis centred on estimating factors associated with premature mortality. Cox's proportional hazard model was used to estimate the magnitude of the association between baseline factors and survival. Age—rather than time-on-study—was used as the time scale, as is now recommended, so that observations were considered left truncated and right censored.[5] The age of the subject at the date of first hospital discharge records during the study period was considered the entry time point, and survival was estimated for each individual, based on whether they died during follow-up or reached the end of follow-up (December 2014) alive. Gender, ethnicity, tobacco smoking and diabetes were considered important confounders and were adjusted for. People with cancer at baseline were excluded from the analysis, since they had a very high rate of premature death.

Ethical approval was not sought as all data was de-identified using encrypted national health identifier and only aggregate measures are reported.

Results

During the period of the study, 1,182 individuals were identified, and 126 (10.6%) died during a median follow-up of 5.7 years (**Table 2**). The cohort had marginally more men than women (607/1,182; 51.4%), and

Table 1: ICD-10 diagnoses used to indicate a hospital admission for which homelessness has been a likely contributor.

Code	Description
Z590	Homelessness
Z591	Inadequate housing
Z592	Discord with neighbours, lodgers and landlord
Z593	Problems related to living in residential institution
Z594	Lack of adequate food
Z596	Low income
Z597	Insufficient social insurance and welfare support
Z598	Other problems related to housing and economic circumstances
Z599	Problem related to housing and economic circumstances, unspecified

Table 2: People with insufficient housing, aged 15 to 75 years, admitted to Counties Manukau inpatient services, 2002 to 2014, by mortality status at the end of 2014.

	No death (col. %)*	**Death (col. %)***	**Total (col. %)***	***P*-value**
Total	1,056	126	1,182	
Gender				
Male	530 (50.2)	77 (61.1)	607 (51.4)	0.026
Age (years)				<0.001
Median (IQR)	38.0 (27.9, 47.9)	52.6 (41.7, 63.8)	39.2 (28.8, 49.8)	
Ethnic Group				0.110
Māori	346 (32.8)	46 (36.5)	392 (33.2)	
Pacific	203 (19.2)	30 (23.8)	233 (19.7)	
Chinese or 'Other Asian'	41 (3.9)	1 (0.8)	42 (3.6)	
Indian	38 (3.6)	1 (0.8)	39 (3.3)	
NZ European or other	428 (40.5)	48 (38.1)	476 (40.3)	
Discharge service				<0.001
Mental Health Crisis	387 (36.6)	26 (20.6)	413 (34.9)	
Adult medicine or paediatrics	201 (19.0)	54 (42.9)	255 (21.6)	
Emergency Medicine	166 (15.7)	13 (10.3)	179 (15.1)	
Intensive care	97 (9.2)	16 (12.7)	113 (9.6)	
Surgery, gynaecology or dental	86 (8.1)	9 (7.1)	95 (8.0)	
Maternity or neonates	58 (5.5)	0 (0)	58 (4.9)	
Other mental health	44 (4.2)	1 (0.8)	45 (3.8)	
Geriatrics	17 (1.6)	7 (5.6)	24 (2.0)	
Clinical Diagnosis				
Diabetes	80 (7.6)	27 (21.4)	107 (9.1)	<0.001
Cancer	9 (0.9)	14 (11.1)	23 (1.9)	<0.001
Obesity	47 (4.5)	13 (10.3)	60 (5.1)	0.009
Tobacco	487 (46.1)	66 (52.4)	553 (46.8)	0.216
Alcohol	144 (13.6)	20 (15.9)	164 (13.9)	0.582
Cannabinoid	93 (8.8)	12 (9.5)	105 (8.9)	0.919
Other drug use (mainly opioid or methamphetamine)	142 (13.4)	6 (4.8)	148 (12.5)	0.008
Depression	165 (15.6)	16 (12.7)	181 (15.3)	0.465
Suicidality	18 (1.7)	1 (0.8)	19 (1.6)	0.694
Psychosis	287 (27.2)	26 (20.6)	313 (26.5)	0.142

* Unless otherwise stated. IQR: interquartile range.

mean age was 39.2 years (interquartile range: 29 to 50). In the cohort, during their first hospital stay, 46.8% (553/1,182) had a code for cigarette smoking, and 9.7% (107/1182) were diagnosed with diabetes, 13.9% (164/1182) had a code representing problem alcohol use, and 8.9% (105/1182) had a diagnosis related to cannabis use (mainly associated with drug-induced psychosis). Other drug use (mostly opioid and methamphetamine use) was present in 12.5% (148/1,182) of the population. The most frequent clinical information obtained during the baseline admissions were for tobacco smoking and psychosis (26.5%; 313/1,182).

The largest ethnic group of the cohort was 'NZ European or Other' ethnic groups (40.2%; 476/1,182), with one third (33%; 392/1,182) Māori, and one fifth Pacific (19.7%; 233/1,182). Numbers in the Asian population were small. This contrasts to the population profile of Counties Manukau district where 15.7% identify as Māori, 21.5% Pacific and 62.8% as 'NZ European or Other' in 2015.[6] The proportion of Māori in the cohort is about twice that expected from the ethnic characteristics of people who live in the district.

Crisis mental health and adult medicine dominated the services from which this population were initially discharged. During the period of the study, the population were most frequently discharged from the Mental Health Crisis team (34.9%; 413/1,182). Adult Medicine was the next most frequent service, followed by Emergency Medicine.

The principal diagnoses of the index admission encompassed a wide variety of different diagnoses (390). Of all the principal diagnoses, 46% (544/1,182) were for mental and behavioural disorders (ICD-10 F00-F99). Psychotic disorders, such as schizophrenia were most common. The next most frequent category was "injury, poisoning and certain other consequences of external causes" (ICD-10 codes F00 to T98) making up 17% (202/1,182) of primary diagnosis codes. Within the injury and poisoning category, benzodiazepine poisoning was most frequently recorded. The next category of primary diagnoses was "Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified" (ICD-10 codes R00 to R99), comprising 6% (75/1,182) of all admissions. Within this category, unspecified chest pain was most frequently coded.

Cause of death information was available in 87 of 126 deaths. The most frequent causes included cardiovascular disease (26.4%; ICD-10 IXX), cancer (22.0%; ICD-10

Figure 1: Scaled rectangle diagram, highlighting the relative size and overlap of different characteristics of the cohort. The figure has a small approximation; there are some low frequency combinations that are not represented.

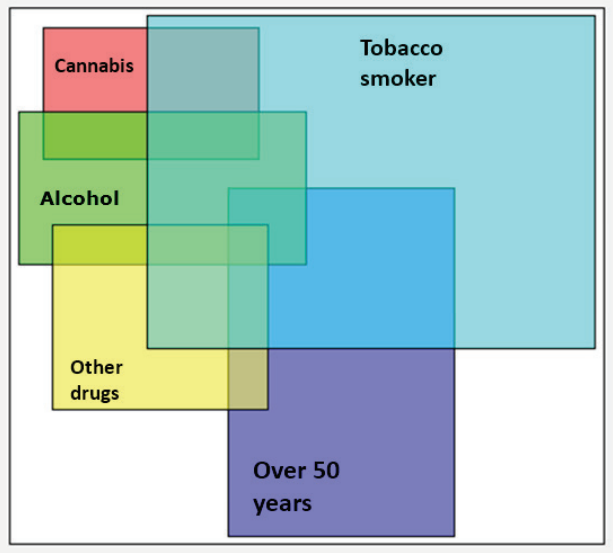


Table 3: Crude and adjusted associations between sociodemographic and clinical factors and death during follow-up (hazard ratio (HR); 95% confidence interval) (*n*=1,159; 112 deaths).

Risk factor	Denominator risk	Numerator risk	Crude HR (95% CI)	Adj. HR (95% CI)*
Gender				
	Female	Male	1.45 (0.47 to 2.13)	1.59 (1.06 to 2.38)
Ethnicity				
	NZ European or Other	Māori	2.20 (1.43 to 3.40)	1.80 (1.14 to 2.85)
		Pacific	1.64 (0.98 to 2.73)	1.08 (0.60 to 1.94)
		Indian	0.56 (0.08 to 4.08)	0.42 (0.06 to 3.13)
		Chinese or Other Asian	0.35 (0.05 to 2.52)	0.44 (0.06 to 3.22)
Hospital service				
	Mental Health Crisis	Emergency Medicine	1.96 (0.99 to 3.84)	1.97 (0.99 to 3.91)
		Geriatrics	1.73 (0.66 to 4.55)	1.58 (0.59 to 4.24)
		Intensive care	1.47 (0.77 to 2.80)	1.58 (0.82 to 3.05)
		Medicine paediatrics and maternity	2.58 (1.54 to 4.32)	2.00 (1.14 to 3.49)
		Other mental health	0.40 (0.05 to 2.95)	0.26 (0.03 to 1.93)
		Surgery gynaecology or dental	2.01 (0.82 to 4.92)	1.84 (0.74 to 4.57)
Clinical condition				
Cannabis use	No	Yes	2.77 (1.44 to 5.31)	2.15 (1.10 to 4.22)
Tobacco use	No	Yes	1.87 (1.28 to 2.72)	1.56 (1.04 to 2.33)
Alcohol use	No	Yes	1.39 (0.85 to 2.27)	1.37 (0.83 to 2.28)
Other drug use	No	Yes	0.54 (0.24 to 1.24)	0.50 (0.22 to 1.16)
Diabetes	No	Yes	1.95 (1.22 to 3.13)	1.75 (1.05 to 2.93)
Obesity	No	Yes	1.68 (0.92 to 3.08)	1.44 (0.77 to 2.70)
Depression	No	Yes	0.74 (0.43 to 1.28)	1.03 (0.58 to 1.84)
Psychosis	No	Yes	0.80 (0.51 to 1.27)	0.74 (0.46 to 1.18)

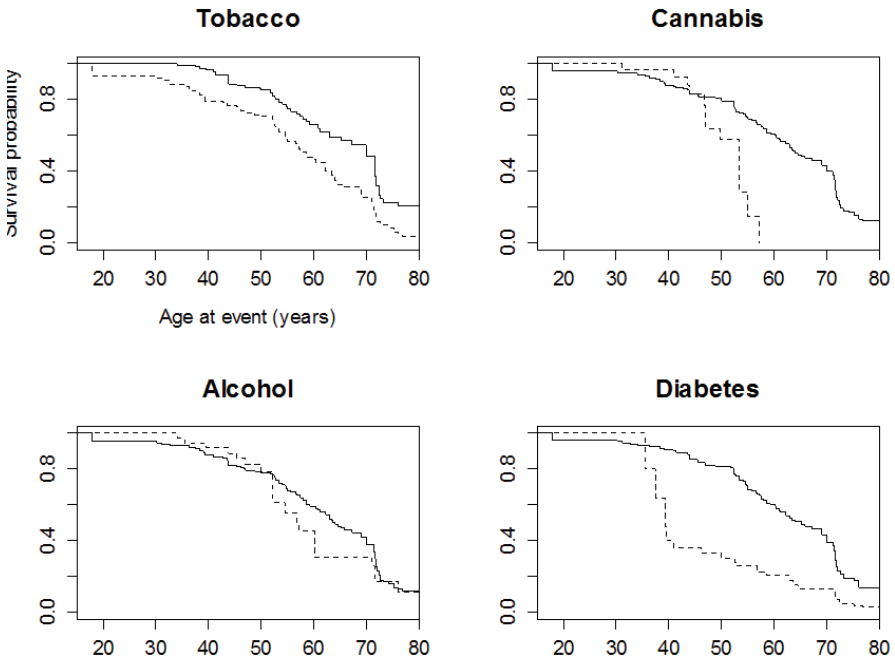
CI: confidence interval. *Adjusted for sex, tobacco use, diabetes and ethnic group.

CXX), and respiratory diseases (17.2%; ICD-10 JXX).

Mean length of stay in these index admissions was right skewed with a median of 4 days, and interquartile range of 15 days. The longest admission was 1,016 days (2.8 years) for a patient with a primary diagnosis of schizophrenia.

Table 2 does not show overlap between these conditions, which are not mutually exclusive, and many individuals in this population have tobacco, cannabis and alcohol addictions which are each severe enough to be recorded as diagnoses (**Figure 1**). The figure shows a scaled rectangle diagram[7] which depicts selected features of the cohort. In this figure, areas are intended to be proportional to frequency. The area of each rectangle that represents an attribute (eg, 'Alcohol') is exactly proportional to frequency, and areas of overlap are approximately proportional to frequency of co-occurrence of attributes. The outer rectangle has an area that is proportional to the total cohort (*n*=1,182). For example, the figure shows substantial overlap between

Figure 2: Kaplan-Meier plots comparing the survival of people with diagnoses associated with substance use or diabetes (dashed line), with those who did not have such a diagnosis (solid line).

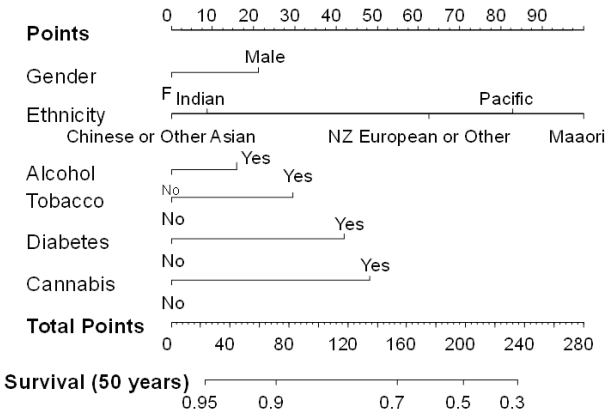


the alcohol, cannabis and tobacco-related conditions. It also reveals that alcohol and cannabis-related disorders are relatively rarely documented in hospital records after the age of 50 years in this population.

The results of Cox modelling, without adjustment, and after adjustment for confounders are shown (**Table 3**).

The crude and adjusted associations (**Table 3**) show an increase in risk of death if subjects had diabetes or were discharged from medicine, paediatrics or maternity services (compared to discharge from mental health services). Cannabis and tobacco-related diagnoses and complications, or a diagnosis of diabetes were most strongly associated with premature death, after adjustment for confounders. Men with insufficient housing were 1.6 times (95% CI: 1.1 to 2.4) more likely to die during follow-up, compared to corresponding women. Māori who were inadequately housed were 1.8 times (95% CI: 1.1 to 1.9) more likely to die during follow-up than NZ European and Other. People with cannabis-related conditions were twice as likely as those without to die during follow-up (adjusted hazard ratio [aHR] 2.15; 95% confidence interval: 1.10 to

Figure 3: Nomogram that illustrates the relationships between selected risk factors and predicted survival at 50 years of age in the study population (n = 1,159; 112 deaths).



NZMJ 19 August 2016, Vol 129 No 1440
ISSN 1175-8716
www.nzma.org.nz/journal

Table 4: Population attributable risks for substance use and diabetes, among people coded with insufficient housing during an admission to Counties Manukau inpatient services, 2002 to 2014.

Risk factor	Hazard ratio	Prevalence (%)	Population attributable risk (%)
Tobacco smoking	1.56	46.8	20.8
Cannabis related disease	2.15	8.9	9.3
Diabetes	1.75	9.1	6.4
Alcohol-related disease	1.37	13.9	4.9

4.22). People diagnosed with diabetes (aHR 1.75; 1.07 to 2.93), and tobacco smokers (aHR 1.56; 1.04 to 2.33) were also at increased risk of death.

Kaplan-Meier survival plots (**Figure 2**) show a steeper reduction in survival for those with diabetes and substance abuse; most notably for diabetes, with median survival 39.4 years in diabetes and 65.3 without. Also, median survival was only 53.5 years in people with cannabis diagnoses, and about 64.5 years in subjects without. Median survival, here, is comparable to life expectancy, calculated in official statistics. The median survival contrasts with the average life expectancy of the New Zealand population being about 83 years in women and 80 years in men, calculated from death rates between 2012 and 2014.[8] The life span of this population is, therefore, about 15 years shorter than the New Zealand average, and considerably lower than for the Māori population (77 years females, compared to 73 years males).

Figure 2 also shows a steep mortality increase in people with diabetes, in the late 30s to 40s, compared to those without the diagnosis. Mortality in people with alcohol-related diagnoses deviates most steeply from those without the diagnosis in the 50-to-60 year age range. A global test for non-proportionality on an adjusted Cox model (*cox.zph*) was not significant (P=0.512).

After adjustment for confounding factors, people with inadequate housing who identified as Māori were associated with a 68% increase (95% CI: 7% to 166% increase) risk of death, compared to 'NZ European and Other' ethnic groups. No other convincing mortality differences were observed by ethnic group.

A regression nomogram,[9] Figure 3, illustrates the relative contribution of different factors to survival probability (taken at the age of 50) in this cohort. The predicted survival for an individual is calculated from the nomogram by summing the individual points per variable for each risk factor, marking this point on the "total points" line and marking a vertical line down to calculate survival at the age of 50 years. For example, a Māori (100 points) man (20 points) who does not smoke tobacco or cannabis (0 points), but has diabetes (40 points) has a total of 100+20+40=160 points, corresponding to a survival probability with these characteristics to the age of 50 years of 70%. This compares to a 'NZ European or Other' man with the same characteristics of the previous example who will have about 120 points, so that survival until 50 years is about 10% higher than his Māori counterpart.

People in the cohort who were discharged from Adult Medical services (as well as Paediatrics and Maternity) were twice as likely to die during follow-up (aHR 2.00; 95% CI: 1.14 to 3.49), compared to those discharged from the Crisis Mental Health team, after adjustment for confounders. Discharge from emergency and geriatric services showed higher crude mortality risks than discharge from the mental health crisis team, but these differences were not significant after adjustment.

When population attributable risks were calculated for the potentially modifiable exposures examined, tobacco accounted for the greatest proportion of premature death, followed by cannabis-related disease, then diabetes, with alcohol-related disease accounting for the lowest proportion of disease (**Table 4**). The population attributable risk can be interpreted as the percentage reduction in the death rate which would occur if the exposure were completely removed from the population, assuming that exposures are causal.

Discussion

This study shows that among the adult population of people with insufficient housing and who present to hospital, about 10.6% (126/1182) will die within 6 years. Māori experience a higher mortality compared to NZ European and other ethnic groups, after adjustment for confounding factors. Substance and tobacco use is relatively common, and tobacco use was associated with the greatest burden of premature death. Diagnoses linked to cannabis use were associated with a two-fold increase in the risk of death.

This study may have some limitations. The variable for selection of the population—that is, the Z codes for insufficient housing—may be subjective and unreliable. The degree of homelessness indicated by this diagnosis is uncertain, as discussed in the introduction. The selection based on hospital treatment and ICD code is likely to bias the people in this study toward more severe forms of homelessness. Other limitations were that subjects were assumed to be in the country and able to be recorded with a death event during follow-up. It is possible that some subjects may have moved overseas and died there. Clinical information is likely to have some measurement error that may bias measures of association. For example, many more subjects in the cohort may use cannabis, as only those with complications of use are likely to be recorded in hospital diagnoses. In the mortality analysis, the comparisons made are within a small population, so that some results—particularly those relating to low risk of mortality among patients with mental health conditions—should be treated with caution. Studies conducted in general populations, for example, show increased risk of mortality in patients with these conditions.[10] The mortality among this group is also likely to be higher than a more general population-based sample of people affected by homelessness, due to the criteria for selection into the study. Further population-based research is needed to more accurately define the burden of mortality among homeless people that do not present to hospital.

Despite the uncertainty about the meaning of the homelessness diagnoses in this study, results from research overseas are relatively concordant with ours, with regard to prevalence of disorders and mortality. In a meta-analysis of 29 eligible surveys, from 7 countries, the most common mental disorders reported were alcohol dependence (prevalence: 8.1 to 58.5%), drug dependence (prevalence: 2.8 to 42.3%), with psychiatric disorders such as major depression and psychosis also common.[11]

The most recent study (2013), describes a cohort of homeless people in Boston, from healthcare records taken from 1 January 2003 to 31 December 2008, which were then linked to death records from the state of Massachusetts. The mean age of the 28,033 people in the cohort was 41 years (standard deviation 12.4), with 66% male. During the average 3.2 years of follow-up, 1,302 deaths occurred (4.6%). The major causes of death included drug overdose (*n*=219), cancer (*n*=206) and heart disease (*n*=203).[2] The overdose deaths involved opioids in 81% of cases, with alcohol use mentioned in 32%. The mean age at death was 51.2 years, with 81% (1,055/1,302) occurring in men. The study authors described a high prevalence of chronic pain and opioid use in the homeless group and described obviating diversion of opioids as a priority for improving the health of this population. Our study found a similar mortality rate (10.6% in 5.7 years compared to 4.6% after mean follow-up of 3.2 years [US study]). Opiates are, however, less available in New Zealand than in the US, and no patients were coded with a death due to overdose in the mortality information that was available in our cohort.

In a Swedish study[4] of 2,283 people registered with the Office for the Homeless in Stockholm between 1995 and 1996, the cohort was followed up until 2005 and mortality rates then compared with the general population. The study found that homeless people had an excess mortality, between 2.5 to 3.0 times that of the general population. Homeless people—compared to people who were not homeless, but had been hospitalised for drug-related treatment—had a similar risk of mortality (relative risk 1.13; 95% confidence interval: 0.93 to 1.38). With the high rate of alcoholism in this study, the authors concluded that alcohol was almost entirely the cause of the excess mortality in their study population. Our study shows that

a range of substance use disorders, as well as diabetes, were associated with high risk of mortality.

This report draws attention to the poor health status of people affected by insufficient housing in Counties Manukau district. This population comprises a disproportionately high number of Māori (about 120% higher than the level expected in the population) and Pacific people (about 60% higher than the level expected in the population), raising issues of equity.

With high mortality associated with substance use, and mental health issues relatively common, these findings highlight some possibilities for intervention. The co-occurrence of mental health and addiction issues suggests that mental health services, particularly crisis services, are an important referral point for addiction treatment.

These findings also raise the issue of whether addiction and mental health issues are likely to be exacerbated by a lack of secure housing. While the lack of housing may be partly caused by mental health and addiction issues, it is likely that lack of secure and safe shelter will also hamper recovery and treatment. There are a number of case-studies from Canada[12] and the US,[13] reporting that state investment in long-term housing of the homeless results in overall cost savings, because homeless people are frequent users of expensive psychiatric, medical, corrections and emergency housing services.[14]

This study highlights the excess mortality and spectrum of disease among people with insufficient housing. Māori are disproportionately represented and have higher adjusted mortality rates. Lack of secure housing is likely to hamper efforts of this population to recover from prevalent addiction and mental health related conditions. Overseas studies indicate that improved health, and cost savings result from programmes to provide secure shelter to populations such as these.

Competing interests:
Nil.

Acknowledgments:
The author thanks Dean Papa, analyst and statistician for help with data linking, and Dr Doone Winnard, Dr Wing Cheuk Chan and Ms Jude Woolston for helpful comments on drafts.

Author information:
Simon Thornley, Public Health Physician, Counties Manukau District Health Board, Manukau, New Zealand; Roger Marshall, Associate-Professor of Biostatistics, Section of Epidemiology and Biostatistics, University of Auckland, New Zealand.

Corresponding author:
Simon Thornley, Public Health Physician, Māori Health Development, Private Bag 94052, South Auckland Mail Centre, Auckland, New Zealand.
sithor@gmail.com

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6975

REFERENCES:

1. Baker MG, Howden-Chapman P. Time to invest in better housing for New Zealand children. N Z Med J. 2012; 125:6–10.
2. Baggett TP, Hwang SW, O'Connell JJ, et al. Mortality among homeless adults in Boston: shifts in causes of death over a 15-year period. JAMA internal medicine. 2013; 173:189–95.
3. Amore K, Viggers H, Baker M, Howden-Chapman P. Severe Housing Deprivation: The problem and its measurement. Official Statistics Research Series, 2013. Wellington: Statistics New Zealand, 2013.
4. Beijer U, Andreasson S, Ågren G, Fugelstad A. Mortality and causes of death among homeless women and men in Stockholm. Scand J Public Health. 2011; 39:121–7.
5. Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med. 2004; 23:3803–20.
6. Ministry of Health. Population of Counties Manukau DHB. Edition.: Ministry of Health, cited 31 March 2016]. Available from: http://www.health.govt.nz/new-zealand-health-system/my-dhb/counties-manukau-dhb/population-counties-manukau-dhb
7. Marshall RJ. Scaled rectangle diagrams can be used to visualize clinical and epidemiological data. J Clin Epidemiol. 2005; 58:974–81.
8. Statistics New Zealand. Life expectancy. Edition.: Statistics New Zealand, cited 15/12/2015 2015]. Available from: http://www.stats.govt.nz/browse_for_stats/health/life_expectancy.aspx
9. Harrell F. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis: Springer, 2015.
10. Healy D, Le Noury J, Harris M, et al. Mortality in schizophrenia and related psychoses: data from two cohorts, 1875–1924 and 1994–2010. BMJ Open. 2012; 2.
11. Fazel S, Khosla V, Doll H, Geddes J. The prevalence of mental disorders among the homeless in western countries: systematic review and meta-regression analysis. PLoS Med. 2008; 5:e225.
12. Medicine Hat Community Housing Society. At home in Medicine Hat: our plan to end homelessness. Medicine Hat, 2014.
13. National Alliance to End Homelessness. The state of homelessness in America 2015. Washington DC: National Alliance to End Homelessness, 2015.
14. Pomeroy S. The cost of homelessness: analysis of alternate responses in four Canadian cities.: National Secretariat on Homelessness 2005.

