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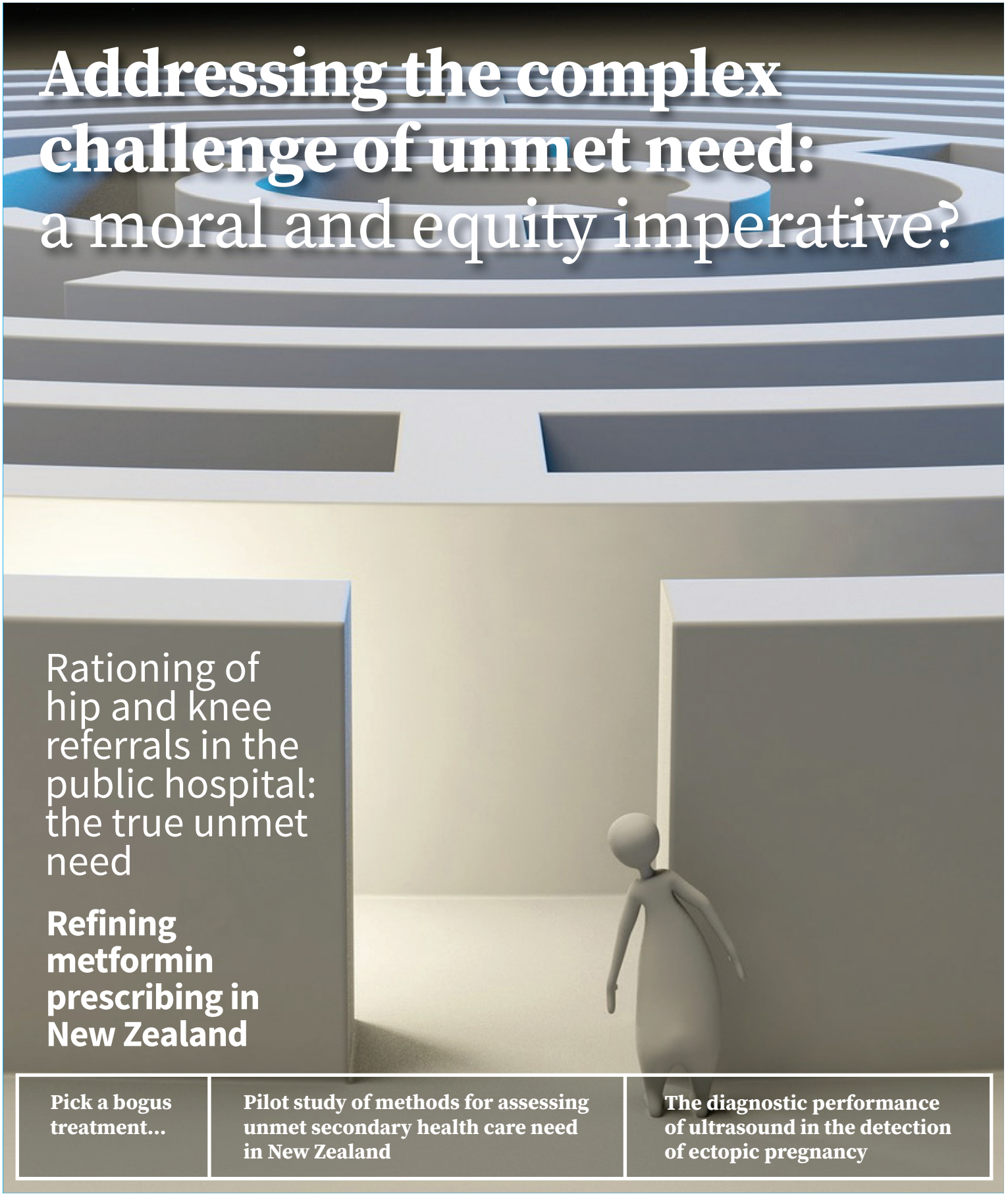

Addressing the complex challenge of unmet need: a moral and equity imperative?

Rationing of hip and knee referrals in the public hospital: the true unmet need

Refining metformin prescribing in New Zealand

Pick a bogus treatment...