In-hospital morbidity and brain metrics of preterm neonates born 1998–2009

Sarah L Harris, Nicola C Austin, Malcolm Battin, Roland Broadbent, John Horwood, Ross Keenan, Scott Wells, Carole Spencer, Patricia Graham, Lianne J Woodward, Brian A Darlow

ABSTRACT

AIMS: To describe the survival, in-hospital morbidity, brain metrics and two-year neurodevelopmental outcomes of two extremely preterm cohorts and discuss the contribution of changes in clinical practice to these outcomes.

METHODS: Retrospective comparative cohort study, of two cohorts of neonates born <28 weeks gestation: 47 infants born 1998–2000 and 39 infants 2006–2009.

RESULTS: Comparing historical to the contemporary cohort respectively, admission temperature (35.9 degrees C, 36.5) and CRIB (Clinical Risk Index in Babies) score (5.4, 3.1) improved. Inotrope support fell significantly (55.3%, 28.2%). High frequency ventilation days fell (8.0, 2.7). CPAP days increased significantly (32.2, 47.9). Chronic lung disease at 36 weeks corrected age fell significantly (61.7%, 38.5%). Red cell transfusions decreased in number (7.1, 4.8) and volume (96.2ml/kg, 70.4ml/kg). Retinopathy of prematurity (ROP) rates dropped significantly (66.0%, 28.2%). Survival was not significantly different. Nutritional improvements included shorter days to first enteral feed (3.4, 2.0), target protein (5.4, 4.3) and lipid levels (7.1, 4.1) with better breastfeeding rates at discharge (19.2%, 38.5%). By 36 weeks z scores for weight (-0.90, -0.39) were improved but not length (-1.94, -1.26) or head circumference (-0.72, -0.69). MRI brain metrics showed a significant improvement in bifrontal (59.2, 65.9), biparietal (73.7, 79.3) and transcerebellar diameter (50.6, 52.6) with improved neurodevelopmental outcome at two years.

CONCLUSION: The contemporary cohort had better initial physiological stability, less chronic lung disease and retinopathy, improved body growth at 36 weeks and brain metrics at term equivalent. Improvement in neurodevelopment at two years has been seen and further analysis will be important to understand the impact of the changes in clinical care.

Since the 1990s, there have been many changes in the care of extremely preterm infants. Antenatal steroids and surfactant revolutionised respiratory outcomes and survival in those born extremely preterm. However, the impact of further technological and clinical care practice changes on broader outcomes requires ongoing review. Comparative cohort studies and data from collaborative networks are important tools to review the effect of practice changes. Comparative analysis of two New Zealand very low birthweight cohorts born in 1986 and 1998–1999 showed improvements in survival, oxygen dependency at 36 weeks, intraventricular haemorrhage (IVH) and retinopathy of prematurity (ROP) in the latter era.[1] The United Kingdom EPICure Studies compared survival and morbidity for infants of 22–25 weeks gestation born in 1995 and 2006. In the more recent cohort, more infants born at 24–25 weeks gestation survived, but with less neurodevelopmental impairment.[2] In contrast, a Canadian Neonatal Network study of infants born at <29 weeks gestation in 1996–1997 and 2006–2007 showed no mortality difference but increased chronic lung disease in the later period.[3]

MRI of the preterm brain has been under study as a tool for predicting neurodevelopmental outcome since the 1990s. Qualitative measures and detailed regional volumes have been reported and outcomes have been assessed from birth to adolescence.[4,5,6,7,8] Brain growth is broadly affected

by the in-utero environment and postnatal care including nutrition and hypoxic injury. More recently, simple brain metrics have been identified as a measure of brain growth encompassing the important motor cortex.[6,9,10] Their utility requires further assessment.

This study reviews local changes in clinical care and in-hospital morbidity, including brain metrics at term and neurodevelopment at two years in two cohorts of extremely preterm neonates born ten years apart in New Zealand and considers network data, where comparable, for regional context.

Methods

The study comprised two convenience cohorts of infants born before 28 weeks gestation. Stillbirths and delivery room deaths were excluded. The historical cohort (n=48, 96% recruitment) included consecutive infants with gestation <28 weeks from a larger preterm (<33 weeks gestation) sample born 1998–2000 at Christchurch Women's Hospital and enrolled in a prospective longitudinal study of neurological consequences of prematurity.[4] One infant was excluded as no MRI brain scan was performed. The contemporary cohort (n=40, 67% recruitment) comprised consecutive infants enrolled in the Benefits Of Oxygen Saturation Targeting (BOOST)-NZ trial from 2007–9,[11] whose parents gave separate consent for cranial MRI scans at term equivalent. One infant was excluded due to agenesis of corpus callosum, leaving 39 for analysis. The aim was to recruit 100 infants to have MRI scans but because of logistical issues this sub-study was terminated when 40 infants had been scanned in three centres (Christchurch 27, Auckland 7, Dunedin 6).

Data were collected on demographic variables, perinatal factors, clinical care and outcomes by chart review. Serial cranial ultrasounds were performed in addition to brain MRI at term equivalent age (47/47 historical cohort on 1.5T scanner, 23/39 contemporary cohort on 3T scanner). MRI scans were reviewed by two neuroradiologists (RK, SW) blinded to the clinical condition of the infant. Brain metric measures (biparietal, bifrontal, transcerebellar distance), adjusted for gestational age at the time of scanning,[12] were undertaken for infants in the historical cohort by HK and the contemporary cohort by SW and RK. A detailed neurodevelopment assessment at two years categorised children as normal, mild, moderate or severe delay. This included a Bayley Scales of Infant Development assessment, however the raw scores have not been compared as the tool changed from Bayley II to III between cohorts. National Ethics Committee approved both studies. All parents gave written informed consent.

Clinical data have been compared with data from the Australian and New Zealand Neonatal Network (ANZNN), which has prospectively collected data on all high risk infants, admitted to the 27 regional neonatal intensive care units (NICUs) since 1995 including New Zealand level 2 units from 1999.

Statistical analysis

Between group differences were tested for statistical significance using chi square test of independence for comparison of percentages, Poisson regression for comparison of count data, and t-test for independent samples for comparison of mean scores for continuous data. Effect size estimates were summarised by mean or percentage difference in outcome between groups with associated 95% confidence interval. The study had 80% power at α=0.05 to detect a difference in means in excess of 0.61 standard deviations suggesting the study had adequate power to detect moderate to large effect sizes.

Results

Basic demographic and perinatal characteristics (Table 1)

Percentage survival of all eligible infants admitted to the Christchurch unit was 71.6 (48/67) for the historical cohort and 80 (40/48) (NS) for the contemporary cohort. ANZNN 1999 survival to discharge for infants admitted at 23–27 weeks was 75.3% and 2008 survival to discharge for infants admitted at 24–27 weeks was 81.7%.[13] There were seven infants born at 23 weeks in the historical cohort and none in the contemporary cohort. An appendix details our analysis excluding these 23 week

Table 1: Basic demographic and perinatal characteristics.

Measure	Historical cohort n=47	Contemporary cohort n=39	Mean/ percentage difference (95%CI)	P value
Mean (SD) gestation	26.0 (1.4)	26.1 (1.1)	0.14 (-0.41, 0.69)	0.62
Mean (SD) birth weight g	804 (237)	888 (165)	84 (-4, 172)	0.07
Mean (SD) birth weight z score	-0.54 (1.18)	-0.16 (0.86)	0.38 (-0.06, 0.82)	0.10
Mean (SD) birth head circumference z score	-1.09 (1.15)	-0.47 (1.11)	0.61 (0.13, 1.09)	<0.05
% Small for gestation (weight z score < -2SD)	19.2	5.1	-14.0 (-27.9, 0.1)	0.053
% Male	42.6	51.3	8.7 (-12.0, 28.5)	0.42
% Singleton	76.6	87.2	10.6 (-6.4, 26.2)	0.21
Ethnicity (%) European Maori Pacific	 87.2 4.3 2.1	 74.4 15.4 5.1	 -12.9 (-29.7, 3.8) 11.1 (-1.8, 25.8) 3.0 (-6.7, 14.8)	 0.27
% Any antenatal steroids	91.5	71.8	-19.7 (-36.1, -3.4)	<0.05
% Complete antenatal steroids †	42.5	41.0	-1.5 (-21.4, 18.8)	0.88

† Defined as two doses of betamethasone 24 hours apart with the last dose > 24 hours and < 7 days before delivery.

infants. Mean gestation was 26 weeks for both cohorts, with 45% in the historical cohort and 46% in contemporary cohort born ≤25weeks. There was no significant difference in mean birth weight, however mean birth weight z score was significantly less when 23-week gestational age infants were excluded from the historical cohort. The percentage of infants receiving any antenatal steroids was lower in the contemporary cohort, but the proportion of infants who received a complete course was not significantly different.

Respiratory support (Table 2)

There was a small but significant decrease in mean number of surfactant doses received. There was no significant

Table 2: Respiratory Support.

Measure	Historical cohort n=47	Contemporary cohort n=39	Mean/ percentage difference (95%CI)	P value
Mean (SD) doses surfactant	1.9 (0.9)	1.4 (0.8)	-0.47 (-0.83, -0.10)	<0.05
Mean(SD) days positive pressure ventilation	14.0 (17.4)	11.4 (13.2)	-2.6 (-9.2, 4.0)	0.41
Mean(SD) days high frequency ventilation	8.0 (14.2)	2.7 (6.9)	-5.3 (-10.2, -0.5)	<0.05
Mean (SD) CPAP/BIPAP days	32.2 (17.3)	47.9 (25.1)	15.7 (6.7, 24.7)	<0.001
Mean (SD) total days respiratory support*	46.2 (22.9)	59.2 (30.8)	13.0 (1.7, 24.3)	<0.05
% Oxygen or respiratory support at 36 weeks	61.7	38.5	-23.2 (-41.7, -2.1)	<0.05
% Postnatal dexamethasone	14.9	15.4	0.5 (-14.7, 16.7)	0.94
Mean (SD) total dose dexamethasone mg/kg/ course	3.6 (1.9)	1.2 (0.5)	-2.4 (-4.0, -0.8)	<0.05
% Caffeine started within 48 hours of birth	51.1	71.8	20.7 (0.0, 38.8)	0.05

* Total days on any ventilation/CPAP/BIPAP/High Flow Oxygen

difference in mean days on any positive pressure ventilation, however mean days on high frequency ventilation (HFV) fell. This was insignificant if infants born at 23 weeks were excluded.

CPAP or BIPAP days increased significantly, accounting for increased total days on respiratory support. The rate of chronic lung disease (CLD), defined as oxygen dependency or respiratory support at 36 weeks was significantly lower in the contemporary cohort, but non-significant if those born at 23 weeks were excluded. Among those born <26 weeks, rates of CLD had nearly halved (90% versus 47%). The 1999 ANZNN incidence of CLD for infants 24–27 weeks gestation was 52.2%[7] and 36.6% in 2008.[13] The proportion of infants receiving postnatal steroids did not change, although total dose fell significantly. All infants in both cohorts received caffeine, but it was commenced significantly earlier in the contemporary cohort. This was non-significant with the exclusion of 23 week gestation infants.

Thermoregulation, initial physiological stability and ROP (Table 3)

Thermoregulation (Table 3)

Mean admission temperature was significantly lower in the historical cohort, 79% versus 44% having admission temperatures <36.5°C. No infants in the historical cohort had admission temperatures >37.4°C, versus 13% in the contemporary cohort. CRIB (Clinical Risk Index in Babies) scores[14] were significantly improved in the contemporary cohort. The proportion of infants receiving early inotropic support dropped significantly.

Red cell transfusion use (Table 3)

There was a significant decrease in number of blood transfusions and total volume of red cells transfused in the later cohort, however these did not reach significance once those born at 23 weeks were excluded.

Retinopathy of prematurity (ROP) (Table 3)

There was a significant drop in any retinopathy and no infants with stage 3 or more in the contemporary cohort. This difference persisted when excluding those born at 23 weeks in the historical cohort. For infants of 24-27 weeks, the ANZNN rates of any retinopathy were 51% in 1999 and 59% in 2008, and for stage 3 or more were 13% and 12% respectively.[13]

Table 3: Thermoregulation and initial physiological stability and ROP.

Measure	Historical cohort n=47	Contemporary cohort n=39	Mean/ percentage difference (95%CI)	P value
Mean(SD) admission temperature	35.9 (0.7)	36.5 (0.7)	0.6 (0.3, 0.9)	<0.001
Mean (SD) CRIB score	5.4 (3.1)	3.1 (2.2)	-2.3 (-3.5, -1.1)	<0.001
% Requiring inotropic support	55.3	28.2	-27.1 (-44.8, -6.1)	<0.05
Mean (SD) number of red cell transfusions	7.1 (5.1)	4.8 (3.3)	-2.3 (-4.2, -0.4)	<0.05
Mean (SD) total red cell transfusion volume (ml/kg)	96.2 (65.9)	70.4 (50.3)	-25.8 (-51.0, -0.6)	<0.05
% any retinopathy of prematurity	66.0	28.2	-37.8 (-54.4, -16.6)	<0.001
% stage 3 or more retinopathy	21.3	0.0	-21.3 (-34.9, -8.4)	<0.005

CRIB score: clinical risk index for babies score

Table 4: Nutrition and Growth.

Measure	Historical cohort n=47	Contemporary cohort n=39	Mean difference (95%CI)	P value
Mean(SD) parenteral protein maximum g/kg/d	2.9 (0.3)	3.8 (0.4)	0.84 (0.69, 0.99)	<0.0001
Mean (SD) days to 3g/kg/d or maximum parenteral protein	5.4 (2.6)	4.3 (1.6)	-1.2 (-2.1, -0.3)	<0.01
Mean (SD) parenteral lipids maximum g/kg/d	2.2 (0.5)	3.0 (0.1)	0.82 (0.66, 0.97)	<0.0001
Mean (SD) days to 3g/kg/d parenteral lipids	7.1 (4.9)	4.1 (3.0)	-3.0 (-4.7, -1.2)	<0.001
Mean (SD) days to first enteral feed (any milk)	3.4 (3.2)	2.0 (1.5)	-1.4 (-2.5, -0.3)	<0.005
Mean days (SD) to full enteral feeds (150ml/kg/day)	17.3 (11.5)	16.5 (16.2)	-0.8 (-6.8,5.1)	0.74
Mean (SD) days to commence fortifier	19.3 (12.1)	16.8 (6.7)	-2.5 (-6.8,1.8)	0.20
% Exclusively / fully breastmilk feeding at discharge	19.2	38.5	29.6 (9.6, 47.0)	<0.05
% Fully Formula fed at discharge	46.8	30.8	-16.0 (-34.6, 4.6)	0.13
Mean (SD) weight z score 42 days	-1.30 (1.09)	-0.53 (0.99)	0.77 (0.32, 1.21)	<0.001
Mean (SD) weight z score 36 weeks	-0.90 (1.22)	-0.39 (0.97)	0.51 (0.04, 0.98)	<0.05
Mean (SD) weight z score difference birth to 42 days	-0.76 (0.78)	-0.36 (0.87)	0.40 (0.05, 0.75)	< 0.05
Mean (SD) weight z score difference birth to 36 weeks	-0.36 (1.11)	-0.22 (0.95)	0.14 (-0.30, 0.58)	0.55
Mean (SD) weight z score difference 42 days to 36 weeks	0.40 (0.87)	0.14 (0.72)	-0.26 (-0.60, 0.08)	0.14
Mean (SD) length z score 36 weeks	-1.94 (1.72)	-1.26 (1.49)	0.68 (-0.04, 1.41)	0.07†
Mean (SD) head circumference z score 42 days	-1.42 (1.53)	-1.45 (1.06)	-0.03 (-0.60, 0.54)	0.92
Mean (SD) head circumference z score 36 weeks	-0.72 (1.23)	-0.69 (1.14)	0.03 (-0.48, 0.54)	0.90

† No comparison could be made from birth to 36 weeks due to the high number of infants missing initial length in the historical cohort

Nutrition and growth (Table 4)

Significant improvements were evident in the mean number of days to first enteral feeds, while days to full enteral feeds and commencing milk fortifier were similar. The contemporary cohort received higher parenteral protein and lipid grams/kg and experienced a significantly shorter time to achieve target protein and lipid levels. Improvements in weight were achieved in the first 6 weeks. However, if infants born at 23 weeks were excluded, neither days to target protein intake or weight gain in the first 6 weeks were significant. We noted improved z scores at 36 weeks for weight (but not if those born at 23 weeks were excluded) but not length or head circumference in the contemporary cohort. Breastfeeding rates at discharge were significantly better in the contemporary group.

Cranial Ultrasound and MRI findings (Table 5)

Two infants in the historical cohort had missing head ultrasound scans. IVH of any grade occurred in 19.1% in the historical cohort and 35.9% in the contemporary group (%difference 16.8, 95% CI -2.0, 34.7). One infant in the historical cohort and 3 in the contemporary cohort had ≥ grade 3 IVH with only one infant in the historical cohort

Table 5: MRI Brain Metrics (adjusted for post conceptual age at MRI).

Measure	Historical cohort n=47	Contemporary cohort n=39	Mean difference unadjusted (95%CI) P value	Mean difference adjusted (1) P value	Mean difference adjusted (2) P value
Mean (SD) bifrontal diameter mm	59.2 (5.0)	65.9 (4.7)	6.7 (4.6, 8.8) <0.0001	4.7 (2.2, 7.1) <0.001	4.9 (2.7, 7.0) <0.001
Mean (SD) biparietal diameter mm	73.7 (5.5)	79.3 (5.1)	5.6 (3.3, 7.9) <0.0001	3.2 (0.8, 5.7) <0.05	3.3 (1.1, 5.5) <0.005
Mean(SD) transcerebellar diameter mm	50.6 (3.9)	52.8 (3.0)	2.2 (0.7, 3.7) <0.01	0.6 (-1.0, 2.2) p=0.47	0.7 (-0.8, 2.2) p=0.34
Neurodevelopmental outcome at 2 years corrected (%)					
No impairment	33.3	68.6	35.3 (13.2,52.8)		
Mild impairment	46.7	25.7	-21.0 (-39.3, 0.0)		
Moderate/severe impairment	20.0	5.7	-14.3 (-28.7, 1.5) <0.01*		

*p-value for the test of the difference in the distribution of neurodevelopmental scores across the two groups

having hydrocephalus. Periventricular leukomalacia was detected in 4 infants in the historical cohort and 3 in the contemporary cohort.

Evaluation using cranial MRI at near term equivalent age, with brain metrics adjusted for age at MRI, revealed significant increases in bifrontal diameter, biparietal diameter and transcerebellar diameter in contemporary cohort. Regression analysis identified birth demographics (gestation, birth weight and head circumference z score, gender, SGA, antenatal steroids), care provision factors (ventilation, CRIB, caffeine, inotropes, dexamethasone) and outcome measures (oxygen at 36 weeks, ROP, growth at 42 days and 36 weeks) for adjustment as a whole and for individual brain metrics. Factors assessed as nonsignificant were CRIB, caffeine, days of ventilation, inotropes, ROP. The observed differences in bifrontal and biparietal diameter were only partially explained by covariate adjustment. Findings were similar when babies who were small for gestational age were excluded, both before and after covariate adjustment.

Adjustment (1) includes all covariates considered: gestation, birth head circumference z score, gender, SGA, antenatal steroids, inotropes, dexamethasone, weight z score at 42 days, weight z score change birth to 42 days, CLD, length z score at 36 weeks.

Adjustment (2)—a reduced/refined set of covariates for each outcome:

For BFD: gestation, birth head circumference z score, gender, CLD, length 36 weeks z score

For BPD: birth head circumference z score, gender, CLD, length 36 weeks z score

For TCD: birth head circumference z score, dexamethasone, weight change birth-42 days z score, CLD, length 36 weeks z score

Neurodevelopment Score

1. **No impairment**: Standardised developmental test 1 to -1 SD, normal clinical examination
2. **Mild**: Standardised developmental test -1 to -2 SD, mild cerebral palsy (Level 1 on Gross Motor Functional Classification System), neurodevelopmental abnormality or developmental delay on clinical assessment.

Table 6: Clinical practice improvements 1998–2009.

Technological	Clinical care
• Plastic bags/wraps at delivery • Improved oxygen saturation monitors and motion sensing probes • Increased use of non-invasive respiratory support • Porcine surfactant • Air-oxygen blenders • Ventilators with improved synchronisation and volume targeting • Bedside echocardiography • Developmentally supportive unit environment	• Lower oxygen at resuscitation • Improved oxygen saturation targeting • Higher protein and lipids targets for Total Parenteral Nutrition • Haemoglobin based transfusion • Developmentally supportive care • Breast milk feeding support

3. **Moderate**: Standardised developmental test -<2 to -3 SD, moderate cerebral palsy + (Level 2 or 3 on GMFCS). Bilateral hearing aids or unilateral/bilateral cochlear implant
4. **Severe**: Standardised developmental test >-3 SD, bilateral blindness (<6/60 in better eye), severe cerebral palsy (Level 4 or 5 on GMFCS)

Discussion

Neonatal intensive care has significantly improved the survival of very premature infants. Our ongoing challenge is to minimise morbidity and disability. A number of neonatal practice changes were introduced between our cohorts. These changes can be categorised into technological and clinical care changes (Table 6). This comparative cohort study demonstrates that between 1998 and 2009 we have seen improvements in initial physiological stability of infants born extremely preterm, decreases in rates of CLD and ROP, and improvements in both somatic and brain growth.

Cold stress can prove fatal to premature newborns.[15] Randomised controlled trials[16] demonstrate the use of polyethylene plastic wraps in the delivery room improves initial thermal stabilisation. It is likely the introduction of these wraps as standard management for extremely preterm infants contributed to improved admission temperatures at the expense of a modest increase in hyperthermia. Temperature on admission was the main contributor to improved CRIB score as well as blood pressure in the first 12 hours.

In the past, inotropic support in the first 24 hours was commonly used despite no definition of hypotension for preterm infants and no clinical outcome-based evidence of the benefit of such treatment.[17] Premature infants often have low systemic blood flow within the first 24 hours but this may not correlate with blood pressure, and maintaining tissue perfusion is clearly more complex than simply maintaining blood pressure.[18] Practice has shifted from administering inotropes when blood pressure falls below a cut off value for the mean BP equal, to the gestational age in the first 24 hours with decisions now influenced by functional echocardiography.[19]

Infants given poractant alfa (Curosurf, Chiesi Pharmaceuticals, Parma, Italy) surfactant compared to beractant (Survanta,Ross Laboratories, Colombus, Ohio) wean from oxygen more rapidly, need fewer subsequent doses and have lower mortality.[20] Our units changed practice accordingly between these époques. Surfactant is now given earlier, combined with earlier extubation to CPAP. Between study periods there was a decline in HFV days but no decrease in total days' positive pressure ventilation. Infants born at 23 weeks in the historical cohort did contribute to, but not completely explain, this difference. Research has shown HFV offers little advantage over conventional ventilation.[21] Delivery of conventional ventilation has also improved following introduction of flow sensors for synchronisation, targeted volume ventilation and better ventilation graphics.

Use of non-invasive modes of respiratory support (CPAP, BIPAP) increased while the incidence of CLD fell significantly, with improvements primarily in infants <26weeks. Different definitions of CLD

affect comparisons between studies and an oxygen dependency-based definition may be affected by different oxygen saturation targets. Between these two time periods our units adopted CPAP delivered via a Neopuff™ device (Fisher and Paykel Healthcare, Auckland, New Zealand) immediately after birth. Air-oxygen blenders were introduced into delivery rooms, facilitating lower inspired oxygen for resuscitation, in line with current evidence.[22]

It is not clear why overall antenatal steroid coverage fell (although not in complete steroid courses) as there was no change in clinical policy between the cohorts. The proportion of infants receiving postnatal steroids did not change between our cohorts despite the established link with adverse neurodevelopmental outcomes,[23] although the total dose given was lower in the contemporary cohort.

Premature infants suffer anaemia from intrinsic and extrinsic factors. The Premature Infants in Need of Transfusion (PINT) trial[24] showed no significant difference in death or major morbidity in restrictive versus liberal haemoglobin thresholds. We saw transfusion frequency and volumes fall significantly as our units adopted judicious phlebotomy and targeted transfusion protocols.

There have been gains in some but not all growth parameters. Improvements in total parenteral nutrition (TPN) reflect evidence that preterm infants need more protein and lipid to optimize growth.[25] Trophic enteral feeding was introduced earlier following reports on the safety of this practice.[26] The benefits of breast milk feeding for preterm infants are well established [27] and over this time we appointed more lactation consultants, strengthened breastfeeding education and provided a more supportive environment. Growth gains in our contemporary cohort were attained in the first 6 weeks, while there is still room for improvement in head growth.

Risk of retinopathy of prematurity (ROP) is inversely related to gestational age and birth weight. Infants born at 23 weeks and lower mean birth weight in the historical cohort contributed to the difference in ROP. However the decrease in ROP was concurrent with improvement in postnatal growth, lowered inspired oxygen for resuscitation and protocols for oxygen saturation targeting.

Children born prematurely are at increased risk of poor brain growth and associated poorer cognitive outcomes in childhood.[5] MRI brain metrics offer a simple tool to assess brain growth and have been shown to be affected by birth weight z score and variables reflecting disease severity such as inotropic support, duration of ventilation and parenteral nutrition.[12] Despite no improvement in head circumference, the contemporary cohort had significantly better brain bifrontal, biparietal and transcerebellar diameters. In our analysis, the difference in brain metrics after adjustment was significant for both bifrontal diameter and biparietal diameter, the latter encompassing the motor cortex area. Head circumference was frequently poor initially followed by rapid growth and head size at 36 weeks did not correlate with brain metrics. The head circumference z score remained non-significantly different between the cohorts at two years. This is at variance with other cohorts where HC at 2 was correlated with MRI volumes.[7] Further research with larger cohorts is needed to confirm the utility of brain metrics as a simple measure to assist in the understanding of neonatal intensive care factors affecting preterm brain growth, and to define the clinical utility of brain metrics and its correlation with neurodevelopmental outcomes.

Weaknesses of this study include the use of convenience cohorts, small sample size, differences in the quality of cranial MRI scans, and differences in practice between units. The historical cohort also included infants born at 23 weeks, the threshold of viability.[28,29] Resuscitating infants under 23 weeks has been discouraged by some consensus guidelines.[30] Although 3T scanners offer higher resolution for detecting white matter injury, brain metrics measurements would be expected to be comparable. We did not perform assessment of intraobserver or interobserver variability between brain metrics. Other studies have reported acceptable intraclass correlation coefficients.[12] Impact of gender on brain metrics showed female gender was associated with smaller measurements however this was included in the adjustment analysis.

The contemporary cohort was part of an oxygen saturation targeting trial which randomly assigned to a higher or lower target saturation level. However there was no difference in any outcomes between the BOOST-NZ groups at hospital discharge.[11] Although generally care provided in all units was similar, larger studies have identified significant centre differences in outcomes[3] and this may have had an impact on our findings. This study reinforces the value of neonatal networks and multi-centre collaborations to improve the quality of data and national guidelines where there is strong evidence to improve consistency of data.

Conclusion

Between 1998 and 2009 we observed a number of changes in neonatal care, some technological, others involving clinical practice; some very simple, others complex. The outcome improvements we observed were reduced rates of CLD and ROP, improved body growth at 36 weeks, better brain growth by term and improved neurodevelopment at two years.

Competing interests:
Dr Harris, Dr Austin, Dr Horwood, Dr Spencer and Dr Darlow report grants from Cure Kids Foundation, grants from New Zealand Lottery Grants Board, grants from NZ Health Research Council, grants from NZ Neurological Foundation during the conduct of the study. Dr Broadbent reports grants from NZ Health Research Council during the conduct of the study.

Acknowledgements:
We would like to thank Hiroyuki Kidokoro, Department of Pediatrics, Nagoya University Graduate School of Medicine, Japan for assessing brain metrics data of the historical cohort and Professor Terrie Inder, Department of Pediatric Newborn Medicine Brigham & Women's Hospital, Boston USA, who established the historical cohort and for her support in ongoing studies.

Funding:
The 1998–2000 cohort study received funding from The Lottery Grants Board, Neurological Foundation and the Health Research Council of New Zealand.
The 2006–2009 cohort were infants enrolled in the BOOST NZ trial which was funded by the New Zealand Health Research Council (Project Grant 04-145). MRI scans were funded by a project grant from the NZ Child Health Research Foundation (Cure Kids).

Author information:
Sarah L Harris, Neonatologist, Neonatal Service, Christchurch Women's Hospital, Department of Pediatrics, University of Otago, Christchurch; Nicola C Austin, Neonatologist, Associate Professor, Neonatal Service, Christchurch Women's Hospital, Department of Pediatrics, University of Otago, Christchurch, Malcolm Battin, Neonatologist, Newborn Services, Auckland City Hospital, Auckland; Roland Broadbent, Neonatologist, Dunedin Neonatal Unit, Dunedin; John Horwood, Statistician, Associate Professor, Department of Psychological Medicine, University of Otago, Christchurch; Ross Keenan, Neuroradiologist, Canterbury Radiology Group, Christchurch; Scott Wells, Neuroradiologist, Canterbury Radiology Group, Christchurch; Carole Spencer, Research Nurse, Neonatal Service, Christchurch Women's Hospital, Christchurch; Patricia Graham, Research Nurse, Neonatal Service, Christchurch Women's Hospital, Department of Pediatrics, University of Otago, Christchurch; Lianne J Woodward, Professor of Pediatrics and Psychology, Department of Pediatric Newborn Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, US; Brian A Darlow, Neonatologist, Professor, Neonatal Service, Christchurch Women's Hospital, Department of Pediatrics, University of Otago, Christchurch.

Corresponding author:
Sarah Harris, Neonatal Unit, Christchurch Women's Hospital, Private Bag 4711, Christchurch, New Zealand.
sarah.harris@cdhb.health.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6976

REFERENCES:

1. Darlow BA, Cust AE, Donoghue DA, on behalf of the Australian and New Zealand Neonatal Network (ANZNN). Improved outcomes for very low birthweight infants: evidence from New Zealand national population based data. Arch Dis Child Fetal Neonatal Ed.2003;88:F23–F28.
2. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006:the EPICure studies. BMJ. 2012;345:e7961 doi:10.1136/bmj.e7961.
3. Shah PS, Sankaran K, Aziz K, Allen AC, Seshia M, Ohlsson A et al; Canadian Neonatal Network. Outcomes of preterm infants <29 Weeks gestation over 10-year period in Canada: a cause for concern? J Perinatol. 2012;32(2):132–8.
4. Woodward LJ, Moor S, Hood KM, Champion PR, Foster-Cohen S, Inder TE et al. Very preterm children show impairments across multiple neurodevelopmental domains by age 4 years. Arch Dis Child Fetal Neonatal Ed. 2009;94(5):339–44. doi:10.1136/adc.2008.146282.
5. Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics. 2003;111(5 Pt 1):939–48.
6. Woodward LJ, Clark CAC, Bora S, Inder TE. Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. PLoS ONE 2012; 7(12):e51879. doi:10.1371/journal.pone.0051879.
7. Cheong JL, Hunt RW, Anderson PJ, Howard K, Thompson DK, Wang HX et al. Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. Pediatrics 2008;121(6):e1534–40.
8. Cheong JL, Anderson PJ, Roberts G, Burnett AC, Lee KJ, Molloy C et al. Contribution of brain size to IQ and educational underperformance in extremely preterm adolescents. PLoS ONE 2013;8(10):e77475. doi:10.1371/journal.pone.0077475
9. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. Am J Neuroradiol 2013;34(11):2208–14.
10. Kidokoro H, Anderson PJ, Doyle LW, Woodward LJ, Neil JJ, Inder TE. Brain injury and altered brain growth in preterm infants: predictors and prognosis. Pediatrics 2014;134(2):e444–53.
11. Darlow BA, Marschner SL, Donoghoe M, Battin MR, Broadbent RS, Elder MJ et al. Benefits of Oxygen Saturation Targeting – New Zealand Collaborative Group. Randomized controlled trial of oxygen saturation targets in very preterm infants: two year outcomes. J Pediatr. 2014;165(1):30–35.
12. Tich S, Anderson PJ, Hunt RW, Lee KJ, Doyle LW, Inder TE. Neurodevelopmental and perinatal correlates of simple brain metrics in very preterm infants. Arch Pediatr Adolesc Med. 2011;165(3):216-22. doi:10.1001/archpediatrics.2011.9.
13. ANZNN (Australian and New Zealand Neonatal Network). Report of the Australian and New Zealand Neonatal Network 1999, and Report of the Australian and New Zealand Neonatal Network 2008 and 2009. Sydney: ANZNN https://npesu.unsw.edu.au/data-collection/australian-new-zealand-neonatal-network-anznn#Previous Reports ANZNN
14. The International Neonatal Network. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. Lancet. 1993;342:193–98.
15. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR; EPICure Study Group. The EPICure Study: Outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics. 2000;106(4):659–71.
16. McCall EM, Alderdice F, Halliday HL, Jenkins JG, Vohra S. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. Cochrane Database of Systematic Reviews. 2010, Issue 3. Art. No.: CD004210. doi:10.1002/14651858.CD004210.pub4.
17. Logan JW, O'Shea TM, Allred EN, Laughon MM, Bose CL, Dammann O et al; ELGAN Study Investigators. Early postnatal hypotension and developmental delay

at 24 months of age among extremely low gestational age newborns. Arch Dis Child Fetal Neonatal Ed. 2011;96(5):F321-8. doi: 10.1136/adc.2010.183335. Epub 2010 Dec 7.

18. Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. J Pediatr. 1996;129(4):506–12.
19. Kluckow M, Seri I, Evans N. Functional echocardiography: an emerging clinical tool for the neonatologist. J Pediatr. 2007;150(2):125–30.
20. Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar K; North American Study Group. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. Am J Perinatol. 2004; 21(3):109–19.
21. Cools F, Henderson-Smart DJ, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD000104. doi: 10.1002/14651858. CD000104.pub3.
22. Saugstad OD, Ramji S, Soll RF, Vento M. Resuscitation of Newborn Infants with 21% or 100% Oxygen: An Updated Systematic Review and Meta-Analysis. Neonatology. 2008;94(3):176–82 doi: 10.1159/000143397.
23. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. BMC Pediatr. 2001;1:1.
24. Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr. 2006;149(3):301-307.
25. Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol. 2007;31(2):48–55.
26. Martin CR, Brown YF, Ehrenkranz RA, O'Shea TM, Allred EN, Belfort MB et al; Extremely Low Gestational Age Newborns Study Investigators. Nutritional practices and growth velocity in the first month of life in extremely premature infants. Pediatrics. 2009;124(2):649–57. doi: 10.1542/peds.2008–3258.
27. American Academy of Pediatrics Policy Statement. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827–e841. doi: 10.1542/peds.2011–3552.
28. MacDonald H, American Academy of Pediatrics, Committee on Fetus and Newborn. Perinatal care at the threshold of viability. Pediatrics. 2002;110:1024–27.
29. Smith PB, Ambalavanan N, Li L, Cotten CM, Laughon M, Walsh MC et al; Generic Database Subcommittee; Eunice Kennedy Shriver National Institute of Child Health Human Development Neonatal Research Network. Approach to infants born at 22 to 24 weeks gestation: relationship to outcomes of more mature infants. Pediatrics. 2012;129(6):e1508–16.
30. Lui K, Bajuk B, Foster K, Gaston A, Kent A, Sinn J et al. Perinatal care at the borderlines of viability: a consensus statement based on a NSW and ACT consensus workshop. Med J Aust. 2006; 185(9):495–500.

Appendix

Supplementary tables showing group comparisons excluding seven infants from the historical cohort born at 23 weeks.

Table A1: Basic demographic and perinatal characteristics.

Measure	Historical cohort n=40	Contemporary cohort n=39	Mean/ percentage difference (95%CI)	P value
Mean (SD) gestation	26.4 (1.0)	26.1 (1.1)	0.3 (-0.2, 0.8)	0.22
Mean (SD) birth weight g	835 (242)	888 (165)	53 (-38, 145)	0.25
Mean (SD) birth weight z score	-0.65 (1.22)	-0.16 (0.86)	0.49 (0.02, 0.95)	<0.05
Mean (SD) birth head circumference z score	-1.11 (1.21)	-0.47 (1.11)	0.64 (0.13, 1.15)	<0.05
% Small for gestation (z score < -2SD)	22.5	5.1	-17.4 (-32.8, -1.8)	<0.05
% Male	40.0	51.3	11.3 (-10.3, 31.5)	0.31
% Singleton	72.5	87.2	14.7 (-3.3, 31.6)	0.10
Ethnicity (%) European Maori Pacific	 85.0 5.0 2.2	 74.4 15.4 5.1	 -10.6 (-28.0, 7.3) 10.4 (-3.7, 25.2) 2.7 (-8.4, 14.6)	 0.40
% Any antenatal steroids	92.5	71.8	-20.7 (-37.0, -3.7)	<0.05
% Complete antenatal steroids †	45.0	41.0	-4.0 (-24.6, 17.2)	0.72

† Defined as two doses of betamethasone 24 hours apart with the last dose > 24 hours and < 7 days before delivery.

Table A2: Respiratory support.

Measure	Historical Cohort n=40	Contemporary Cohort n=39	Mean/Percentage Difference (95%CI)	P value
Mean (SD) doses surfactant	1.8 (0.8)	1.4 (0.8)	-0.38 (-0.75, -0.01)	<0.05
Mean(SD) days positive pressure ventilation	9.5 (13.5)	11.4 (13.2)	1.9 (-4.0, 7.8)	0.48
Mean(SD) days high frequency ventilation	4.9 (9.5)	2.7 (6.9)	-2.2 (-5.9, 1.5)	0.14
Mean (SD) CPAP/BIPAP days	32.1 (18.0)	47.9 (25.1)	15.8 (6.0, 25.3)	<0.005
Mean (SD) total days respiratory support*	41.6 (21.5)	59.2 (30.8)	17.6 (5.9, 29.3)	<0.005
% Oxygen or respiratory support at 36 weeks	57.5	38.5	-19.0 (-38.5, 2.8)	0.09
% Postnatal dexamethasone	7.5	15.4	7.9 (-6.9, 23.1)	0.27
Mean (SD) total dose dexamethasone mg/kg/course	3.2 (1.3)	1.2 (0.5)	-2.0 (-3.2, -0.8)	<0.05
% Caffeine started within 48 hours of birth	60.0	71.8	11.8 (-8.9, 31.1)	0.27

* Total days on any ventilation/CPAP/BIPAP/High Flow Oxygen

Table A3: Clinical care and short term outcomes.

Measure	Historical Cohort n=40	Contemporary Cohort n=39	Mean/Percentage Difference (95%CI)	P value
Mean(SD) admission temperature	36.0 (0.6)	36.5 (0.7)	0.5 (0.2, 0.8)	<0.005
Mean (SD) CRIB score	4.9 (3.1)	3.1 (2.2)	-1.8 (-3.0, -0.6)	<0.005
% Requiring inotropic support	50.0	28.2	-21.8 (-40.6, -0.3)	<0.05
Mean (SD) number of red cell transfusions	5.8 (4.0)	4.8 (3.3)	-0.93 (-2.56, 0.70)	0.26
Mean (SD) total red cell transfusion volume (ml/kg)	79.4 (53.1)	70.4 (50.3)	-9.0 (-31.8, 13.8)	0.44
% any retinopathy of prematurity	60.0	28.2	-31.8 (-49.8, -9.9)	<0.005
% stage 3 or more retinopathy	20.0	0.0	-20.0 (-34.8, -6.9)	<0.005

CRIB score: clinical risk index for babies score

Table A4: Nutrition and Growth.

Measure	Historical Cohort n=40	Contemporary Cohort n=39	Mean Difference (95%CI)	P value
Mean(SD) parenteral protein maximum g/kg/d	2.9 (0.3)	3.8 (0.4)	0.84 (0.68, 1.00)	<0.0001
Mean (SD) days to 3g/kg/d parenteral protein	5.2 (2.7)	4.3 (1.6)	-0.9 (-1.9, 0.1)	0.06
Mean (SD) parenteral lipids maximum g/kg/d	2.2 (0.5)	3.0 (0.1)	0.79 (0.63, 0.95)	<0.0001
Mean (SD) days to 3g/kg/d parenteral lipids	6.8 (4.9)	4.1 (3.0)	-2.7 (-4.5, -0.9)	<0.001
Mean (SD) days to first enteral feed (any milk)	3.1 (3.3)	2.0 (1.5)	-1.1 (-2.2, -0.0)	<0.05
Mean days (SD) to full enteral feeds (150ml/kg/day)	16.6 (11.3)	16.5 (16.2)	-0.1 (-6.2, 6.0)	0.97
Mean (SD) days to commence fortifier	18.4 (11.8)	16.8 (6.7)	-1.6 (-5.9, 2.7)	0.43
% Exclusively / fully breastmilk feeding at discharge	20.0	38.5	18.5 (-1.6, 36.8)	0.07
% Fully Formula fed at discharge	45.0	30.8	-14.2 (-33.7, 7.0)	0.19
Mean (SD) weight z score 42 days	-1.26 (1.17)	-0.53 (0.99)	0.73 (0.25, 1.21)	<0.005
Mean (SD) weight z score 36 weeks	-0.89 (1.26)	-0.39 (0.97)	0.50 (-0.01, 1.01)	0.052
Mean (SD) weight z score difference birth to 36 weeks	-0.23 (1.05)	-0.22 (0.95)	0.01 (-0.42, 0.45)	0.98
Mean (SD) weight z score difference birth to 42 days	-0.60 (0.70)	-0.36 (0.87)	0.24 (-0.10, 0.59)	0.17
Mean (SD) weight z score difference 42 days to 36 weeks	0.38 (0.85)	0.14 (0.72)	-0.24 (-0.59, 0.11)	0.18
Mean (SD) length z score 36 weeks	-1.80 (1.81)	-1.26 (1.49)	0.54 (-0.24, 1.32)	0.18†
Mean (SD) head circumference z score 42 days	-1.32 (1.54)	-1.45 (1.06)	-0.13 (-0.71, 0.45)	0.67
Mean (SD) head circumference z score 36 weeks	-0.76 (1.28)	-0.69 (1.14)	0.07 (-0.47, 0.61)	0.79

† No comparison could be made from birth to 36 weeks due to the high number of infants missing initial length in the historical cohort

Table A5: MRI brain metrics (adjusted for post conceptual age at MRI).

Measure	Historical Cohort n=40	Contemporary Cohort n=39	Mean Difference (95%CI)	P value
Mean (SD) bifrontal diameter mm	59.4 (4.9)	65.9 (4.7)	6.5 (4.4, 8.6)	<0.0001
Mean (SD) biparietal diameter mm	74.1 (4.9)	79.3 (5.1)	5.2 (3.0, 7.4)	<0.0001
Mean(SD) transcerebellar diameter mm	51.0 (2.9)	52.8 (3.0)	1.8 (0.5, 3.1)	<0.01
Neurodevelopmental impairment - 2 years corrected (%)				
None	39.5	68.6	29.1 (6.2,48.0)	
Mild	44.7	25.7	-19.0 (-38.4, 2.9)	<0.05
Moderate/severe	15.8	5.7	-10.1 (-25.3, 5.3)	

Little risk of severe complications associated with Zika infection in New Zealand

Gareth J Parry, Matthew Peacey, Eric J Buenz

ABSTRACT

Zika virus infection has raised considerable concern in New Zealand, but the risks faced by most New Zealanders, while real, are quite small as New Zealand does not harbor the primary mosquito vector. Furthermore, in individuals with a competent immune system, the acute illness caused by Zika virus infection is generally mild. Serious complication associated with Zika virus infections include microcephaly and Guillain-Barré Syndrome. Pacific Island countries have reported cases of Zika virus infection and these climates support the mosquito vector. Thus, travelers to these areas are at risk of infection. New Zealand travelers returning from endemic areas have developed the illness associated with the virus, but the probability of autochthonous transmission in New Zealand is very small.

Zika infection typically results in a mild, unremarkable, viral infection

Zika virus infection causes a generally mild febrile illness similar to many acute viral infections.[1] The incubation period is unknown, but is likely a few days to two weeks. A pruritic maculopapular rash is common, as are arthralgias, myalgias, headache and conjunctivitis. Symptoms persist for a few days and resolve without treatment. Only about 20% of infected individuals are symptomatic and those with symptoms rarely seek medical attention. Death during the acute illness is rare and is restricted to the elderly or those with concomitant illnesses. None of the manifestations of the acute infection are sufficiently characteristic to enable a confident clinical diagnosis in patient seen in non-endemic area such as New Zealand, but a history of travel to an endemic area is a critical clue.[2]

During times of epidemic infection in endemic areas, the diagnosis is straightforward, but at other times or in non-endemic regions, such as New Zealand, a high index of suspicion is needed so that appropriate testing can be employed. In the earliest stages of infection, the presence of virus can be identified by reverse-transcriptase polymerase chain reaction (RT-PCR) with specific assays able to identify genetic sequences unique to the Zika virus and so distinguish from other endemic flavivurses such as Dengue. By the end of the first week of illness, IgM and neutralising antibodies can be measured, but they cross-react with the other flaviviruses, which do not seem to be associated with the same complications as Zika, making a specific serological diagnosis challenging.[3]

Zika virus similar to other viruses in mosquito-transmitted Flavivirus family

Zika virus is a positive-sense, single-stranded RNA virus approximately 11,000 nucleotides in length. The genome is encapsulated by the virus's structural proteins and enveloped in a host-derived membrane, 40 nm in diameter, modified with viral glycoproteins. The Zika virus is most closely related to the Spondweni virus, belonging to the Flavivirus genus and so is related to West Nile, yellow fever, Japanese encephalitis and dengue viruses. Like other arboviruses, Zika virus is maintained through a transmission cycle between host and vector.[4]

ISSN 1175-8716

Vector-mediated transmission occurs when Zika virus present in the saliva of mosquitoes is injected by blood-feeding females into the skin of the host. In humans, infection initially occurs via the interaction of the viral envelope protein with specific receptors of skin immune cells, including dermal fibroblasts, epidermal keratinocytes and immature dendritic cells.[5] The outcome of infection is determined by the interplay of viral proliferation and the resulting immune response. As seen with other Flavivirus epidemics, Zika virus has adapted to infect humans, reaching viral titres high enough to infect the mosquito vector, negating the need for a non-human host reservoir to maintain the transmission life-cycle.[6]

Recent phylogenetic analysis of the Zika virus shows three distinct lineages, two from Africa and one from Asia, sharing a common ancestor estimated to have emerged around 1920 (1892–1947). The emergence of the Asian lineage from Africa has subsequently led to the seeding of this Asian genotype across the Pacific and into the Americas.[7]

Mutations in the other members of the Flavivirus genus have resulted in their increased rate of spread and clinical severity, but the role viral mutation and population susceptibility have played in the spread of Zika virus is still unknown.[8] Changes in the glycosylation patterns of the structural E protein of Zika virus have been implicated in enhanced viral infectivity in certain mosquito vectors.[7] Recently it has been hypothesised that selective pressure has resulted in viral mutations adapting the codon usage for more efficient transcription of viral proteins in the human host.[9] This, in turn, could result in an increased viral titre allowing the spread of Zika virus from human host to mosquito vector to human host and the outbreak of Zika in human populations. As yet, with comparatively little sequence data, these reports do not conclusively demonstrate the spread of Zika virus is the result of virus mutation alone.

New Zealand Ministry of Health guidance for clinicians addressing potential Zika virus infection

The New Zealand Ministry of Health has provided a centralised resource on Zika virus infection for health professionals.[2] This resource provides an overview of Zika virus, guidance on dealing with Zika virus in pregnancy, sexual transmission of Zika virus, symptoms of Zika virus infection, and links to other resources global Zika virus resources.

Low probability of autochthonous (individual to individual) Zika virus transmission in New Zealand

Zika virus was first identified in Africa in 1947, but few cases of human disease were identified over the next six decades. Surveillance programs tracked its passage across to Asia and the Pacific but it was not until the last five years that it has invaded high-population areas such as Central and South America, and may have increased infectivity. This increase in viral fitness may be related to a mutation in the virus.[7,8] Despite this apparent increase in infectivity, the acute illness generally remains mild.

The *Aedes* genus of mosquitoes is the vector for Zika virus, with *A. aegypti* almost exclusively responsible for human transmission cycles. It is of concern that the virus has adapted to *A. albopictus*,[10] a much more widely distributed mosquito[6] which is found throughout tropical regions but also in the US and parts of Europe. It has been suggested that the *Aedes* genus is adapting to colder climates as yellow fever, another flavivirus infection transmitted by *Aedes*, was endemic across the US, at the time of the Revolutionary War. The presence of this flavivirus suggests that the requisite mosquito vector is capable of adapting to the North American climate.

The *Aedes* mosquito is not endemic in New Zealand, but our major trading partners Australia, the Pacific Islands and Southeast Asia harbor the mosquito. The New Zealand climate is capable of supporting a population of the *Aedes* mosquito and the mosquito is occasionally identified at the borders, so continuing vigilance is essential.[11] New Zealand had 57 confirmed human cases of Zika infection in 2014, 6 in 2015 and 11 through the end of January this year, coinciding with the spread across the Pacific, the Americas and elsewhere. There has been one case of Guillain-Barré syndrome associated with Zika infection in New Zealand. All cases were thought to have been contracted overseas.

The virus has been identified in human saliva and semen as well as blood, and direct human-to-human transmission is strongly suspected by sexual transmission,[12,13] by blood transfusion[14] and from infected mothers to their infants at parturition.[15] No transmission has been documented through saliva, but the World Health Organization has urged caution regarding kissing any potentially infected patient. The NZ Blood Service has instituted measures to minimize the risk of contracting Zika virus infection from transfusions. This includes routinely questioning donors about their recent travel history and not allowing people to donate blood for 28 days after leaving an endemic area.

Microcephaly a possible complication of Zika virus infection for infants in utero

While there are case reports of intrauterine infection with Zika virus and microcephaly,[16,17] a causal relationship between the infection and microcephaly has not been established.[18] Nonetheless, two epidemiologically-associated outbreaks of Zika virus and microcephaly have formed the basis for establishing this relationship,[6,19] and recent molecular data[20] further strengthen this correlation. A recent report[20] documented direct persistent viral infection of the brain of a fetus whose mother had become infected in the 13th week of pregnancy. Ultrasound showed the head circumference to be increasing normally at 14 and 21 weeks of pregnancy but thereafter, fetal growth and particularly head circumference dramatically slowed and the pregnancy was terminated at 32 weeks. Virus was identified in amniotic fluid and in brain tissue but not in other organs, suggesting strong neurotropism of the virus. Based on the strength of this association, the World Health Organization has issued a Public Health Emergency of International Concern[21] and guidelines have been developed for pregnant women to mitigate the risk of Zika virus infection during pregnancy.[22]

In the event that a link between Zika virus and microcephaly is established, questions such as the proportion of pregnancies with infection that lead to microcephaly, a potential mechanism of action, and the risk of microcephaly at specific stages of pregnancy will be important to address. In the meantime, New Zealand women should avoid pregnancy while travelling in endemic areas and, if pregnant, should avoid sexual contact with potentially infected partners since the virus can probably be transmitted sexually.

Guillain-Barré Syndrome (GBS) a complication of Zika virus infection

GBS is an acute paralytic illness that, in about 70% of cases, can be linked to an antecedent infection[23] or, in a single incident, vaccination, specifically the 1976 strain of influenza.[24] Although most cases follow an upper respiratory infection, the exact microbe is seldom identified. The most commonly identified antecedent infection is *Campylobacter jejuni*, a particularly common cause of acute gastroenteritis in New Zealand.[25] The worldwide incidence of GBS is 1.5–2.0 cases/100,000 annually although the incidence in New Zealand is higher, up to 2.9 cases/100,000/year, with the excess being entirely attributable to *C. jejuni* infection.[26] About 70% of GBS cases make a full motor recovery and about 5% die, with the remainder showing varying degrees of residual weakness.[23]

Several countries have noted a striking increase in the number of cases of GBS coincident with the spread of Zika virus infection throughout the Pacific and the Americas. French Polynesia in 2014 saw 73 cases of GBS in a population of 270,000, a 10–20-fold increase in GBS over that expected.[6] Brazil saw a 19% increase of GBS cases in 2015 compared to 2014. Similar increases have been seen in Mexico and several Central America countries including Ecuador, Guatemala and El Salvador. One report in the popular press noted a mortality rate of over 50% but this has not been confirmed by others and may represent the poor standard of care in impoverished areas that typically see most cases of Zika. The association between Zika virus infection and GBS does not prove that the association is causative; it is possible that some other infection has increased simultaneously. However, it seems highly likely that the Zika virus itself is causing these cases of GBS. At the moment little is known of the exact clinical and electrophysiological manifestations of GBS associated with Zika virus infection and more research is needed.

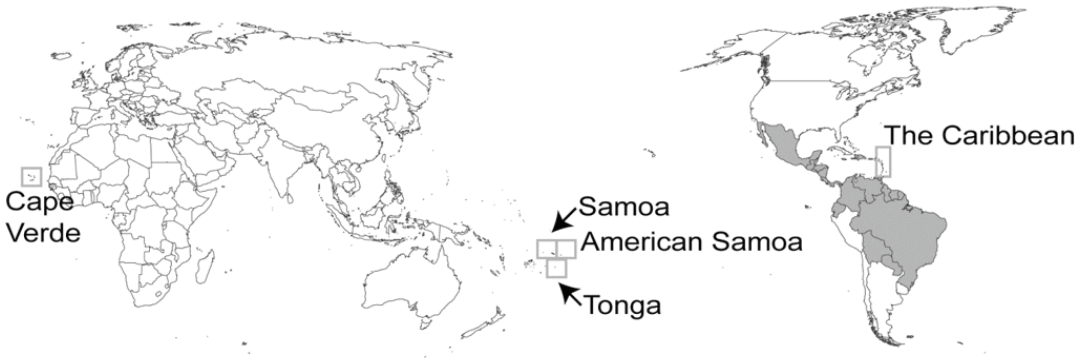
The exact mechanism whereby Zika might trigger GBS is unknown. The only established mechanism for any infection to trigger GBS is molecular mimicry of the glycolipids in the peripheral nerve with the surface lipo-oligosaccarides in *C. jejuni*[27] but this has not been established for other antecedent infections, including Zika virus. Research into the molecular sequence of Zika virus searching for homology with components of peripheral nerve axons or myelin will be important to determine this mechanism.

Treatment of GBS with plasma exchange[28] or intravenous immunoglobulin[29] improves speed of recovery but not degree of recovery or mortality which remains around 5%.[30] Treatment is most effective if initiated early, within a week of onset of weakness. Any individual returning to NZ from a Zika-endemic area with a febrile illness should be promptly evaluated for possible Zika infection and, if positive, carefully followed for signs of GBS so that early treatment can initiated if necessary.

Travelers returning to New Zealand most at risk of Zika virus complications

As the risk of autochthonous transmission of Zika virus in New Zealand is low, returning travelers to regions with active epidemics (Figure 1) are most at risk of infection. These patients will present with typical symptoms of a viral infection and the infection is generally self-limiting. Medical practitioners in New Zealand most need to be aware of the potential increased risk of post-infectious GBS which can be managed using established protocols[31] and the potential risk of microcephaly resulting from intrauterine infection; however currently these two risks of infection need to be considered associations and a causative relationship has not been established.

Figure 1: World map indicating countries (grey) that have documented transmission of the Zika virus during the current epidemic as of 22 February 2016. It is important to consider that travelers in juxtaposition locations to countries with documented epidemics may also warrant suspicion—there is little reason to assume that Zika virus is not in Peru or Uruguay, for example.



Competing interests:
Dr. Buenz reports personal fees from Terumo BCT, from null, outside the submitted work.

Author information:
Gareth Parry, Nelson Marlborough Institute of Technology, New Zealand; Matthew Peacey, Nelson Marlborough Institute of Technology, New Zealand; Eric J Buenz, Nelson Marlborough Institute of Technology, New Zealand.

Corresponding author:
Gareth Parry, Nelson Marlborough Institute of Technology, 322 Hardy Street, Nelson.
gareth.parry@nmit.ac.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6977

REFERENCES:

1. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika Virus. The New England journal of medicine. Apr 21 2016;374(16):1552–1563.
2. Ministry of Health. Zika virus. 2016; http://www.health.govt.nz/our-work/diseases-and-conditions/zika-virus. Accessed 22 April, 2016.
3. Haug CJ, Kieny MP, Murgue B. The Zika challenge. New England Journal of Medicine. 2016;374(19):1801–1803.
4. Lamb RA, Krug R, Knipe D. Fields virology. Fields Virology. 2001;1.
5. Hamel R, Dejarnac O, Wichit S, et al. Biology of Zika Virus Infection in Human Skin Cells. Journal of virology. Sep 2015;89(17):8880–8896.
6. Fauci AS, Morens DM. Zika Virus in the Americas - Yet Another Arbovirus Threat. The New England journal of medicine. Jan 13 2016.
7. Faye O, Freire CC, Iamarino A, et al. Molecular evolution of Zika virus during its emergence in the 20(th) century. PLoS neglected tropical diseases. 2014;8(1):e2636.
8. Tsetsarkin KA, Vanlandingham DL, McGee CE, Higgs S. A single mutation in chikungunya virus affects vector specificity and epidemic potential. PLoS pathogens. Dec 2007;3(12):e201.
9. de Melo Freire CC, Iamarino A, de Lima Neto DF, de Andrade Zanotto PM. Spread of the pandemic Zika virus lineage is associated with NS1 codon usage adaptation in humans. bioRxiv. 2015:032839.
10. Grard G, Caron M, Mombo IM, et al. Zika virus in Gabon (Central Africa)--2007: a new threat from Aedes albopictus? PLoS Negl Trop Dis. Feb 2014;8(2):e2681.
11. Holder P, George S, Disbury M, Singe M, Kean JM, Mcfadden A. A biosecurity response to Aedes albopictus (Diptera: Culicidae) in Auckland, New Zealand. Journal of medical entomology. 2010;47(4):600–609.
12. Foy BD, Kobylinski KC, Chilson Foy JL, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerging infectious diseases. May 2011;17(5):880–882.
13. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerging infectious diseases. Feb 2015;21(2):359–361.
14. Musso D, Nhan T, Robin E, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2014;19(14).
15. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2014;19(13).
16. Ventura CV, Maia M, Bravo-Filho V, Gois AL, Belfort R, Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. Lancet. Jan 16 2016;387(10015):228.
17. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. Jan 2016;47(1):6–7.
18. Rubin EJ, Greene MF, Baden LR. Zika Virus and Microcephaly. The New England journal of medicine. Feb 10 2016.
19. Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. MMWR. Morbidity and mortality weekly report. 2016;65(3):59–62.
20. Mlakar J, Korva M, Tul N, et al. Zika Virus Associated with Microcephaly. The New England journal of medicine. Feb 10 2016.
21. Heymann DL, Hodgson A, Sall AA, et al. Zika virus and microcephaly: why is this situation a PHEIC? Lancet. Feb 11 2016.
22. Petersen EE, Staples JE, Meaney-Delman D, et al. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak - United States, 2016. MMWR. Morbidity and mortality weekly report. 2016;65(2):30–33.
23. Parry G. Guillain-barré syndrome. Stuttgart/New York: Georg Thieme Verlag; 1993.
24. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barre syndrome following vaccination in the National Influenza

Immunization Program, United States, 1976--1977. American journal of epidemiology. Aug 1979;110(2):105–123.

25. Sears A, Baker MG, Wilson N, et al. Marked campylobacteriosis decline after interventions aimed at poultry, New Zealand. Emerging infectious diseases. Jun 2011;17(6):1007–1015.

26. Baker MG, Kvalsvig A, Zhang J, Lake R, Sears A, Wilson N. Declining Guillain-Barre syndrome after campylobacteriosis control, New Zealand, 1988-2010. Emerging infectious diseases. Feb 2012;18(2):226–233.

27. Yuki N, Susuki K, Koga M, et al. Carbohydrate mimicry between human ganglioside GM1 and Campylobacter jejuni lipooligosaccharide causes Guillain-Barre syndrome. Proceedings of the National Academy of Sciences of the United States of America. Aug 3 2004;101(31):11404–11409.

28. Raphael JC, Chevret S, Hughes RA, Annane D. Plasma exchange for Guillain-Barre syndrome. The Cochrane database of systematic reviews. 2012;7:CD001798.

29. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. The Cochrane database of systematic reviews. 2014;9:CD002063.

30. Yang J, Jia L. Predictors for mechanical ventilation and short-term prognosis in patients with Guillain-Barre syndrome. Critical care. 2015;19:407.

31. Hughes R, Wijdicks E, Barohn R, et al. Practice parameter: Immunotherapy for Guillain–Barré syndrome Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2003;61(6):736–740.

Why are those most in need of Sudden Unexplained Infant Death (SUDI) prevention information the least likely to receive it? A comment on unconscious bias and Māori health

Carla A Houkamau, Kathrine Clarke

Our goal in this commentary is to expand discussions of unconscious bias into the New Zealand health care arena. We begin with a review of international research which links health provider bias to inequitable health outcomes for ethnic minorities. Local studies indicating Māori may be vulnerable to bias will then be reviewed. We then discuss data taken from the 2014 *Well Child/Tamariki Ora (WCTO) Programme Delivery Report* which shows Māori are less likely to receive SUDI prevention information from their Well-child health provider than other ethnic groups in New Zealand.[1] We then discuss the impact of stereotyping on Māori before offering suggestions for addressing unconscious bias.

The theoretical framework for the role of unconscious (sometimes referred to as implicit) bias in health care is well-established and based on empirical findings in social psychology and research on health-care processes.[2–3] Unconscious bias has been recognised in cognitive science and social psychology for decades where it is understood as an automatic tendency for humans to perceive people, situations and events in stereotypical ways. Banaji and Greenwald[4] have shown how unconscious biases reflect deeply held stereotypes associated with different social categories (including ethnicity, age, gender, socio-economic status and religion). These perceptions trigger responses which occur outside of the perceiver's conscious awareness.[5] Humans are inclined to display in-group favouritism (a preference and affinity for their own in-group) as well as out-group derogation (discrimination toward out-groups).[6] These two cognitive phenomena combined create a natural predisposition to negatively stereotype out-group members and respond positively to similar others.[4]

Consequently, leading researchers have defined unconscious bias in health care as occurring when a provider 1) automatically/unconsciously classifies a patient as a member of a group, 2) applies stereotypes to the patient based on their group membership and 3) makes decisions based on those stereotypes.[3] The circumstances under which health care services are delivered are often characterised by time pressure and complexity. According to Smedley, Stith and Nelson[7] these factors increase the likelihood that unconscious biases will influence a providers' behaviour as they are more likely to be relying on instinctive responses rather than rational thought processes.

Direct or explicit bias differs from unconscious bias in two ways. While explicit bias tends to be obvious and intentional, unconscious biases are generally unintentional and manifest covertly.[8] Health research has demonstrated unconscious bias from a

provider towards their client may manifest in the form of subtle social cues which signal avoidance, anxiety, discomfort or dislike.[9] Examples include body language (moving away, avoiding direct eye contact, leaning back from clients, crossing arms across the chest and other forms of closed body language). Facial expression (flattened affect) and voice tone/speed can also suggest disdain (eg speaking slowly may be construed as patronising while speaking too quickly may signal a desire to end a conversation quickly). Thus unconscious bias can manifest surreptitiously in a range social slights and exclusions that make the patient feel uncomfortable and at the worst offended.

Although unconscious bias has received scant research attention in the New Zealand context, the issue has received considerable research attention in the United States (US) and the United Kingdom (UK) in recent years. For example, the detrimental impact of unconscious bias was evinced by a 2002 American Institute of Medicine (IOM) report titled *Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare* which reviewed over 100 healthcare studies on US populations to reveal Black-Americans and other ethnic minorities receive poorer quality health care and less medical interventions than White-Americans—partly due to bias and stereotyping on the part of health providers.[7]

Several US based studies have demonstrated that higher health provider biases are associated with poorer patient outcomes. When the provider and the patient come from different cultural or racial groups, health providers tend to be less proactive, less 'patient centred' and generally fail to establish optimal levels of rapport.[10–13] Cooper et al., have shown that clinicians with higher negative race biases are more likely to dominate conversations with their patients, show less interpersonal warmth and spend less time explaining various treatment options. Accordingly, patients who have clinicians with higher unconscious bias are more likely to leave appointments feeling dissatisfied, untrusting and are more likely to rate their clinicians poorly on interpersonal skills.[2] These perceptions may have serious consequences. For example, if patients do not trust their health providers they may less likely to adhere to treatment regimens or book follow-up appointments.

Local research shows Māori experiences within the health care system parallel international studies. Stereotypes may contribute to the problem. Analyses of newspaper, television and radio reports of Māori health demonstrate Māori are consistently presented as poorer and sicker as a group—largely due to lifestyle choices (rather than structural issues or processes within the health system).[14,15] Data suggests these stereotypes are mirrored in health care settings. McCreanor and Nairn interviewed 25 GPs from urban Auckland on the topic of Māori health and found that practitioners perceived Māori as sickly and non-compliant. They also attributed Māori health problems to cultural and lifestyle choices.[16] The presence of these attitudes among health care professionals suggests that biases may play a role in differential outcomes for Māori.

A number of data sources demonstrate a bias in the way medical services, procedures and treatments are prescribed for Māori as opposed to other ethnic groups.[17] For example, Westbrooke, Baxter and Hogan[18] found Māori men are less likely to receive medical intervention for cardiac disease compared with Pākehā men. Ministry of Health data indicates Māori women are less likely to receive epidural pain relief during child birth compared to non-Māori women.[19] Hill et al.[20] demonstrate that Māori have a significantly poorer cancer survival rate than non-Māori: partly due to differences in the standard of medical treatment Māori receive. Jansen and Jansen[21] report that Pākehā doctors spent 17 percent less time (2 minutes out of a 12-minute consultation) interviewing Māori than patients from other ethnic groups. In an older, but relevant study in the context of this paper, Mitchell[22] found New Zealand general practitioners (GPs) are less likely to prescribe prophylactic therapy to Māori and Polynesian children. He concluded "the higher asthma mortality and admission rates in Māori and Pacific Island children compared with European children is not due to ethnic differences in prevalence, genetic or socioeconomic factors. The most important

factor appears to be differences in medical management." (p835). According to Mitchell anecdotal evidence suggests some GPs do not prescribe prophylactic drugs because of the difficulty in communicating appropriate instructions to Māori and Polynesian parents. This, he notes, amounts to stereotyping according to ethnicity—because medical practitioners make "assumptions about the appropriateness of prescribing asthma prophylactic therapy for these ethnic minority groups" (p.835). This sentiment is substantiated by an analysis of the 2002/03 New Zealand Health Survey, where Māori reported the highest prevalence of ever experiencing racial discrimination in their interactions with health care providers compared with non-Māori.[23]

Research with Māori and Pākehā GPs shows some Pākehā GPs find it harder to communicate with Māori patients and Māori are less comfortable, trusting and forthcoming in their interactions with Pākehā GPs.[13] Jansen, Bacal and Crengle[24] found similar data in a large nationwide survey of 651 Māori consumers of health and disability services. Māori reported their health care workers did not communicate with them effectively, failed to take time to carefully explain their treatment options and inform them of additional health services they could utilise. Arlidge et al.[25] examined the hospital experiences of Māori and Pacific and Pākehā families. Interviews revealed many Māori and Pacific whānau/families felt alienated within the hospital setting, Māori reported receiving less focussed attention, less discussion and less information from their health care providers. Māori and Pacific respondents felt medical staff were unapproachable (either because they were too busy or seemed unavailable to help) this made them feel that they could not ask for information or support. Pākehā families did not report having these same experiences.

The issue of Māori engagement with public health services is crucial in relation to SUDI in New Zealand where Māori babies die of SUDI at almost five times the rate of non-Māori babies. SUDI prevention ("safe sleep") information is delivered to New Zealand parents through the Ministry of Health's Well Child/Tamariki Ora (WCTO) programme which is free to all New Zealand children from birth to five years. WCTO services are delivered by a range primary health providers; midwives, doctors, nurses and hospital specialists. The programme is comprised of 13 "wellness checks" or "core visits" with health providers. These checks include 12 core visits plus a GP health check at six weeks (linked to the six-week immunisations). According to the WCTO National Schedule 2013 SUDI prevention information should be provided during core contacts 1–5 by WCTO providers.[26]

WCTO National Programme Delivery Reports for 2014 (which reported ethnicity data for Māori and *Pasifika* only) revealed only 43.4% of Māori babies received all core contacts 1–5, compared to the national average for all babies which was 57.7%. For those who received core 1 visits 48% of Māori received SUDI information compared to 59.5% of all births.[3] One might not think that this is not such a significant gap and may reflect some other trend, however, we noted that 64% of *Pasifika* parents did receive information compared to 48% Māori.[1]

The fact that Māori are less likely to receive their Core 1 visits is in itself a concern—however we find it particularly concerning that even when Māori *do* receive visits—they are less likely to be provided with SUDI safe sleep information. What is different about the way in which Māori are engaged by WTCO providers? Typically, when there is some kind of health inequity experienced by Māori this is attributed to lower socio-economic status, poor access to health care services or poorer service uptake on the part of Māori. However, we believe the possibility of unconscious bias towards Māori on the part of health care providers should be considered.

To substantiate that view, a 2013 study conducted by Pacific Perspectives,[27] which analysed the maternity and health care experiences of Māori and Pacific mothers, underlines the extent of stereotyping young women experience in their interactions with health professionals. The report revealed significant shortcomings in the quality of services younger women receive throughout the maternity care system and shows this population are subject to significant stigma: stating "vulnerable young mothers felt interactions with staff stereotyped, judged and stigmatised them" (p.8).

This report is substantiated by other qualitative studies which demonstrate young Māori mothers have significant challenges dealing with health professionals and believe they are judged, frowned on and spoken down to by doctors and nurses alike.[28] For young Māori mothers the expectation of discrimination may also contribute to poor outcomes. It may be that expectations of having a negative experience can lead to distrust/anxiety about health care professionals—which discourages them from accessing health services. Jansen, Bacal and Crengle[24] noted that some Māori prefer Māori health providers. However, it is important to note that Māori are a minority in the health care workforce meaning the vast majority of interactions Māori have will be with health providers who are non-Māori. This is also the case for Māori mothers who are mainly dealing with non-Māori GPs, Plunket nurses and midwives.

We acknowledge that a complex array of factors underpin Māori health inequities. We believe interpersonal dynamics within the health care system also are a major influencing factor. Where traditional approaches to dealing with inequities in health have focussed on overt exclusionary practices (ie racism) and cultural competency training, we believe little change will be made unless these deeper (hidden, rationalised and largely unchecked) unconscious biases are addressed. To precipitate change we need to find a way to talk about inequities constructively. We believe the language of biases provides a framework for this discussion to occur in an inclusive and non-blaming way. Unconscious biases may be at odds with the practitioner's conscious beliefs—and reflect attitudes they would not consciously endorse. Māori must also be aware of their own biases. If Māori perceive they have had negative experiences with health providers in the past they will be apprehensive about future interactions. If Māori are primed to have negative experiences, they may misinterpret health provider behaviour incorrectly (ie see bias when it isn't there). These perceptions can unconsciously undermine health provider's efforts to care for them.

For our original question: *Why are those most in need of information about sudden infant death the least likely to receive it?* There are many answers—however, we believe some health providers may hold stereotypes that inhibit their ability to connect effectively with young Māori mothers. This manifests in the amount of time they spend with each client, their tone of voice, the extent to which they express sensitivity and ultimately the amount of information they provide. Māori may read non-verbal behaviour negatively and withdraw from their engagement with service providers (ask less questions, feel sceptical about the advice they are given, feel reluctant to make follow up appointments). This explains not only Māori dissatisfaction with health provider services—but also why Māori are less likely to receive the safe sleep information they should be given.

Burgess et al.,[29] outline a number of important steps towards addressing unconscious bias among health providers. As a first step they recommend helping providers understand the cognitive bases of biases, openly acknowledging stereotypes (so they can be constructively addressed), enhancing health provider's confidence in their ability to interact with patients from a different cultural background and enhancing provider empathy (which is seen as important for improving patient-provider interactions generally).

A range of instruments have been developed for the purpose of assessing personal levels of unconscious bias. The most commonly used is the Implicit Association Test (IAT). The IAT is a computer-based measure that measures the strength of associations between social categories (female, ethnic minorities) and evaluations and stereotypes. IAT has been used in hundreds of studies across a wide array of disciplines to reveal implicit biases. The test is free – and only takes five minutes to complete https://implicit.harvard.edu/implicit/education.html

At the present time there is no research that we know of in New Zealand which has directly investigated the extent to which unconscious bias among health professionals impacts on the quality of health care delivered. There is certainly a need for such research to begin. In addition, we believe health providers need to be educated about how subtle and unconscious biases may

affect the way they deal with Māori patients and how these attitudes influence their decisions. Dovidio[30] has demonstrated that making health professionals more conscious of how cognitive biases work (and how biases influence medical encounters) helps to motivate them to correct their own bias. Although having a greater awareness of bias will not automatically eliminate it, awareness of the issue is certainly needed to open up discussion and promote understanding.

Competing interests:
Dr. Houkamau reports personal fees from Whakawhetu/Mokopuna Ora, outside the submitted work.

Author information:
Carla A. Houkamau, University of Auckland, New Zealand; Kathrine Clarke, National Director, Whakawhetū, Sudden Unexplained Infant Death (SUDI) Prevention for Māori, New Zealand.
Corresponding author:
Carla A. Houkamau, University of Auckland, New Zealand.
c.houkamau@auckland.ac.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6978

REFERENCES:

1. Ministry of Health. 2015. Well Child / Tamariki Ora Programme Delivery Reports for 2014. Wellington: Ministry of Health. Unpublished report.
2. Cooper LA, Roter DL, Carson KA, Beach M, Sabin J, Greenwald A et al. The Associations of Clinicians' Implicit Attitudes about Race with Medical Visit Communication and Patient Ratings of Interpersonal Care. Am J Public Health. 2012 May;102(5):979–87.
3. Blair IV, Steiner JF, Havranek EP. Unconscious (Implicit) Bias and Health Disparities: Where Do We Go from Here? Perm J. 2011 Spring;15(2):71–8.
4. Mahzarin R, Banaji A, Greenwald G. Blindspot: hidden biases of good people New York: Delacorte Press; 2013.
5. Hewstone M, Rubin M, Willis H. Intergroup bias. Annu Rev Psychol. 2002;53:575–604.
6. Dovidio JF, Kawakami K, Johnson C, Johnson B, Howard A. On the nature of prejudice: Automatic and controlled processes. J Exp Psychol. 1997 Sep; 33:510–540.
7. Smedley B, Stith A, Nelson A. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, D.C; National Academies Press; 2003 p. 6–251
8. Mahzarin R, Banaji A, Greenwald G. Blindspot: hidden biases of good people New York: Delacorte Press; 2013.
9. Cooper LA, Roter DL, Carson KA, Beach M, Sabin J, Greenwald A et al. The Associations of Clinicians' Implicit Attitudes about Race with Medical Visit Communication and Patient Ratings of Interpersonal Care. Am J Public Health. 2012 May;102 (5):979–87.
10. Van Ryn M. Research on the provider contribution to race/ethnicity disparities in medical care. Med Care. 2002; 40(1 Suppl): 140–51.
11. Penner LA, Dovidio JF, West TV, Gaertner SL, Albrecht TL, Dailey RK et al. Aversive racism and medical interactions with Black patients: a field study. J Exp Soc Psychol. 2010 Mar 1;46(2):436–440.
12. Green AR, Carney DR, Pallin DJ, Ngo LH, Raymond KL, Iezzoni LI et al. Implicit bias among physicians and its prediction of thrombolysis decisions for black and white patients. J Gen Intern Med. 2007. Sep; 22(9):1231–8.
13. Thomas DR, Arlidge B, Arroll B, Elder H. General practitioners' views about diagnosing and treating depression in Māori and non-Māori patients. J Prim Health Care. 2010 Sep 1;2(3):208–16.
14. Nairn R, Moewaka Barnes A, Rankine J, Borell B, Abel S, McCreanor T. Mass media in Aotearoa:

an obstacle to cultural competence. NZ Journ Psych 2011, 40(3), 168–175.

15. Hodgetts D, Masters B, Roberston N. Media Coverage of 'Decades of Disparity' in Ethnic Mortality in Aotearoa. J Community Appl Soc Psychol. 2004, 14(6), 455–472
16. McCreanor T, Nairn R. Tauiwi general practitioners' talk about Māori health: interpretative repertoires. NZMJ. 2002, 13;115 (1167):U272.
17. Alexander H, Irwin C, Purdie G, Hunn M. Incidence and management of high grade glioma in Māori and non-Māori patients. Journal of Clinical Neuroscience. J Clin Neurosci. 2010 Sep;17(9):1144–7.
18. Westbrooke I, Baxter J, Hogan J. Are Māori under-served for cardiac interventions? N Z Med J. 2001 Nov 9;114(1143):484–7.
19. Ministry of Health. (2004). Report on maternity. 2002. Wellington: Ministry of Health.
20. Hill S, Sarfati, D, Blakely T, Robson B, Purdie G, Dennett E et al. Ethnicity and management of colon cancer in New Zealand: Do indigenous patients get a worse deal? Cancer. 2010 Jul 1;116(13):3205–14.
21. Jansen P, Jansen D. Māori and health. In: St George I, editor. Cole's medical practice in New Zealand 12th ed. Wellington: Medical Council of New Zealand. 2013:52–65.
22. Mitchell EA. Racial inequalities in childhood asthma. Soc Sci Med. 1991; 32:831–836
23. Harris R, Cormack D, Tobias M, Yeh L-C, Talamaivao N, Minster J, Timutimu R. The pervasive effects of racism: experiences of racial discrimination in New Zealand over time and associations with multiple health domains. Soc Sci Med. 2012 Feb;74(3):408–15.
24. Jansen, P, Bacal K, Crengle S. (2008). He Ritenga Whakaaro: Māori experiences of health services. Auckland: Mauri Ora Associates.
25. Arlidge B, Abe S, Asiasiga L, Milne S, Crengle S, Ameratunga S. Experiences of whānau/families when injured children are admitted to hospital: a multi-ethnic qualitative study from Aotearoa/New Zealand, Ethn Health. 2009 Apr;14(2):169–83.
26. Ministry of Health. 2013. Well Child / Tamariki Ora National Schedule 2013. Wellington: Ministry of Health. [cited 08 April 2016]. Available from: https://www.google.co.nz/search?q=WCTO+National+Schedule+2013+-SUDI&ie=utf-8&oe=utf-8&gws_rd=cr&ei=N5k-GV-nTJ4Hc0gTsy4QI
27. Pacific Perspectives Ltd. Maternity Care Experiences of Teen, Young, Māori Pacific and Vulnerable Mothers at Counties Manukau Health. Wellington NZ: Pacific Perspectives; 2013 p. 6–69.
28. Lee R, North N. Barriers to Māori sole mothers' primary health care access. J Prim Health Care. 2013 Dec 1;5(4):315–21.
29. Burgess D, van Ryn M, Dovidio J, Saha S. Reducing racial bias among health care providers: lessons from social-cognitive psychology. J Gen Intern Med. 2007 Jun;22(6):882–7.
30. Dovidio J, Penner L, Albrecht T, Norton W, Gaertner S, Shelton N. Disparities and distrust: The implications of psychological processes for understanding racial disparities in health and health care Soc Sci Med. 2008 Aug;67(3):478–86.

Screening for colorectal cancer: spoiled for choice?

Diana Sarfati, Caroline Shaw, Melissa McLeod, Tony Blakely, Ian Bissett

ABSTRACT

There are many different potential screening strategies for colorectal cancer (CRC) that vary both in the likely magnitude of their benefits on CRC mortality and their impact on health services. Many approaches to CRC screening are cost-effective, but there is substantial uncertainty about the optimal approach. Decision models using Markov or microsimulation modelling that compare the cost-effectiveness of different screening strategies are useful in this regard. We have reviewed recent decision models that compare the cost-effectiveness of one-off flexible sigmoidoscopy screening with immunochemical faecal occult blood (FIT) based screening. Models consistently show that any population-based screening is cost-effective compared with no screening, and that FIT-based screening is more effective than one-off sigmoidoscopy screening. The combination of one-off sigmoidoscopy with FIT is more effective in saving lives than either modality alone, but has the greatest impact on health service resources. The recent decision to proceed with biennial FIT-based screening is consistent with current evidence.

Background

In May 2016, the Minister of Health announced the national rollout of a colorectal cancer (CRC) screening programme using immunochemical faecal occult blood tests (FIT).[1] For CRC, there are a number of potential screening modalities (including guaiac faecal occult blood tests, immunochemical faecal occult blood tests, flexible sigmoidoscopy, colonoscopy, faecal DNA samples); randomised controlled trial (RCT) information, however, is currently available only for guaiac faecal occult blood tests (FOBTs) and flexible sigmoidoscopy (sigmoidoscopy). In New Zealand there has been some debate about which screening modality would be best in terms of reducing CRC mortality, and cost-effectiveness, with a particular focus on the relative benefits and harms of FIT and one-off sigmoidoscopy.[2]

Decision models offer one way to make head-to-head comparisons between different screening modalities (eg, sigmoidoscopy vs immunochemical FOBT), or different screening strategies (eg, one-off versus five-yearly sigmoidoscopy within the same population) drawing on the best available evidence (including RCTs where available), while also incorporating uncertainty around input parameters such as screening uptake rates and test performance. In this paper we provide a brief overview of existing CRC screening modalities and review recent decision models that compare the cost-effectiveness of one-off flexible sigmoidoscopy screening with immunochemical faecal occult blood based screening.

What are the screening tests and strategies?

The most commonly evaluated test strategies for colorectal cancer (CRC) screening include the following:

Faecal occult blood tests (FOBT): There are two types of FOBTs; guaiac and immunochemical. The original RCTs of CRC screening used guaiac tests.[3–6] Up to three samples were required per screening round, with dietary restrictions prior to the tests being completed. These tests had low sensitivity for cancer and were poor at detecting adenomas. Subsequently both higher sensitivity guaiac tests and immunochemical FOBTs (FITs) have been developed.[7,8] FITs have a number of advantages over the older guaiac tests. In particular, they have been found to have higher neoplasia detection rates, they usually require only one test sample and they are quantitative tests so it is possible to adjust positivity rates to suit a given population.[6–10] However, they are also

more expensive and can result in a higher colonoscopy referral rate (depending on the positivity cut-off used).

The early trials of bowel cancer screening using guaiac tests were almost all population-based and demonstrated a reduction in bowel cancer mortality of 16% among those invited for screening.[11] Newer tests, with their higher capacity to detect adenomas and cancer, would be expected to have a somewhat different impact on both the benefits (given their higher sensitivity they may be expected to have a greater impact on cancer mortality and incidence) and harms (depending particularly on their specificity, they may have a greater or lesser impact on colonoscopy services) of screening compared to the original RCTs.

Flexible sigmoidoscopy: there have been four long-term trials assessing the efficacy of sigmoidoscopy published since 2009.[12-15] Three of the four trials were able to demonstrate a reduction in CRC mortality (ranging from 20 to 31% amongst those invited to be screened), and all showed a reduction in incidence of CRC. The main area of uncertainty in relation to sigmoidoscopy-based programmes arises because three of the RCTs were carried out within populations who had previously indicated a willingness to participate in screening.[12,13,15] This means that participation rates were higher than would be expected if the entire population was invited, and so the estimates of reduction in both incidence and mortality are likely to be greater than would be expected in a population-based programme. For example, in the UK-based trial, participation rates were 71%, while in the population-based setting it has recently been found to be 43%.[12,16]

Other screening modalities: To date there are no RCTs evaluating the effectiveness of colonoscopy-based screened, although some are underway.[17,18] Issues for colonoscopy-based screening include the substantial colonoscopy capacity required to deliver a population-based programme, and the costs and human resources associated with that, as well as potentially higher rates of harms such as intestinal perforation and bleeding.[19]

There is no RCT evidence on the potential mortality benefits for CT colonography, faecal DNA testing or serological tests, and these will not be further considered here.

How do we decide between different screening tests and strategies?

It is neither possible nor sensible to require an RCT to be performed for every new screening test modality or variation of screening strategy. One common way to assist decision-making in relation to cancer screening in a given context is by using decision models. These models use information from RCTs, as well as other inputs. They can be used to address a number of questions, including whether screening is likely to be cost-effective at all; which screening strategy is likely to be most cost-effective; what impact screening will have on health services; and whether screening will differentially affect different sub-populations. They also have the advantage of being able to incorporate uncertainty around assumptions made within them.

Two main types of model have been used in this context: Markov/state transition models and microsimulation models. Markov models consist of a series of mutually exclusive health 'states' through which groups of simulated individuals can move, based on specified transition probabilities. For example, states could include 'no neoplastic lesions', 'low risk adenoma', 'high risk adenoma', 'stage I colon cancer' etc, with the proportions of individuals within a cohort transitioning to each state based on evidence about the population patterns of these states.

Microsimulation models, in contrast, simulate individual life histories. These models are both more flexible and more complex to build and run. Both types of model incorporate data relating to background and disease characteristics within a population (for example, background population mortality and colorectal cancer incidence), and data relating to screening modalities (eg, likely participation rates, sensitivity of tests etc). Importantly, most also allow for uncertainty around these key input parameters to provide a quantitative assessment of the extent to which assumptions around these parameters might alter recommendations. That is, they

can identify which specific inputs in the model that, when varied, cause substantial changes in the outcome and thus might alter recommendations. The outputs from these models vary but will usually include measures of cost effectiveness (such as cost per Quality Adjusted Life Year or QALY), estimates of total benefit (such as predicted reduction in colorectal cancer incidence and mortality), and estimates of likely costs and harms (such as predicted number of colonoscopies).

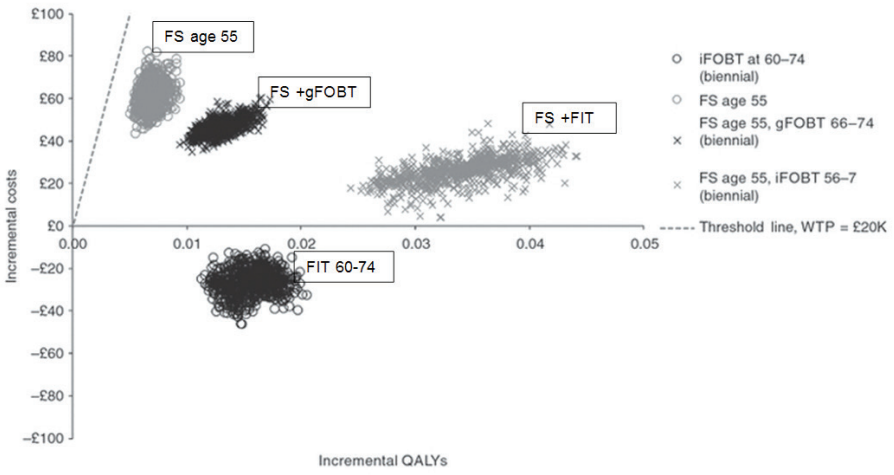
The most useful decision models to assess the pros and cons of different screening modalities are those that examine all the different screening modality and strategy options within the one model, to allow direct comparisons. To date, there are no published examples of models developed to make comparisons between modalities specifically in the New Zealand context, but several that have been published internationally which are informative.

What are the results from decision models relating to bowel cancer screening?

Several countries have developed and/or used decision models to assist them in decision-making related to bowel cancer screening. We identified models that compared strategies most relevant in the New Zealand context, ie, those that compared FIT-based screening and one-off sigmoidoscopy at a minimum. We searched Medline on 15 March 2016 using the following MeSH index terms: 'colorectal neoplasm'; 'mass screening'; 'sigmoidoscopy'; and 'cost-benefit analysis' or 'cost and cost analysis', or key words 'decision analysis', 'cost effectiveness' or 'cost benefit'. We limited studies to those published since 2010, since evidence on the effectiveness of sigmoidoscopy-based screening has only been available since then. We found three relevant studies, summarised in Table 1.

The English bowel cancer screening programme was started in 2006 based on biennial gFOBT screening. Whyte et al (2012) used a Markov model to update earlier modelling to assess effectiveness, cost-effectiveness and resource requirements of various screening strategies using FIT and sigmoidoscopy compared to gFOBT.[20,21] They found that biennial FIT for ages 60–74 years would be expected to be cost saving and result in more QALY gains compared to their current system of biennial gFOBT for 60–74 year olds. They also found that adding a one-off sigmoidoscopy to their current screening strategy resulted in a more effective programme in terms of reducing mortality, and was still cost effective (given a willingness-to-pay of £20,000). The strategy resulting in the greatest reduction in incidence, mortality and treatment costs was one that combined one-off sigmoidoscopy at age 55 with FIT between the ages 56–74. However, this

Figure 1: marginal cost effectiveness plane compared with biennial gFOBT age 60–74 in England.[20]



FS, flexible sigmoidoscopy; iFOBT, immunochemical faecal occult blood test; gFOBT, guaiac faecal occult blood test; QALYs, quality adjusted life years

Fig 1 reproduced with permission from John Wiley and Sons. Originally published in Whyte et al 2012[20]

strategy also had the highest endoscopic requirements of all tested strategies, with nine times the number of endoscopic procedures of the existing gFOBT programme. Figure 1 is a marginal cost effectiveness plane that shows the incremental costs (y-axis), QALYs gained (x-axis) and cost-effectiveness (indicated by the dashed line) of various screening options compared with biennial gFOBT. Each point in the cluster represents one simulation of the model, which randomly draws from a range of values for each input parameter, for example, from a range of plausible values of screening uptake rates, sensitivity and specificity of tests and endoscopy costs. It shows that relative to the current biennial gFOBT programme, biennial FIT screening at ages 60–74 was cost saving (with the entire cluster producing negative incremental costs), and produced more QALYs than one off sigmoidoscopy at age 55. Sigmoidoscopy at age 55 years followed by biennial FIT produced the greatest QALY gains, ie, was the most effective of all assessed strategies in terms of QALYs gained, and remained highly cost effective (Figure 1).[20]

Figure 1 shows a cost-effectiveness plane relative to the established gFOBT programme already in place in the UK. The same authors, in a background report, also compared all the interventions shown in Figure 1 to no screening (Figure 4.2.2. in Whyte et al 2011).[22] The pattern of findings was the same, with biennial FIT screening being cost saving with large QALY gains, and one-off sigmoidoscopy screening being both more costly and resulting in fewer QALYs gained.

The Health Information and Quality Authority and Health Research Board Ireland funded work to inform policy decisions relating to proposed population-based bowel cancer screening in Ireland.[23] They assessed the incremental cost-effectiveness of screening compared with no screening using a Markov model. The strategies they assessed were: 1) biennial gFOBT with second-line FIT for those aged 55–74 yrs; 2) biennial FIT for those aged 55–74; or 3) once only sigmoidoscopy at age 60 years. They found all three of the above screening strategies were likely to be cost-effective compared to no screening, with a cost-effectiveness threshold of €45,000. Of the three strategies examined, they found that one-off sigmoidoscopy would be the least expensive, but the benefits in terms of QALYs gained were higher for FIT-based screening. FIT-based screening was estimated to result in a 15% decrease in incidence and 36% reduction in mortality from CRC over the lifetime of the modelled cohort, compared with 5% and 8% respectively for one-off sigmoidoscopy. Their conclusion was that all screening scenarios they assessed were cost-effective, but they considered FIT the optimal strategy based on it achieving the greatest modelled health gains at an acceptable cost.

Similarly a Markov model was used to compare the cost effectiveness of a range of screening strategies for those aged 50 to 75 years in Singapore.[24] Strategies explored included single and 5-yearly sigmoidoscopy, single and 10-yearly colonoscopy, 5-yearly colonoscopy or barium enema, annual FIT-based screening, barium enema and 5-yearly stool DNA or combined sigmoidoscopy/ FIT strategies. The authors of this work assumed similar compliance regardless of primary screening modality, which is an assumption that tends to favour more invasive screening modalities (such as colonoscopy and sigmoidoscopy) because participation rates are—in reality—generally lower for these.[6,10] As with other models, all screening approaches were predicted to be cost effective compared with no screening in a population with high CRC incidence, using a cost-effectiveness threshold of USD 50,000. Single sigmoidoscopy was the cheapest option and was predicted to reduce CRC deaths by 16% and incidence by 19%. Compared with no screening, FIT was the most cost effective and was predicted to reduce CRC deaths by 27% and incidence by 25%. Colonoscopy every 10 years was more expensive than FIT or one-off sigmoidoscopy, but produced greater QALY gains, predicted to reduce CRC mortality by 38% and incidence by 35%. The authors' concluded that at "*the lowest end of willingness-to-pay threshold, single sigmoidoscopy at age 60 years was the screening strategy of choice, If one can afford to pay more, FIT saves more lives and is more cost effective at an estimated overall adherence rate of 50%*".

Modelling used by the US Preventive Services Taskforce (USPSTF)

Perhaps the best known cancer screening modelling programme comes from the National Cancer Institute's CISNET consortium which consists of three independently developed microsimulation models all designed to assess the cost-effectiveness of cancer screening. The US Agency for Healthcare Research and Quality recently released a report based on the findings of this group, which involved modelling 204 separate colorectal cancer screening strategies and which were instrumental in the development of the most recent recommendations from the USPSTF.[25–27] This work was not included in our review above because they did not assess a one-off sigmoidoscopy option on the basis that sigmoidoscopy alone has been consistently shown to be inferior in terms of health gain to sigmoidoscopy combined with FOBT, thus would not be recommended as a strategy.

However this work is described briefly here because of the prominence of the USPSTF recommendations. This group reviewed CRC screening strategies that included different age ranges, screening intervals and screening modalities (or combinations of modalities) including gFOBT, FIT, multi-target stool DNA test, sigmoidoscopy, CT colonography and colonoscopy. All strategies were found to reduce colorectal cancer incidence and mortality compared with no screening. They found that all three models included in the CISNET consortium demonstrated consistent rankings for screening strategies, albeit that they differed slightly in terms of absolute measures of benefits and harms of each strategy. Based on the results of the models and assuming 100% adherence, four optimal strategies were identified, with similar balance of benefits (in terms of life years gained) and burdens (in terms of number of required colonoscopies): screening those aged 50 to 75 years using one of a) colo-

Table 1: Summary of modelling studies.

Authors/ Date	Setting	Type of model	Options assessed	Measure of benefit	Cost effectiveness results	CRC mortality reduction	Endoscopy requirements (including surveillance colonoscopies)	Comment
Dan et al 2012[24]	Singapore	Markov	A. once only FSIG (60), B. Annual FIT C. 5 yearly FSIG and annual FIT * Comparator: no screening	QALY	A. 27 843 USD B. 27 399 USD, C. 40000 USD. Cost per QALY gained compared to no screening.	A 16%, B 25% C. 33%	A . 29000, B. 66000, C. 40345 (this only includes colonoscopies, not the sigmoidoscopies required in option A)	The authors assumed the same participation for all screening scenarios.
Sharp et al 2012[23]	Ireland	Markov	A. Biennial gFOBT with second line FIT (55-74), B. biennial FIT (55-74), C. once only FSIG (60) Comparator: no screening	QALY	ICER* cost per QALY gained: A. €4428, B. €1696, C. €589. ICER for FIT (B) vs flex sig (C): €2058 per QALY gained	A. 11.8% B. 36% C. 7.5%	A. 3386 colonoscopies, B. 34632 colonoscopies, C. 42720 procedures (2543 colonoscopies and 40177 sigmoidoscopies).	FIT recommended as the most suitable screening modality
Whyte et al 2012[20]	England	Markov	A. biennial FIT (60-74), B. FSIG (55), C. FSIG (55) and biennial FIT (56-74). Comparator: biennial gFOBT	QALY	Net Monetary Benefit ** A. £352 B. £57 C. £665 (larger numbers are more favourable)	A. 28 % B. 11 % C. 35%	A. 160 935 B. 340 871 sigmoidoscopies and 27 968 colonoscopies C. 340 871 sigmoidoscopies and 201 563 colonoscopies.	Strategies that included FIT and FS would add additional benefits to the current UK screening programme and be cost effective.

*Incremental cost-effectiveness ratio. Lower number indicates higher cost effectiveness.

** Net Monetary Benefit is calculated by subtracting the marginal costs from the marginal benefits, with the latter calculating by applying willingness to pay criteria to QALYs gained. A higher number is better.

noscopy every 10 years; b) annual FIT; c) sigmoidoscopy every 10 years with annual FIT; or d) CT colonography every 5 years.[27,28] The first three of these were listed as the optimal three screening strategies in the draft recommendations of the USPSTF.[28,29]

The final recommendations of the USPSTF state that "*screening for colorectal cancer in average-risk, asymptomatic adults aged 50-75 years is of substantial net benefit*".[26] They recommend that individuals should decide on the optimal strategy for themselves having taken account of their health and previous screening history, without specifying optimal strategies.

Is there any New Zealand-specific evidence that helps?

To date, there have been no published models for New Zealand that compare test modality and screening strategy. McLeod et al (Burden of Disease Epidemiology Equity and Cost Effectiveness Programme team) have developed a Markov model to assess the cost effectiveness of a national biennial FIT-based programme in New Zealand—with results in press.[30] They found such a programme would be highly cost effective given a threshold of NZD $45,000, and even cost saving for some 5-year age groups (65–69 year and 70–74 years). They also found that greater modelled health gains per capita were achieved for non-Māori compared with Māori, primarily due to the lower CRC incidence among Māori, but that the most cost-effective age range to screen was the same for both Māori and non-Māori (ie, 60–74, 60–79 and 55–79 for 15, 20 and 25 year age ranges respectively).

What have other countries done?

Ireland, the Netherlands and England have all recently undertaken substantial processes to review the evidence on population-based screening for CRC. In all three cases, colonoscopy capacity was considered one of the major limiting factors. After a substantial review process including the modelling detailed previously, Ireland decided to implement a biennial FIT based programme in 2013. Because of the need to expand colonoscopy services, they decided to start with 60–69 year olds with the intention to extend it to those aged 55–74 years as colonoscopy capacity increased.[23,31]

The UK National Screening Committee has recently reviewed evidence in relation to bowel cancer screening and recommended in January 2016 that FIT should be used as the primary test for bowel cancer in the UK screening programmes.[32] The English bowel cancer screening programme is in the process of adding a single sigmoidoscopy to its existing gFOBT-based programme because of evidence that this addition would result in a greater reduction in CRC mortality than FOBT alone, and would be cost-effective (as outlined above).[20,33] They are also planning to change from a gFOBT to the more effective FIT test, but there are no plans to move to a sole sigmoidoscopy-based programme (personal communication 2016, John Davy, National Bowel Cancer Screening Programme Manager, Public Health England).

The Netherlands embarked on perhaps the most extensive programme of any country to assess which screening strategy to use.[34] They carried out an RCT that assessed participation rates for bowel cancer screening using similar invitation approaches but three different screening modalities: gFOBT, FIT and sigmoidoscopy (49.5%, 61.5% and 32.4% respectively).[10] They trialled each of these approaches in terms of their impact on services, particularly endoscopy services. They were particularly concerned about this because colonoscopy services were already beyond capacity at the time that screening was implemented.[34] They also used a microsimulation model to assess the cost effectiveness of different approaches.[34,35] Their final decision was to implement a biennial FIT-based programme with implementation beginning in a single region in 2013. The decision was made on the basis of three main factors: 1. FIT had a substantially higher yield of CRCs and was predicted to have a greater impact on CRC mortality than either gFOBT or one-off sigmoidoscopy; 2. participation was higher for FIT; 3. sigmoidoscopy had a larger impact than expected on endoscopy facilities (personal communication 2016, Professor Ernst Kuipers, National Colorectal Cancer Screening Board for the Netherlands).

In a recent review of existing CRC screening programmes, of 47 organised CRC screening programmes, 28 used FIT, 10 used gFOBT, 7 used mixed modalities, one used colonoscopy and one region of Italy used one-off sigmoidoscopy.[36]

Where to from here?

In the absence of a published model contrasting different screening modalities for New Zealand and the absence of empirical local data to inform many of the inputs for such a model, we have to rely on international comparison studies to inform the best option for a New Zealand screening programme. Fortunately, these international studies consistently point to biennial FIT, with a possible extension to also include FS once a FIT programme and service capacity are in place. Policy-makers have to weigh up different strategies based on their likely cost effectiveness, acceptability to the population and impact on services—all of which may be slightly different in New Zealand compared to other countries.

Based on these findings, it seems the recent decision to proceed with a national population-based biennial FIT based programme in New Zealand is consistent with international evidence and entirely in line with similar decisions made in countries with similar health care systems and resource constraints.

Competing interests:
Ian Bissett is the chair of the National Bowel Cancer Working Group that provides oversight for the Bowel Cancer Screening programme. This is an unpaid position.

Author information:
Diana Sarfati, Professor, Director Cancer Control and Screening Research Group, University of Otago, Wellington; Caroline Shaw, Senior Research Fellow and Public Health Physician, Department of Public Health, University of Otago, Wellington; Melissa McLeod, Senior Research Fellow and Public Health Physician, Department of Public Health, University of Otago, Wellington; Tony Blakely, Professor, Director Burden of Disease Epidemiology Equity and Cost Effectiveness Programme, Department of Public Health, University of Otago, Wellington; Ian Bissett, Professor, Colorectal Surgeon, Faculty of Medical and Health Sciences, University of Auckland, Auckland.

Corresponding author:
Diana Sarfati, University of Otago, PO Box 7343, Wellington.
diana.sarfati@otago.ac.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6979

REFERENCES:

1. Colman J. Bowel Screening Programme Roll-out. https://www.beehive.govt.nz/release/bowel-screening-programme-roll-out 26 May, 2016.
2. Cox B. Flexible sigmoidoscopy is the best approach for a national bowel screening programme. NZ Med J 2016; 129(1430): 14–7.
3. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. [see comment]. Lancet 1996; 348(9040): 1472–7.
4. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996; 348(9040): 1467–71.
5. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000; 343(22): 1603–7.
6. Kuipers EJ, Rosch T, Bretthauer M. Colorectal cancer screening--optimizing current strategies and new directions. Nat Rev Clin Oncol 2013; 10(3): 130–42.
7. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med 2014; 160(3): 171.
8. Tinmouth J, Lansdorp-Vogelaar I, Allison JE. Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer

screening programme organisers need to know. Gut 2015; 64(8): 1327–37.

9. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population.[see comment]. Gastroenterol 2008; 135(1): 82–90.
10. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010; 59(1): 62–8.
11. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev 2007; (1): CD001216.
12. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010; 375(9726): 1624–33.
13. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst 2011; 103(17): 1310–22.
14. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014; 312(6): 606–15.
15. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012; 366(25): 2345–57.
16. McGregor L, Bonello B, Kerrison R, et al. Uptake of bowel scope (flexible sigmoidoscopy) screening in the English national programme: the first 14 months. J Med Screening 2015; 23(2): 77–82.
17. Kaminski MF, Bretthauer M, Zauber AG, et al. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. Endoscopy 2012; 44(7): 695–702.
18. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012; 366(8): 697–706.
19. Canadian Taskforce of Preventive Healthcare. Recommendations on screening for colorectal cancer in primary care. CMAJ 2016; DOI: 10.1503/cmaj.151125 (early release).
20. Whyte S, Chilcott J, Halloran S. Reappraisal of the options for colorectal cancer screening in England. Colorectal Dis 2012; 14(9): e547–61.
21. Tappenden P, Chilcott J, Eggington S, Patnick J, Sakai H, Karnon J. Option appraisal of population-based colorectal cancer screening programmes in England. Gut 2007; 56(5): 677–84.
22. Whyte S, Chilcott J, Cooper K, et al. Re-appraisal of the options for colorectal cancer screening. Full Report. Sheffield, UK: School of Health and Related Research, University of Sheffield, 2011.
23. Sharp L, Tilson L, Whyte S, et al. Cost-effectiveness of population-based screening for colorectal cancer: a comparison of guaiac-based faecal occult blood testing, faecal immunochemical testing and flexible sigmoidoscopy. Br J Cancer 2012; 106(5): 805–16.
24. Dan YY, Chuah BY, Koh DC, Yeoh KG. Screening based on risk for colorectal cancer is the most cost-effective approach. Clin Gastroenterol Hepatol 2012; 10(3): 266–71.e1-6.
25. Zauber AG, Knudson A, Rutter C, Landsdorp-Vogelaar I, Kuntz K. Evaluating the benefits and harms of colorectal cancer screening strategies: a collaborative modeling approach. AHRQ Publication No. 14-05203-EF-2. Rockvill, MD: Agency for Healthcare Research and Quality, 2015.
26. U. S. Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2016; 315(23): 2564–75.
27. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016; 315(23): 2595–609.
28. U.S. Preventive Services Taskforce. Draft recommendation statement. Colorectal cancer: screening. Available at http://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement38/colorectal-cancer-screening2#figure-benefits-harms-and-burdens-of-recommend-

ed-screening-strategies-over-a-lifetime. 2016 (accessed 4 Mar 2016).

29. Ransohoff DF, Sox HC. Clinical Practice Guidelines for Colorectal Cancer Screening: New Recommendations and New Challenges. JAMA 2016; 315(23): 2529–31.

30. McLeod M, Kvizhinadze G, Boyd M, et al. Colorectal cancer screening: Variation in health gain and cost-effectiveness by ethnic group, and the optimal age-range to screen. BMC Cancer in press.

31. Sharp L, Tilson L, Whyte S, et al. Using resource modelling to inform decision making and service planning: the case of colorectal cancer screening in Ireland. BMC Health Services Research 2013; 13: 105.

32. UK National Screening Committee. The UK NSC recommendation on bowel cancer screening in adults. http://legacy.screening.nhs.uk/bowelcancer 2016.

33. Geurts SM, Massat NJ, Duffy SW. Likely effect of adding flexible sigmoidoscopy to the English NHS Bowel Cancer Screening Programme: impact on colorectal cancer cases and deaths. Br J Cancer 2015; 113(1): 142–9.

34. van Hees F, Zauber AG, van Veldhuizen H, et al. The value of models in informing resource allocation in colorectal cancer screening: the case of The Netherlands. Gut 2015; 64(12): 1985–97.

35. Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res 1999; 32(1): 13–33.

36. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015; 64(10): 1637–49.

Sialolithiasis in the Stensen's duct

Ryoko Watanabe, Kenta Watanabe

A 67-year old woman presented with swelling and pain in the left parotid region, causing difficulty in opening her mouth. She had been treated for autoimmune hepatitis and Sjögren's syndrome and had been administered oral glucocorticoids for immunosuppression. Oral observation revealed a purulent discharge spontaneously draining from the opening of the left Stensen's duct. Enhanced computed tomography (CT) revealed marked swelling of the left parotid gland, suggesting abscess formation (Figure 1), a sialolith in the left Stensen's duct (arrows in Figures 1 and 2) and dilation of the duct (arrowhead in Figure 2). After intravenous antibiotic administration, the swelling gradually ameliorated. Furthermore, manual compression of the parotid gland was performed daily. On day 12 of the hospitalisation, the sialolith was discharged into the oral cavity (Figures 3 and 4) and the patient checked out of the hospital on day 14.

Although the exact aetiology of the sialolithiasis is unclear,[1] chronic inflammation can be a factor in calculus formation.[2] Reportedly, sialolithiasis commonly occurs in the submandibular duct (Wharton's duct) because of the length and calibre of the duct, and the flow and viscosity of the saliva.[2] However, we speculated that it developed in Stensen's duct in this case because of chronic parotitis.

Figure 1:

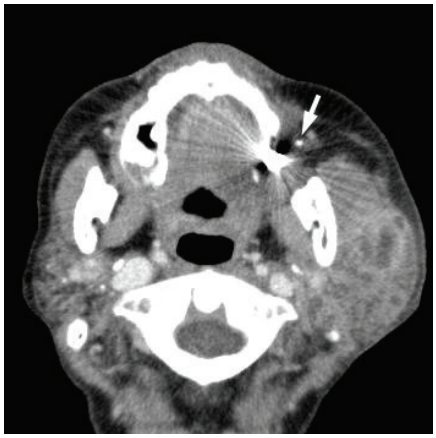


Figure 2:

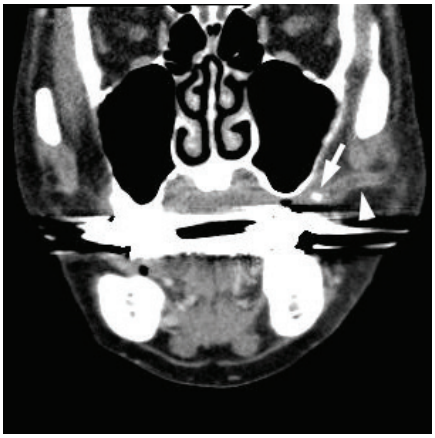


Figure 3:

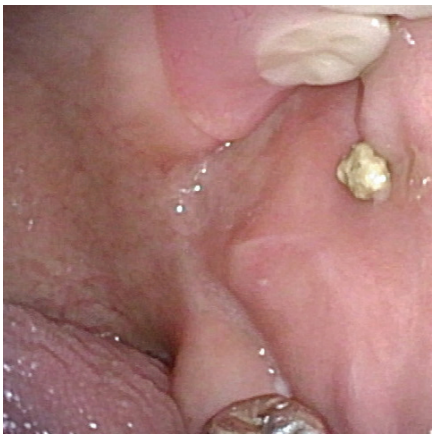
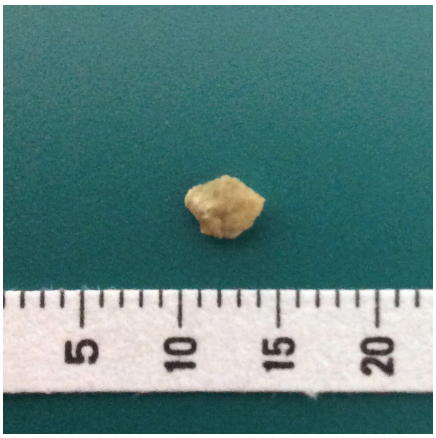


Figure 4:



Competing interests:
Nil.

Author information:
Ryoko Watanabe, Otolaryngologist - Head and Neck Surgeon, Department of Otolaryngology, Toranomon Hospital, Tokyo, Japan; Kenta Watanabe, Chief Otolaryngologist - Head and Neck Surgeon, Department of Otolaryngology, Toranomon Hospital, Tokyo, Japan.

Corresponding author:
Ryoko Watanabe, Otolaryngologist - Head and Neck Surgeon, Department of Otolaryngology, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo, 105-8470, Japan.
kma00041@gmail.com

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6980

REFERENCES:

1. Houh KC, Eisele DW. Etiologic factors in sialolithiasis. Otolaryngol Head Neck Surg. 2011; 145(6): 935–9.
2. Williams MF. Sialolithiasis. Otolaryngol Clin North Am. 1999; 32(5): 819–34.

A rare case of bacterial conjunctivitis: the importance of pre-antibiotic swabs for microbiology

Peter Murray, Annette Nesdale, Michelle Balm

Primary meningococcal conjunctivitis (PMC) is a rare but potentially dangerous condition. The following describes a recent case of PMC and explores the clinical and public health issues it raises.

Background

A 22-year-old male was reviewed at a DHB hospital eye clinic with a two-day history of a discharging, red, painful right eye, but was otherwise systemically well. The patient was prescribed topical ciprofloxacin and chloramphenicol and a conjunctival swab was taken, with follow-up arranged in three days.

The patient went on holiday with his family and three days later cancelled the follow-up appointment stating he was unwell. On the same day, the conjunctival culture isolated *N.meningitidis*. Numerous attempts to contact the patient were unsuccessful and the local public health unit was notified.

The following day, contact was made when the patient returned to the region. On review in the emergency department, he remained systemically well and his conjunctivitis was now improving. He received IV ceftriaxone and continued topical antibiotics. All close contacts were reviewed by Public Health and received chemoprophylaxis and education about meningococcal disease. The isolate was typed as Group C and monovalent (C) vaccination was administered to the case and close contacts.

The patient's symptoms resolved by day four and he remained well on follow-up. The final diagnosis was PMC. All close contacts remained well.

Discussion

N.meningitidis is a well-recognised human pathogen most commonly associated with invasive meningococcal disease (IMD). It is also a potential cause of acute bacterial conjunctivitis, which can be classified as primary or secondary in nature.[1,2]

PMC is a rare condition, though its true incidence is unknown as many cases of bacterial conjunctivitis are treated empirically without culture.[3] PMC is more common in children and caused mostly by serogroup B strains.[2,4]

Clinically, PMC can present as an acute or hyperacute bacterial conjunctivitis, and commonly affects only one eye.[5] PMC can result in ocular and systemic complications. Ocular complications (eg, corneal ulceration) can occur in up to 15.5% of cases.[2,6] The feared systemic complication is IMD. Case series suggest this can occur in 10–29% of PMC cases and usually occurs within 40 hours of ocular symptoms.[2,6] IMD has been shown to occur more commonly in patients who only received topical treatment.[2] As a consequence, it is now recommended that PMC be treated with topical and systemic therapy, the latter of which eliminates carriage of *N.meningitidis* and risk of developing IMD.[3,5] The choice of systemic therapy should be guided by an infectious disease specialist.

Evidence suggests close contacts of a PMC case are also at risk of developing IMD.[3,5] Consequently, awareness of the significance of *N.meningitidis* from eye cultures by microbiologists, ophthalmologists and GPs, rapid communication between labo-

ratories, clinical doctors and public health and a public health response is required for appropriate management.[3,5,7] The key aspects of the response include contact tracing, offering chemoprophylaxis and/or vaccination (if indicated) to close contacts, and educating contacts on IMD.[7] The purpose of chemoprophylaxis is to eradicate *N.meningitidis* carriage and reduce the risk of secondary IMD cases.[3,7]

Notwithstanding the risk posed by PMC, it does not currently meet the case definition of IMD in New Zealand and details of notifications have been inconsistent.[7] Changing the case definition to include PMC may help improve our understanding of the disease and better manage the public health risk.

In conclusion, PMC has the potential to cause local and systemic complications. Close contacts of a PMC case are also at risk of developing IMD and public health management is necessary to reduce the risk of secondary cases. It is recommended PMC be included in the case definition of IMD in New Zealand.

Competing interests:
Nil.

Author information:
Peter Murray, Regional Public Health, Hutt Hospital, Lower Hutt, New Zealand, Annette Nesdale, Regional Public Health, Hutt Valley District Health Board, New Zealand; Michelle Balm, Microbiology, Aotea Pathology, New Zealand.

Corresponding author:
Peter Murray, Regional Public Health, Hutt Hospital, Lower Hutt, New Zealand.
iworldpete@gmail.com

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6981

REFERENCES:

1. Andreoli CM, Wiley HE, Durand ML, Watkins LM. Primary meningococcal conjunctivitis in an adult. Cornea. 2004;23(7):738–9.
2. Barquet N, Gasser I, Domingo P, Moraga FA, Macaya A, Elcuaz R. Primary meningococcal conjunctivitis: report of 21 patients and review. Rev Infect Dis. 1990;12(5):838–47.
3. Poulos R, Smedley EJ, Ferson MJ, Bolisetty S, Tapsall JW. Refining the public health response to primary meningococcal conjunctivitis. Commun Dis Intell. 2002;26(4):592–5.
4. Andersen J, Lind I. Characterization of Neisseria meningitidis isolates and clinical features of meningococcal conjunctivitis in ten patients. Eur J Clin Microbiol Infect Dis. 1994;13(5):388–93.
5. Bigham J, Hutcheon M, Patrick D, Pollard A. Death from invasive meningococcal disease following close contact with a case of primary meningococcal conjunctivitis--Langley, British Columbia, 1999. Can Commun Dis Rep. 2001;27(2):13–8.
6. Orden B, Martínez R, Millán R, Belloso M, Pérez N. Primary meningococcal conjunctivitis. Clin Microbiol Infect. 2003;9(12):1245–7.
7. Ministry of Health. Communicable Disease Control Manual 2012. Wellington, New Zealand, 2012. Available at http://www.health.govt.nz/publication/communicable-disease-control-manual-2012.

Residential mobility: diluting the potential of public health programmes

Leanne Young, Stephanie McLennan, Madeleine Kirk, Elaine Rush

When families move house it is often more than a change of address; it is a repeated change of school, workplace, health service and community. While the reason for moving may be positive such as families relocating to take up new employment, for some, in particular young children, it is mainly due to altered 'housing tenure'.[1] High housing mobility or transience is associated with poorer health and education engagement and outcomes, and may limit the success of health promotion programmes located in these sectors.

Early life development and environment is increasingly recognised as influencing adult health outcomes.[2] Minimising adverse exposures during this period will enhance child health and development and consequently adult health.[3] Residential mobility is of interest as an environmental factor influencing health outcome because it features in the early part of life for many children in New Zealand.[4] The reasons for high residential mobility are complex and interrelated, and may be an indicator of the presence of other negative effects on child health and development such as poverty, family instability, unemployment and single parenthood.[5]

New Zealand has a highly mobile population with 51 percent of the population reporting a change of address between 2001 and 2006.[4] Population residential mobility rates, using age standardised data, show more New Zealanders move in a year compared to other developed countries.[6] Population subgroups experiencing higher rates include families with young (1–4 years) children,[4] Māori (due in part to a young population age structure)[4] and the economically disadvantaged.[7]

Poor health outcomes in childhood and adolescence have been associated with high residential mobility in school age children with the strongest evidence for behavioural problems in childhood and more risk-taking behaviours among teenagers.[3] Lower levels of health service utilisation and disrupted continuity of care are other possible negative effects.[3] Interruption in education is also likely with resulting negative impacts on educational outcomes.[7] An evaluation of the early childhood Participation Initiative Programme found that around one in three children left the initiatives after enrolling for unknown reasons, although the early childhood education providers interviewed commented that transience was a common reason for leaving the services.[8] Transience was highlighted as a cause of non-participation in a survey of Māori mothers to determine knowledge of sudden infant death syndrome prevention during which over a third of the identified sample of mothers were unable to be contacted.[9] Non-participation in research was also noted by Jelleyman and Spencer, stating that 'residential mobility may affect inclusion in studies potentially obscuring these children from research'.[3]

Under 5 Energize (U5E) is a health promotion programme operating since July 2013 in 121 early childhood centres across the Waikato region in four high deprivation cluster areas. An audit in 2015 of 87 participating early childhood centres (excluding four-year old children transitioning to school) found that one in four children moved in the previous year and almost half the centres had three or more staff change. The reported mean number of teachers per centre at programme initiation was suggesting a turnover of around half the staff in these centres. Enrolment and staff turnover was greater in lower equity index (Equity index [EI] is the Ministry of Education measure of the extent to which the early childhood centre enrols children from low socioeconomic areas. An EI of one indicates a centre with children from a

ISSN 1175-8716

high deprivation area and five is low deprivation) early childhood centres. Project Energize, another similar health promotion programme in primary schools, found lead teachers from schools identified a high school roll turnover as a barrier to 'the levels of engagement and participation' in Project Energize but had the advantage that all primary schools in the Waikato region receive the Energize service[10] if the move was within the region. This has implications for programme delivery and implementation, increasing cost and reducing potential impact. Areas experiencing high mobility require new relationships to be established and ongoing regular message delivery sessions to accommodate new educators and families. A focus on embedding programme aims into policy and practices nationwide is imperative to avoid loss of programme gains when staff and families move.

In conclusion, high turnover of a population is limiting health programme engagement, participation, evaluation and outcomes. Frequent residential change should be an important consideration in the design, implementation, evaluation and funding of health promotion programmes especially in populations experiencing transiency.

Competing interests:
Nil.

Acknowledgements:
We gratefully acknowledge the early childhood centre representatives who gave freely of their time to complete the audit. Gravida: National Centre for Growth and Development provided financial support for this work (LY Doctoral Scholarship). Under 5 Energize is funded by the Ministry of Health.

Author information:
Leanne Young, Faculty of Health and Environmental Science, Auckland University of Technology, Auckland; Stephanie McLennan, Project Energize, Sport Waikato, New Zealand; Madeleine Kirk, Under 5 Energize, Sport Waikato, New Zealand; Elaine Rush, Centre for Child Health Research, Auckland University of Technology, Auckland.

Corresponding author:
Leanne Young, Faculty of Health and Environmental Science, Auckland University of Technology, Private Bag 92006, Auckland.
leanne.young@aut.ac.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6982

REFERENCES:

1. Morton SMB, Atatoa Carr PE, Berry SD, et al. Growing up in New Zealand: A longitudinal study of New Zealand children and their families. Residential Mobility Report 1: Moving house in the first 1000 days. Auckland: Growing Up in New Zealand; 2014.
2. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: Physiology or pathophysiology? Physiol Rev. 2014;94(4):1027–1076.
3. Jelleyman T, Spencer N. Residential mobility in childhood and health outcomes: a systematic review. J Epidemiol Community Health. 2008;62(7):584–592.
4. Statistics New Zealand. 2006 Census of population and dwellings. Wellington: Statistics New Zealand; 2009.
5. Dong M, Anda RF, Felitti VJ, et al. Childhood residential mobility and multiple health risks during adolescence and adulthood: The hidden role of adverse childhood experiences. Arch Pediatr Adolesc Med. 2005;159(12):1104–1110.
6. Long L. International perspectives on the residential mobility of America's children. J Marriage Fam. 1992;54:861–869.
7. Wynd D. The revolving door: Student mobility in Auckland schools. Auckland: Child Poverty Action Group; 2014.
8. Mitchell L, Meagher-Lundberg P, Davison C, et al. ECE participation programme evaluation. Wellington: Ministry of Education; 2016.
9. Tipene-Leach D, Hutchison L, Tangiora A, et al. SIDS-related knowledge and infant care practices among Maori mothers. NZ Med J. 2010;123(1326):88–96.
10. Mrkusic A. School engagement in the Project Energize health intervention programme. 'What works, what does not work, what next?' [Master's Thesis] Auckland: Auckland University of Technology; 2012.

Re: The clinical consequences of underfunding elective healthcare: A second red flag warning

Philip Bagshaw

Under the influence of a long period of neo-liberal ideology, there has been a gradual downgrading of the English NHS using salami tactics.[1] Progressive underfunding has occurred, with more and more privatisation of separate parts of the service.[2,3] Funding has been generally maintained for acute "shop-front" services but the more mundane elective services have been allowed to slowly wither on the vine.

In this environment, managers of the Birmingham and Solihull primary care trust developed a policy of restricting access to elective surgery in order to save money. As a result, a sentinel warning article in 2014 showed the serious consequences of a reduction in elective hernia surgery, with consequent implications for patient safety.[4] It was no surprise that such a red flag was first raised with this type of surgery. It is the most common operation performed in the Western world and was therefore likely to be the type of treatment where adverse clinical outcomes would first become apparent.

Using Official Information Act requests, it was shown last year that some New Zealand DHBs had implemented a similar policy of restricting access to elective hernia surgery.[5]

Now, a second red flag publication, just this this month, has again shown the serious consequences of this policy. Another NHS trust imposed funding restrictions for elective hernia surgery in 2011.[6] When the 12-month periods before and after the introduction of the policy were compared, there was a 53% increase in emergency hernia surgery, a 13-fold increase in associated bowel resections, a large increase in the median length of hospital stay, and a higher hospital readmission rate. The ultimate irony is that the financial implications are enormous.

How will New Zealand now respond to this second red flag warning? Such problems will inevitably appear in many areas of neglected elective healthcare beyond hernia surgery. So will we continue to blindly follow the path trodden by the disintegrating NHS, with chronic underfunding that will lead us to an American-style healthcare system, where a large proportion of our population must pay for some basic healthcare services or go without?

The Royal College of Surgeons of England has finally woken to the reality of the progressive disintegration of the NHS and is now speaking out frequently and publicly about the dire consequences.[7] Whilst this development is laudable, it may be just 'too little and too late' for the NHS. Will our New Zealand medical colleges remain silent or speak out publicly about what is happening to our elective healthcare services before it is too late?

Our politicians continue to claim, contrary to the evidence, that our healthcare system is a rapacious beast, which will never be satiated with whatever funding they apportion to it. Indeed, the facts show that they have been progressively underfunding our healthcare system for years.[8] Such an approach is old-fashioned economic thinking. It is now clear to forward-thinking economists that investing in health pays very large fiscal dividends.[9] In any event, who will want to live in a country that does not provide a high standard of healthcare for the whole of its population?

ISSN 1175-8716

Competing interests:
Nil.

Author information:
Philip Bagshaw, Clinical Associate Professor, University of Otago - Christchurch, Christchurch.

Corresponding author:
Philip Bagshaw, Clinical Associate Professor, University of Otago - Christchurch, Christchurch.
bagshaw@clear.net.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6983

REFERENCES:

1. El-Gingihy Y. How to Dismantle the NHS in 10 Easy Steps. Zero Books 2015.
2. Stuckler D, Basu S. The Body Economic. Chapter 6. Penguin Books, London 2013.
3. Iacobucci G. Government is in "denial" over NHS funding crisis, says BMA chair. BMJ 2016;353:i2507.
4. Hwang MJ, Bhangu A, Webster CE, et al. Unintended consequences of policy change to watchful waiting for asymptomatic inguinal hernias. Ann R Coll Surg Eng 2014;96:343–7.
5. Bagshaw PF. What should be the management policy for asymptomatic inguinal hernias? NZ Med J. 2015;128;83–8.
6. Orchard MR, Wright JA, Kelly A, McCabe DJ, Hewes J. The impact of healthcare rationing on elective and emergency hernia repair. Hernia 2016;20:405–9.
7. RCS raises concerns over rationing of surgery at West Midlands CCGs. 8th April 2016. Accessed at http://ecomms.rcseng.ac.uk/linkapp/cmaview.aspx?LinkID=pageid-100909346znqqh~njrztfq-j~nxqjf~nqzhhx~z~x~f~f~n on 3rd June 2016.
8. Keene L, Bagshaw P, Nicholls MG, et al. Funding New Zealand's public healthcare system: time for an honest appraisal and public debate. NZMJ 2016;129:10–20.
9. Reeves A, Basu S, McKee M, et al. Does investment in the health sector promote or inhibit economic growth? Globalization and Health 2013;9:43 http://globalizationandhealth.biomedcentral.com/articles/10.1186/1744-8603-9-43

Is New Zealand's visual acuity screening programme in school-age children justified?

Nishanthan Ramachandran, Nick Wilson, Graham A Wilson

New Zealand has a nationwide school-based screening programme to detect defective vision in children aged 11 or 12 (Year 7) and colour vision deficiency in boys aged 11 or 12.[1] This is on top of the 'B4 School' vision screening at age four, which aims to detect and correct refractive error and amblyopia if present.[1] However, from 1 July 2016,[2] the colour vision screening component of the Year 7 screening is being discontinued, as there is little association between colour vision deficiency and adverse outcomes, and as there are no treatment options.[3] Now is therefore an opportune time to consider the value of the remaining aspects of the Year 7 vision screening programme.

Vision screening after the critical amblyopia reversal period (up to eight years of age),[4] is predominantly aimed at detecting refractive errors (myopia, hypermetropia and astigmatism) that can be corrected to improve visual function.[5] Uncorrected refractive error can lead to poorer educational outcomes,[6] with possible detrimental effects on future occupational choice, and can thus affect quality of life adversely.[7]

But despite these plausible adverse associations, a Cochrane systematic review in 2006 concluded that there were no robust trials available that measure the benefit of vision screening in school-aged children.[5] Other reviews have also found little evidence in support of screening school-aged children.[6, 8] It appears that relatively few new cases of refractive errors are found in this age-group, as such problems have nearly always been detected earlier in life.[5, 6, 8] Similarly our MEDLINE search to cover any new research that may have emerged after the Cochrane review,[5] from the year 2006 to March 2016, failed to find any studies that provide convincing support of continuing the current vision screening programme in school children. This lack of adequate evidence and low yield of cases, may explain the general decline in school-based vision screening programmes in the UK.[5]

This overall picture also suggests it is time for New Zealand health authorities to critically review the case for the Year 7 programme—so that we can tell if it is a good use of precious health sector resources and of displaced educational time in schools. In particular, what is the current effectiveness and cost-effectiveness of this programme in the New Zealand setting?

If it is not cost-effective nationally, however, might it still be cost-effective in deprived communities or in communities with high Asian populations (given some evidence for higher prevalence and severity of myopia in such populations)?[5, 9, 10] Such analyses also need to take into account two notable trends:

- the rising incidence of myopia globally[10] (though we have no clear data on this for New Zealand)
- what the market is offering in terms of some optometry practices in New Zealand providing a free full eye exam to under 16 year olds (with no cost for glasses of children of Community Services Card holders).[11]

In summary, all screening programmes need a robust scientific basis in terms of effectiveness and cost-effectiveness. Therefore there is a need to clarify such issues for the current Year 7 vision screening programme in New Zealand schools.

ISSN 1175-8716

Competing interests:
Nil.

Author information:
Nishanthan Ramachandran, Postgraduate Year 2 Doctor, MidCentral District Health Board, Palmerston North; Nick Wilson, Professor of Public Health, University of Otago, Wellington; Graham A Wilson, Ophthalmologist, Tairawhiti District Health Board, Gisborne.

Corresponding author:
Nishanthan Ramachandran, Palmerston North Hospital, Private Bag 11036, Palmerston North 4442, New Zealand.
nishan.rama@gmail.com

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6984

REFERENCES:

1. Ministry of Health. National vision and hearing screening protocols: Revised 2014. Wellington: Ministry of Health. 2014.
2. Waikato District Health Board - Press Release. Colour blindness testing discontinued in schools. 2016. Available from: http://www.waikatodhbnewsroom.co.nz/2016/02/25/colour-blindness-testing-discontinued-in-schools/ [Accessed 20th March 2016].
3. Ramachandran N, Wilson GA, Wilson N. Is screening for congenital colour vision deficiency in school students worthwhile? A review. Clin Exp Optom. 2014;97(6):499–506.
4. Powell C, Hatt SR. Vision screening for amblyopia in childhood. Cochrane Database Syst Rev. 2009;(3).
5. Powell C, Wedner S, Hatt SR. Vision screening for correctable visual acuity deficits in school-age children and adolescents. Cochrane Database Syst Rev. 2004;(4).
6. Mathers M, Keyes M, Wright M. A review of the evidence on the effectiveness of children's vision screening. Child Care Health Dev. 2010;36(6):756–80.
7. Sharma A, Congdon N, Patel M, Gilbert C. School-based approaches to the correction of refractive error in children. Surv Ophthalmol. 2012;57(3):272–83.
8. Morcos A, Wright M. National children's vision screening project: Final report. Melbourne: Murdoch children's research institute: Centre for Community Child Health. 2009.
9. Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. Ophthalmic Physiol Opt. 2012;32(1):3–16.
10. Dolgin E. The myopia boom. Nature. 2015;519(7543):276–8.
11. Specsavers Optical Group. Free eye exam for under 16s. 2015. Available from: http://www.specsavers.co.nz/special-offers/free-eye-exam-for-under-16s [Accessed 20th March 2016].

Ghosts in the machine: just how accurate is PubMed?

Frank Houghton

PubMed has a long and distinguished history. Its origins are in the work of John Shaw Billings, Head of the Library of the Surgeon General's Office of the US Army (now the US National Library of Medicine [NLM]). Billings initiated the development of *Index Medicus* in 1879, which after being amalgamated with the American Medical Association's *Quarterly Cumulative Index to Current Literature* would eventually become MEDLARS (Medical Literature Analysis and Retrieval System) in 1964. It later went online for institutional facilities, under the name MEDLINE (an abbreviation of MEDLARS Online). In 1996, with the development of the World Wide Web and browsing software, MEDLINE went truly online, under the name PubMed, which was offered free to the public in 1997.[1–3]

PubMed now boasts over 25 million citations in 'the fields of biomedicine and health, covering portions of the life sciences, behavioral sciences, chemical sciences, and bioengineering'.[4] A 2007 study of PubMed queries noted 2,689,166 searches in a 24-hour period,[5] while a later study found 2,996,301 searches in a similar period.[6]

This enormous and growing volume of searches is indicative of how PubMed has become a routine and invaluable resource.

Despite its impact, critiques of PubMed are rare. One issue for many is that access is usually given only to abstracts rather than the full text. A recent examination[7] noted that approximately 13% of articles in PubMed were available for free (approximately three million). Obviously health practitioners and academics in industrialised countries are at a significant advantage compared to many less privileged groups locally and globally in tackling the digital and information divide. However, even among this privileged group, it is interesting to ponder how often a lack of quick, easy or affordable access impinges on obtaining items identified in database searches, including PubMed. Resistance to this knowledge divide includes the tragic case of Aaron Swartz who was allegedly behind one biblioleaks scandal involving 70GB of information from JSTOR.[8]

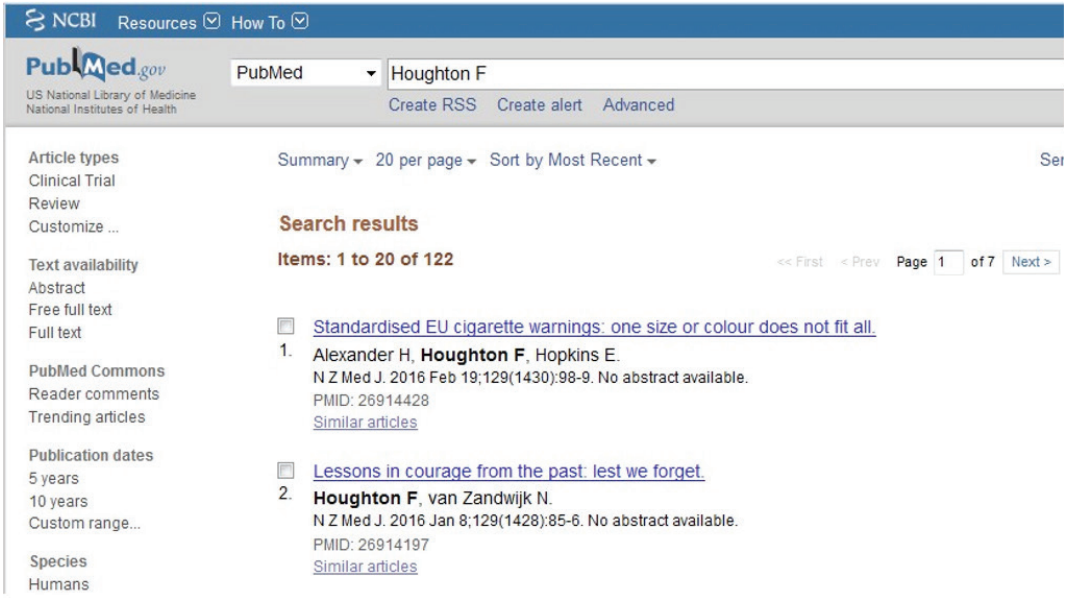
Another criticism of PubMed is its focus on English-language journals, which serves to reinforce the dominance of English globally.[9] Alternatively, PubMed may be criticised for being both over and under inclusive. In relation to its lack of coverage, PubMed's coverage of relevant articles in journals in the social sciences, humanities and arts is patchy at best. In relation to over-inclusion, PubMed may justifiably be criticised for referencing many poor-quality articles. Some evidence of this can be seen in the high rates of articles rejected in reviews such as those conducted by the Cochrane Collaboration.

Although there has been a considerable body of research examining reference citation accuracy involving medical journals from both New Zealand, Australia[10–11], and further afield,[12–28] relatively few studies have examined this issue in PubMed.[29–31] Examinations of accuracy of Spanish and Hispanic names in PubMed report its performance as *'poor'*,[30] while another more vehemently states that *'bibliographic databases produced in English-speaking countries have been mishandling non-AngloSaxon names for years'*.[31]

My concerns over the accuracy of PubMed were raised when I searched for two of my recent publications. As can be seen from Figure 1, a number of errors were evident. The authors of item 1 were in reality just Houghton & Hopkins,[32] while the second item was a solo publication.[33] In relation to item 1, I note from the contents page of the NZMJ that Alexander published in the same issue,[34] while Zandwijk, referenced in item 2, published in the NZMJ in December 2015.[35]

ISSN 1175-8716

Figure 1:



Another PubMed error in my publications listing is also evident. I previously published in the *Irish Medical Journal* discussing the 2001 Census. However, the PubMed citation starts *'Census 200'* rather than *'Census 2001'* as it should.[36] Other concerns in relation to PubMed include how one of my publications on mortality maps[37] from the journal *Irish Geography* is included, while another 11 publications in the same journal on health topics are not. The inclusion of either all or none of these publications would not have raised a red flag for me.

In due course I will contact the NLM and attempt to have these errors addressed. Mistakes are inevitable, particularly given the size of the database. However, even putting aside the issue of coverage in *Irish Geography*, to identify at least three errors on PubMed in relation to just one author raises concerns as to the level of accuracy and reliability of the database as a whole.

A wider review of quality and inaccuracies in PubMed may be appropriate. Examination of the software used to auto-extract information from PDFs is ongoing.[38] In the meantime it may be wise to follow the discerning advice of McLellan et al. who suggest 'Trust, but verify'.[12]

Editor's comment

While it would be nice to blame PubMed for the errors, in the case of the NZMJ, it is the Journal's error not PubMed's. The data that PubMed uses to make up the listing comes directly from journal staff. At times the production staff member who loads the information makes errors (ie, is human). We do try to keep these errors down as much as possible and undertake to correct them as soon as we know they exist. Unfortunately these corrections can also take time and can't be done by the Journal, but must be undertaken by the PubMed staff. Sorry about the loading error—we are in the process of correcting it.

Competing interests:
Nil.

Author information:
Frank Houghton, MPH Program Director, Department of Public Health & Health, Administration, Eastern Washington University, Spokane, Washington, US.

Corresponding author:
Frank Houghton, Program Director MPH & HSAD, Eastern Washington University, Rm 232, Phase 1 Building, 668 N. Riverpoint Blvd, Spokane, Wa, 99202, US.
fhoughton@ewu.edu

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6985

REFERENCES:

1. US National Library of Medicine. The Story of the NLM Historical Collections. Accessed on 11th March 2016 at: https://www.nlm.nih.gov/hmd/about/collectionhistory.html
2. Lindberg DAB. Internet Access at the National Library of Medicine. Eff Clin Pract. 2000;4:256–260.
3. US National Library of Medicine. Fact Sheet MEDLINE. Accessed on 11th March 2016 at: https://www.nlm.nih.gov/pubs/factsheets/medline.html
4. NCBI. PubMed help. 2015. http://www.ncbi.nlm.nih.gov/books/NBK3827/ 5 Herskovic JR, Tanaka LY, Hersh W, Bernstam EV. A Day in the Life of PubMed:
5. Analysis of a Typical Day's Query Log. Journal of the American Medical Informatics Association: JAMIA. 2007;14(2):212–220. doi:10.1197/jamia.M2191.
6. Yoo I, Mosa ASM. Analysis of PubMed User Sessions Using a Full-Day PubMed Query Log: A Comparison of Experienced and Nonexperienced PubMed Users. JMIR Medical Informatics. 2015;3(3):e25. doi:10.2196/medinform.3740.
7. Dunn AG, Coiera E, Mandl KD. Is Biblioleaks Inevitable? J Med Internet Res 2014;16(4):e112. DOI: 10.2196/jmir.3331
8. The Guardian. Remembering Aaron Swartz: the open web icon. 12th February 2014. Accessed on 11th March 2016 at: http://www.theguardian.com/technology/2014/feb/11/aaron-swartz-icon-open-web-surveillance-nsa
9. Tardy C. The Role of English in Scientific Communication: "Lingua Franca" or "Tyrannosaurus Rex"? Journal of English for Academic Purposes 2004;3(3):247–269.
10. Holt S, Siebers R, Suder A, Loan R, Jeffery O. The accuracy of references in Australian and New Zealand Medical Journals. N Z Med J 2000;113(1119):416-7.
11. Ngan Kee WD, Roach VJ, Lau TK. How accurate are references in the Australian and New Zealand Journal of Surgery. Australian and New Zealand Journal of Surgery 1997;67(7):417:9.
12. McLellan MF, Case LD, Barnett MC. Trust, but verify. The accuracy of references in four anesthesia journals. Anesthesiology 1992;77(1):185–7.
13. Goldberg R, Newton E, Cameron J, Jacobson R, Chan L, Bukata WR, Rakab A. Reference accuracy in the emergency medicine literature. Ann Emergency Med 1993;22(9):1450–4.
14. Siebers R, Holt S. Accuracy of references in five leading medical journals. Lancet 2000;21;356(9239):1445.
15. O'Connor AE. A review of the accuracy of references in the journal Emergency Medicine. Emergency Medicine 2002;14(2):139–41.
16. Jackson K, Porrino JA, Tan V, Daluiski A. Reference accuracy in the Journal of Hand Surgery. J Hand Surg Am. 2003;28(3):377–80.
17. Gosling CM, Cameron M, Gibbons PF. Referencing and quotation accuracy in four manual therapy journals. Man Ther. 2004;9(1):36–40.
18. Aronsky D, Ransom J, Robinson K. Accuracy of references in five biomedical informatics journals. J Am Med Inform Assoc 2005;12(2):225–8.
19. Raja UY, Cooper JG. How accurate are the references in Emergency Medical Journal? Emerg Med J. 2006;23(8):625–6.
20. Reddy MS, Srinivas S, Sabanayagam N, Balasubramanian SP. Accuracy of references in general surgical journals-an old problem revisited. Surgeon. 2008;6(2):71–5.
21. Al-Benna S, Rajgarhia P, Ahmed S, Sheikh Z. Accuracy of references in burns journals. Burns. 2009;35(5):677–80. doi: 10.1016/j.burns.2008.11.014.
22. Unver B, Senduran M, Unver Kocak F, Gunal I, Karatosan V. Reference accuracy in four rehabilitation journals. Clin Rehabil 2009;23(8):741–5.
23. Singh S, Chaudhary R. Accuracy of references cited in articles published in Indian Journal of Dermatology, Venereology and Leprology: a pilot study. Indian J Dermatol Venereol Leprol. 2009;75(5):488–91. doi: 10.4103/0378-6323.55392.
24. Adhikari P. Accuracy of references in Indian journal of otolaryngology and head & neck surgery. Indian J Otolaryngol Head Neck Surg. 2010;62(4):338–41. doi: 10.1007/s12070-010-0048-y.
25. Davids JR., Weigl DM, Edmonds JP! Blackhurst DW. Reference accuracy in peer- reviewed pediatric orthopaedic literature. J Bone Joint Surg Am 2010;92(5):1155–61.
26. Awrey J, Inaba K, Barmparas G, Recinos G, Teixeira PG, Chan LS, Talving P, Demetriades D. Reference accuracy in the general surgery

literature. World J Surg. 2011;35(3):475–9. doi: 10.1007/s00268-010-0912-7.

27. Samad A, Khanzada TW, Kumar B, Malik KA. Accuracy of references: comparison between two premier Pakistani medical journals. J Pak Med Assoc. 2013;63(4):445–7.

28. Luo M, Li CC, Molina D, Andersen CR, Panchbhavi VK. Accuracy of citation and quotation in foot and ankle surgery journals. Foot Ankle Int. 2013;34(7):949–55. doi: 10.1177/1071100713475354.

29. Ruiz-Pérez R, Delgado López-Cózar E, Jiménez-Contreras E. Spanish personal name variations in national and international biomedical databases: implications for information retrieval and bibliometric studies. J Med Libr Assoc. 2002;90(4):411–30.

30. Fernandez E, Garcia AM. Accuracy of referencing of Spanish names in Medline. Lancet 2003;361(9354):351–2.

31. Ruiz-Pérez R, López-Cózar ED, Jiménez-Contreras E. Spanish name indexing errors in international databases. Lancet 2003;10;361(9369):1656–7.

32. Houghton F, Hopkins E. Standardised EU cigarette warnings: one size or colour does not fit all. N Z Med J. 2016;129(1430):98–9.

33. Houghton F. Lessons in courage from the past: lest we forget. N Z Med J. 2016;129(1428):85–6.

34. Alexander H, Bartlett A, Poole G. Reporting risk-adjusted outcomes for surgical procedures in New Zealand. N Z Med J. 2016;129(1430).

35. Soeberg MJ, van Zandwijk N. Incidence of malignant mesothelioma in New Zealand and Australia: a global snapshot. N Z Med J. 2015;128(1427).

36. Houghton F. Census 2001 – Steps in the right direction, but still room for improvement', Irish Medical Journal 2001;94(6):185.

37. Houghton F. A review of mortality maps included in the annual reports on vital statistics for Ireland, 1864-1998. Irish Geography 2002;35(2):213–15.

38. Ramakrishnan C, Patnia A, Hovy E, Burns GA. Layout-aware text extraction from full-text PDF of scientific articles. Source Code for Biology and Medicine. 2012;7:7. doi:10.1186/1751-0473-7-7.

Untreated poultry litter as a source of antibiotic resistance

Lance Gravatt

The New Zealand poultry industry remains dependent on the use of antibiotics, despite the New Zealand Veterinary Association setting an aspirational goal of being antibiotic free by 2030. The 2010–2011 MPI report on the sale of antibiotics found that around 25,000kg of zinc bacitracin was used in feed in the poultry industry, which represented around an 8% decline on the five-year average. Bacitracin is the largest antibiotic used by weight in New Zealand.[1] Rates of resistance to bacitracin have been reported as high as 60% in *Enterococcus faecium* and *Enterococcus faecalis* in poultry.[2] *E faecalis* resistance to bacitracin in Belgium poultry was reported as 16% and 41% for *E faecium*.[2] Zinc bacitracin was withdrawn from use in EU in 1999 as an antibiotic growth promoter.[3]

The use of antibiotics in food-producing animals has significantly increased animal health by lowering mortality and the incidence of diseases.[4] While antibiotics are thought to have improved the productivity of farming, there is no conclusive evidence from Europe that the banning of agricultural antibiotics has led to a sustained decrease in productivity. Moreover, antibiotic usage in general and the relevance of non-therapeutic antibiotics (growth promoters) in feed need to be re-evaluated, especially because bacterial pathogens of humans and animals have developed and share a variety of antibiotic resistance mechanisms that can easily be spread within microbial communities.

Poultry litter, a mixture of materials including bedding, faeces and feathers, is a valuable soil fertiliser that is rich in nutrients and can improve soil physical, chemical, and biological properties for agricultural crops. Most of the antimicrobial agents such as bacitracin and ionophores for coccidiosis administrated through feed or water are not fully absorbed in the chicken gut and up to 90% of the administered dose of these antimicrobials can be excreted in the faeces.[4]

From one Canadian study, the *Escherichia coli* contaminating poultry litter obtained from commercial farms were all multidrug resistant to at least 7 antibiotics.[5]

Antibiotic resistance genes in the ubiquitous but numerically minor group of *Enterobacteriaceae* intestinal bacteria are the major agents of gene transfer which include the conjugative plasmids where the greatest variety of resistance integrons occur. Integrons are effectively transposable cassettes of resistance DNA and have been found in abundance in Gram-positive bacteria that comprise >85% of the poultry litter microbiome.[6]

It is important that poultry litter is pre-treated before release as a fertiliser. Any pre- treatment will need to ensure that it has negated the presence of any residual antibiotics and integrons. Moreover, efforts to replace antibiotics are paramount. Public pressure and concerns about food and environmental safety (antibiotic residues, antibiotic-resistant pathogens) have driven researchers to actively look for alternatives to antibiotics. Some of the alternatives include pre-and probiotics, organic acids and essential oils, particularly *oreganum vulgaris* oil in concentrations of 0.01% of drinking water.[7]

ISSN 1175-8716

Competing interests:
Nil.

Author information:
Lance Gravatt, Chairman, Te Arai BioFarma Ltd, Herne Bay, Auckland, New Zealand.
Corresponding author:
Lance Gravatt, Chairman, Te Arai BioFarma Ltd, 91 Red Hill Road, Wellsford, New Zealand.
gravatt@ihug.co.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6986

REFERENCES:

1. Ministry for Primary Industries. Antibiotics Sales Analysis: 2009–2011
2. Butaye P, Devriese L A, and Haesebrouck F. Antimicrobial Growth Promoters Used in Animal Feed: Effects of Less Well Known Antibiotics on Gram-Positive Bacteria. Clin Microbiol Rev. 2003: 16(2); 175–188.
3. Marshall B M and Levy S B. Food Animals and Antimicrobials: Impacts on Human Health. Clin Microbiol Rev. 2011: 24(2); 718–733.
4. Diarra M and Malouin F. Antibiotics in Canadian poultry productions and anticipated alternatives. Frontier Microbiol. 2014: 4(282); 1–15.
5. Furtula V et al., Veterinary pharmaceuticals and antibiotic resistance of Escherichia coli isolates in poultry litter from commercial farms and controlled feeding trials. Poultry Sci. 2010: 89; 180–188.
6. Nandi S et al., Gram-positive bacteria are a major reservoir of Class 1 antibiotic resistance integrons in poultry litter. Proc Nat Acad Sci. 2004: 101(18); 7118–7122.
7. Yitbarek M B. Phytogenics as feed additives in poultry production: a review. Int J Ext Res. 2015: 3; 49–60.

Better health or better business: a critique of the childhood obesity plan

Gerhard Sundborn, Simon Thornley, Bodo Lang, Rob Beaglehole

Dr Jonathan Coleman, Minister of Health, announced on 12 February 2015, that he would lead the development of a comprehensive plan to address New Zealand's obesity crisis. This was celebrated by those working with obesity and its related consequences, who have long called for action. Here, we critically examine the plan and its strategies to reduce obesity.

FIZZ New Zealand is a Public Health Advocacy group that aims to address child and adult obesity by reducing sugary drink consumption to zero by 2025. Sugar sweetened beverages (SSBs) are the largest contributor of added sugar to the diets of New Zealanders (children and adults); evidence shows SSB intake is strongly associated with the onset of obesity.[1]

On 19 October 2015, the Childhood Obesity Plan (ChOP) was announced. The **ChOP** comprises 22 initiatives (9 new) that seek to achieve two broad goals: i) target obese individuals and those at risk of developing obesity, and ii) create broad opportunities to make healthier choices easier.

1. Critique of Initiatives in the Childhood Obesity Plan

More than half (12) of the 22 initiatives that comprise the **ChOP** are educational, and a further four focus on treating obesity in children and pregnant women. Increased activity and sport opportunities as well as policy initiatives each comprise another two initiatives. Healthy Families NZ (HFNZ) is the only whole-of-community intervention (**table**).[2]

The majority of the **ChOP** initiatives are *'business as usual'* and are unlikely to make a difference to NZ's obesity crisis. Evidence shows that we cannot educate or exercise our way out of the obesity epidemic.[3,4] Identification and treatment of obese pre-schoolers and pregnant mothers does not address the causes of obesity. Instead, it is the *'ambulance at the bottom of the cliff'*.

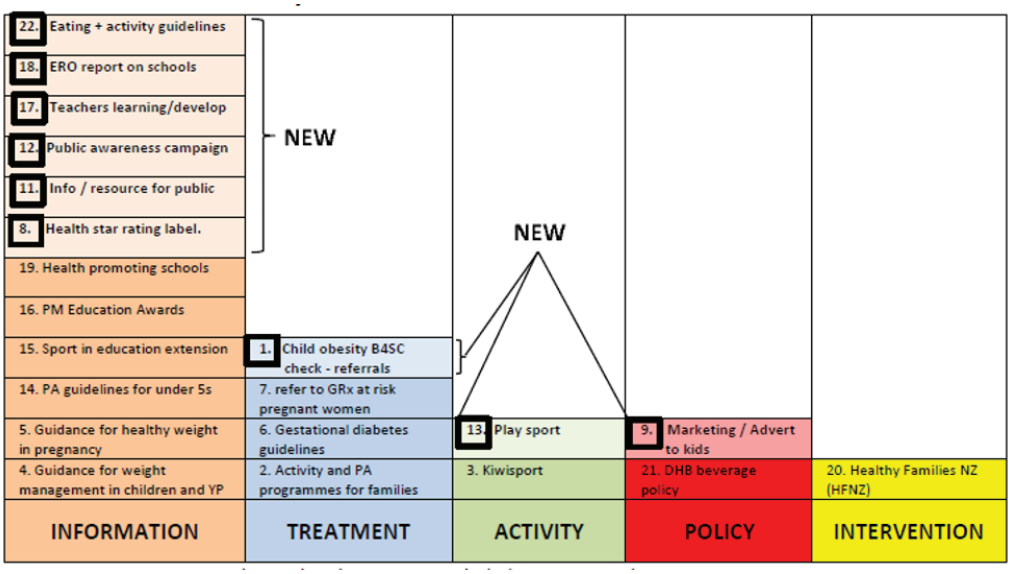
The use of a food labelling system offered promise; however, the Government adopted the most industry-friendly labelling system. The current health star labelling system is flawed, because it is voluntary, confusing, and rates many foods with high concentrations of sugar as healthy. For example, Sanitarium Natural Muesli breakfast cereal is rated 4.5 stars (out of 5), and has 20g sugar/100g (which equates to 2 teaspoons per 40g serve). Conversely, macadamia nuts, which contain little sugar, instead are rated near the bottom of the scale at 2.5 health stars. These examples illustrate that the system that is heavily weighted toward saturated fat and salt content and underestimate the role of sugar.

Research has shown that policy and regulation is the most effective approach to change behaviours by creating a more health-promoting environment to reduce obesity prevalence.[3] These regulations need to be targeted at the major cause of the epidemic, which is increasingly shown to be excess sugar. Targeted regulation is the most cost-effective type of initiative in obesity prevention.[3]

The **ChOP** has two initiatives in the policy area. Firstly, the **Advertising Standards Authority** (ASA) have been instructed to review their codes of advertising to children and code of advertising food to children. The ASA is funded by industry and there is no monitoring of these codes by an independent party which means improvements are unlikely to be made.

ISSN 1175-8716

Table: Childhood Obesity Plan – 22 Initiatives.



Note: Initiative 10. *Partnership with Industry* – not included at conceptual stage.

From our perspective, the only policy initiative that shows promise in the **ChOP** is the beverage policy which bans the sale of sugary drinks in hospital premises throughout NZ. HFNZ is a whole of community initiative that may also show promise.[3]

2. The ChOP focuses on energy density rather than sugar

The plan is focused on a philosophy and apparent evidence that "*Energy (kilojoule) intake is key – the amount of food consumed and its energy density is the single biggest driver of obesity*".[5]

The greatest determinant of energy density is fat content, making a low-energy focus a low-fat approach.[6] However, trials of low-fat approaches are not effective for weight loss in individuals[7] and are unlikely to be successful for populations. Furthermore, over the last few decades, a low-fat approach has underpinned obesity treatment and prevention efforts in New Zealand as well as other Western countries. Despite this, the prevalence of obesity and type 2 diabetes has risen. New trial and observational evidence has highlighted the unique role of sugar (concentrated fructose) in the development of unhealthy weight gain,[8] type 2 diabetes,[9] gout,[10] cardiovascular disease[11] and dental caries.[12] Considering this new evidence, sugar restriction needs to be prioritised.

Recently, the Government evaluated the utility of a sugar tax. However, seen through the lens of energy density, policy advisors have been lukewarm toward this strategy. Importantly, the evidence linking sugar intake with a wide range of diseases was absent from these reports.[5]

With a renewed focus that prioritises sugar (concentrated fructose), initiatives included in the **ChOP** would be transformed. ***Education and information***—initiatives would be centred around communicating risks of a high sugar diet, highlighting maximum daily intake of sugar, and raising health literacy to enable consumers to calculate sugar content based on back of pack nutrition labels. A simple label that gives the number of teaspoons of sugar per serve, we believe, would be more effective than the current confusing star system.

In ***treatment*** settings, brief opportunistic screening of sugar and SSB intake could be adopted, as is done with smoking cessation. ***Policy and regulation*** need to prioritise sugar restriction, making SSBs and products with concentrated sugar content absent in schools and other education providers.

Perhaps the most effective measure would be introducing fiscal measures to deter intake of sugary products, as well as incentivising industry to reformulate their products to reduce sugar content or offer zero sugar alternatives.

3. The case for a sugar sweetened beverage tax

An initiative that was not included in the **ChOP**—despite being called for by many authorities—was a sugar-sweetened beverage tax (SSB tax). An SSB tax is the second recommendation made by the World Health Organization (WHO) Ending Childhood Obesity Commission and was recommended by the Technical Advisory Group (a group of New Zealand experts in the field of obesity prevention established by the Ministry of Health). However, it was not supported by the Industry Forum Group who contributed to the development of the **ChOP**. Other organisations that also recommend a SSB Tax include the New Zealand Medical Association and the NZ Beverage Guidance Panel.[13,14] Renewed calls for an SSB tax in NZ have been fueled since the UK announced that it would implement a SSB tax from 2018. Our Minister of Health and Government remain unconvinced about an SSB tax, stating instead that they are awaiting 'definitive evidence' before they consider action.

The most recent and comprehensive evidence on SSB taxes (in Mexico) was reported in the British Medical Journal in January 2016.[15] The study found a 12% reduction in sales following the introduction of a 10% sugary drink tax.[15] Here in NZ, an open letter was submitted to cabinet ministers—supported by 74 health professors—calling for an SSB tax.[16] Most importantly, New Zealand public support for a SSB tax has increased dramatically. A recent NZ Herald poll reported 83% support for a SSB tax from 11,700 respondents.[17]

Conclusion

The Childhood Obesity Plan is unlikely to solve New Zealand's obesity crisis. It is based on a dated paradigm of energy density and does not address what we believe to be the greatest cause of the epidemic: excess sugar intake. The Government's plan lacks meaningful regulation of food and drink containing concentrated sugar, instead listing soft initiatives that are unlikely to be beneficial.

It shows that the Government values corporate profit over public good. The New Zealand public are becoming increasingly vocal in their support of a SSB tax, and frustrated with the complacent attitude of decision makers tasked with addressing NZ's growing obesity crisis.

We reiterate that the introduction of an SSB tax is an important step toward addressing obesity, and will make a strong statement that NZ, as a society, value health over corporate profits. We call for the current Minister of Health and government to embrace the opportunity to reduce NZ's worsening obesity epidemic by adopting such a step. There is no question that a SSB tax will come, the only question is who will initiate it?

Competing interests:
Nil.

Author information:
Gerhard Sundborn, Epidemiology and Biostatistics, University of Auckland, Auckland; Simon James Thornley, Independent Epidemiologist, Auckland, New Zealand; Bodo Lang, Department of Marketing, Business School, University of Auckland, New Zealand; Rob Beaglehole, NZ Dental Association, New Zealand.

Corresponding author:
Gerard Sundborn, Epidemiology and Biostatistics, University of Auckland, Temuri Place Auckland, New Zealand.
g.sundborn@auckland.ac.nz

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6987

REFERENCES:

1. Woodward-Lopez G, Kao J, Ritchie L. (2010) To what extent have sweetened beverages contributed to the obesity epidemic? Public Health Nutr, 1–11.
2. Healthy Families New Zealand. (2016, June 1) What is Healthy Families New Zealand? Retrieved from http://www.health.govt.nz/our-work/preventative-health-wellness/healthy-families-nz
3. Gortmaker S, Swinburn B, Levy D, Carter R, Mabry P, Finegood D, Huang T, Moodie M. (2011, August 27) Changing the future of obesity: science, policy, and action. The Lancet , Volume 378, Issue 9793 , 838–847.
4. Triggle, Nick. Exercise 'not key to obesity fight'. BBC News, 23 April 2015. Accessed 1 June 2016. http://www.bbc.com/news/health-32417699
5. Ministry of Health. (2015) Cabinet Social Policy Committee Paper: Reducing childhood obesity [online]. Available: http://www.health.govt.nz/system/files/documents/pages/cabinet_paper_reducing_childhood_obesity.pdf [accessed 1 June 2016]
6. Centers for Disease Control and Prevention. (2011) Low-Energy-Dense Foods and Weight Management: Cutting Calories While Controlling Hunger. [online]. Available: http://www.cdc.gov/nccdphp/dnpa/nutrition/pdf/r2p_energy_density.pdf [accessed 1 June 2016]
7. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. (2015) The Lancet Diabetes & Endocrinology. 3:968–79.
8. de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. N Engl J Med. 2012; 367:1397–406.
9. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care. 2010;33:2477–83.
10. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ. 2008; 336:309–12.
11. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation. 2012; 125:1735–41, S1.
12. Sheiham A, James WP. A new understanding of the relationship between sugars, dental caries and fluoride use: implications for limits on sugars consumption. Public Health Nutr. 2014; 17:2176–84.
13. New Zealand Medical Association. (2014) Policy Briefing: tackling obesity. [online]. Available: https://www.nzma.org.nz/data/assets/pdf_file/0015/32082/NZMA-Policy-Briefing-2014_Tackling-Obesity.pdf [accessed 1 June 2016]
14. New Zealand Beverage Guidance Panel. (2014) Policy brief: Options to reduce sugar sweetened beverage (SSB) consumption in New Zealand. Pacific Health Dialog: Vol 20 Number 1, p98–102.
15. MA Colchero, BM Popkin, JA Rivera, SW Ng. Beverage purchases from stores in Mexico under the excise tax on sugar sweetened beverages: observational study. BMJ 2016;352:h6704
16. University of Auckland. (2016) An open letter to Cabinet Ministers from 74 health professors calling for a sugary drinks tax. [online]. Available: https://www.fmhs.auckland.ac.nz/assets/fmhs/faculty/ABOUT/newsandevents/docs/SSB%20tax%20open%20letter%20final%2002April2016.pdf [accessed 1 June 2016]
17. Bezzant, Niki. "Sugary Drinks Tax - It's Time." The New Zealand Herald, 27 Mar. 2016. Web. 1 June 2016. http://www.nzherald.co.nz/lifestyle/news/article.cfm?c_id=6&objectid=11612259

Randomised trial of introduction of allergenic foods in breast-fed infants

In this trial the researchers have evaluated whether the early introduction of allergenic foods in the diet of breast-fed infants would protect against the development of food allergy.

1,303 exclusively breast-fed infants who were three months of age were randomly assigned to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish and wheat; early-introduction group) or to the current practice recommended in the UK of exclusive breast-feeding to approximately six months of age. The primary outcome was food allergy to one or more of the six foods between one and three years of age.

Early introduction of all six foods was safe but the trial did not demonstrate efficacy in terms of subsequent allergy.

N Engl J Med 2016;374:1733–43

Potato intake and incidence of hypertension

Is a higher intake of baked, boiled or mashed potatoes, French fries/chips or potato crisps associated with the incidence of hypertension?

This hypothesis is examined in this study which reviews data from two Nurse's Health Studies and a Health Professionals study in the US. Over 187,000 non-hypersensitive subjects (80% females and 20% males) were involved.

The findings of this study suggest that eating four or more servings of boiled, baked or mashed potatoes or French fries a week increases the risk of incident hypertension. It is suggested that the glycaemic load of the potato might explain the findings.

BMJ 2016;353:i2351

Associations of demographic and behavioural factors with glycaemic control in young adults with type 1 diabetes mellitus

Optimal glycaemic control is known to be associated with long-term reduction in micro- and macro-vascular complications and improved beta-cell function. This is often difficult to achieve particularly in adolescents and young adults.

In this report, data from 93 young diabetics has been reviewed and associations between demographic, social and behavioural factors and good glycaemic control have been evaluated.

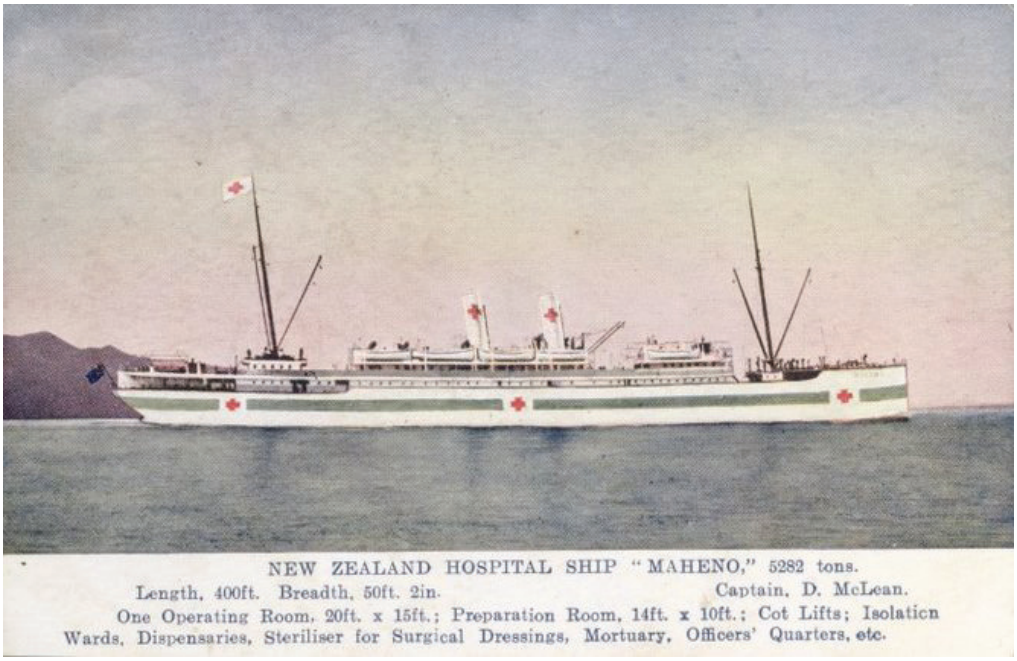
The conclusions reached were that geographical separation, socioeconomic disadvantage and risk-taking behaviours did not influence glycaemic control. Longer duration of diabetes identifies young adults at higher risk of poor control, while attendance at a multidisciplinary clinic and engagement in work or study was associated with better glycaemic control.

Internal Medicine Journal 2016;46, 332–338

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6988

A short voyage on a hospital ship

December 1916



Taylor, Charles, fl 1981. [Postcard]. New Zealand hospital ship Maheno, 5282 tons. [ca 1915].
Ref: Eph-B-POSTCARD-vol-4-041.
Alexander Turnbull Library, Wellington, New Zealand. http://natlib.govt.nz/records/22402146

The white ship, having disembarked her living freight, leaves the quay-side and anchors a few miles away. The shades of evening gather, and the red cross and the green lamps are illuminated, and the orderlies cease their cleaning and tidying in the wards, and are soon sound asleep in their bunks. The ship is to sail for France at midnight, but at that hour all the lights ashore suddenly go out, and in response the ship is plunged in darkness. A whirring noise overhead indicates the presence of a Zeppelin, and the antiaircraft guns begin to rattle, and aeroplanes from the shore are whizzing aloft. There are flashes of light in the sky and the noise of guns for half an hour, and then peace once more, for the unwelcome visitor is now away. The ship, again illuminated, begins her journey across the Channel, where the sleepless destroyers and trawlers keep watch and ward.

Passing through boom and breakwater in the morning, she is made fast to the French quay-side, and Cassidy of the Rifles, installed master of the corps of stretcher-bearers, cheerily directs the mooring and the handling of the gangways. Cassidy repays some observation. His accent and his adjectives are common in the army. He is not down-hearted: he is breezy and contented, easy with his equals, respectful to his superiors, not remarkable in his appearance, and he will always accomplish what he is ordered to do within the scope of a mortal. In tense situations his type is known to do almost more. Cassidy is one of the few who held back at Mons the great war machine of the "All-Highest." Time was when he would have been equally at home striving in the fields of France or on the burning plains of Hindustan, but now he will inform the inquiring stranger that he

is a P.B., with D.A.H. This, being interpreted, means Permanent Base class and Disordered Action of the Heart.

A hospital train, direct from the front, draws alongside the platform on the quay, and the stretcher-bearers begin to carry the wounded from the train to the ship. A constant stream of wounded men flows up two gangways to the forward and after lifts, and this continues for three hours. The patients are distributed in various wards, are fed, and then a beginning is made with the dressing of their wounds; and late in the evening a second hospital train arrives, from which the wounded are transferred to the ship. More wounded arrive the next morning, and the floating hospital sails with eight hundred and fifty on board. Included in this number are two hundred wounded German prisoners, some of them cot cases, but the majority, being slightly wounded, are accommodated on the deck aft. They have mattresses, pillows, and blankets, and appreciate the rest and comfort. The British and the Germans fraternise in a way strange to behold, and the more sociable Fritzes part with their buttons as souvenirs. A few Tommies wear German helmets or caps, and many sport aluminium rings, which are now the fashion. The Huns are doubtful and anxious as regards the safety of the passage, as they have heard much of the prowess of their submarines and minelayers, but within sight of England their spirits rise, and some even sing songs of Zion. A goodly number of our best-known tunes are German, or else the Germans have appropriated some of ours.

During the passage, on deck the slightly wounded patients are sleeping or chatting, and every now and again a pailful of dirty dressings from the wards goes over the rails. Below, nurses and orderlies are constantly moving, attending to the wants of the patients; some require sleeping draughts, or splints adjusted, and occasionally there are sharp bursts of haemorrhage from septic wounds that tax the skill of the medical officers. Here is a youth mortally wounded through the spine and paralysed; there another smoking a cigarette, his face serene and his mind apparently oblivious of a bandaged stump resting outside the bedclothes, where his leg, all except the upper twelve inches of the thigh, has been amputated. "There is no word of complaint or of regret, no groan to be heard. These men are obedient even unto death.

It is a great mystery, and the words of Sir Thomas Browne come to mind—"Man is a noble animal, splendid in ashes and pompous in the grave, celebrating nativities and deaths with equal lustre, nor omitting ceremonies of bravery in the infamy of his nature." There is scope for a new psychology to explain the fresh spirit awakened in a people that considered but yesterday the pursuit of pleasure and of wealth the greatest good.

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1440/6989