Pilot study of methods for assessing unmet secondary health care need in New Zealand

The diagnostic performance of ultrasound in the detection of ectopic pregnancy

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Trends in genital warts diagnoses in New Zealand five years following the quadrivalent human papillomavirus vaccine introduction

Jeannie Oliphant, Joanna Stewart, Peter Saxton, Min Lo, Nicky Perkins, Daniel Ward

There was an 83.4% decrease in diagnoses of genital warts in young women seen at Auckland Sexual Health Service, from the introduction of the HPV vaccine (Gardasil) school programme in 2009 to five years later. The speed of the decline in genital warts diagnoses was significantly greater in young women who were in the eligible age group for the vaccine than older women. This supports an early population effect of the HPV vaccination programme for young women in New Zealand. The largest decreases in genital warts were seen in both young Māori and Pacific women (93.4%) compared to NZ European women (80.2%). HPV vaccination rates for Māori and Pacific girls in Auckland were notably higher than for other girls in Auckland. There was no statistically significant difference in the rate of decline in genital warts diagnoses between younger and older men, suggesting that men were receiving at best only minimal benefit from a vaccination programme that was funded only for girls and young women.

The diagnostic performance of ultrasound in the detection of ectopic pregnancy

Lee Young, Cecilia Barnard, Elisabeth Lewis, Matthew Jones, Jana Furlan, Angela Karatasiou, Martin Necas

Ectopic pregnancy is a common but potentially serious clinical problem that still poses significant diagnostic challenges. We showed that a vast majority of women can be successfully diagnosed on the first examination with only a small number of women requiring further reassessment. The likelihood that an ectopic pregnancy will escape detection on repeat ultrasound is very low.

Pilot study of methods for assessing unmet secondary health care need in New Zealand

Philip Bagshaw, Susan Bagshaw, Christopher Frampton, Robin Gauld, Terri Green, Charlotte Harris, Andrew Hornblow, Ben Hudson, Antony Raymont, Ann Richardson, Carl Shaw, Les Toop

There is growing concern about the number of people who are unable to access hospital treatment for non-urgent conditions, including mental, medical, surgical and dental problems. Some studies have indicated that the number of people with such unmet need might be large. However, there is dispute about what is the best method for measuring it. The present study compared four possible methods in population groups from Auckland and Christchurch. One estimate came for numbers of patients seen by GPs in their routine clinics; three methods included population surveys by face-to-face interviews, telephone interviews and internet surveys. Results from our study indicated that the best method for use in this country would be a population survey along a similar line to the New Zealand Health Survey, which only collects information on primary health statistics. We conclude that a national survey of all district health boards is needed to accurately estimate the level of unmet need for non-urgent hospital level care. This will require large random sample sizes to cover all ethnic and socio-economic groups around the country.

Rationing of hip and knee referrals in the public hospital: the true unmet need

Tom Inglis, Paul Armour, Graehame Inglis, Gary Hooper

This study details the implementation of a triage system for elective hip and knee referrals to the CDHB, and with accurate data we have been able to determine the large number of patients unable to access a specialist opinion. Approximately 60% of hip and 50% of knee referrals do not get above the threshold to offer a first surgical assessment despite failing all conservative management options. These patients represent the unmet need within our community and highlight the degree of rationing taking place within the public hospital.

Refining metformin prescribing in New Zealand

Sisira Jayathissa, Paul Dixon, Raymond Bruce, David Reith

With recent changes to New Zealand data sheet, practitioners may be able to prescribe lower dose of metformin for patients with renal impairment. This may help patients to take metformin for a longer period. Dose reduction also may help in safe prescribing.

Getting the foundations right for the measurement of medication safety: the need for a meaningful conceptual frame

Jerome Ng, Shane Scahill, Jeff Harrison

A significant number of patients admitted into New Zealand hospitals are harmed by the medications intended to help them. Many initiatives aimed at improving medication safety have been introduced over recent years in and across New Zealand hospitals. Has progress been made? What further improvements are required? In this viewpoint, we argue the need for better and more meaningful surveillance systems and propose how one can be developed.

Addressing the complex challenge of unmet need: a moral and equity imperative?

Anna Matheson, Lis Ellison-Loschmann

If unmet need is not a measure of the effectiveness of a health system, how do we really know how well it is doing and how to improve it? There is plenty of support in the literature for unmet need to be recognised as a key indicator of the success of a health system—however, to date, the lack of effective translation of this evidence into action has drawn criticism.[1,2]

In New Zealand, despite continual system reform and possessing a number of the foundations for an enviable health system, it appears that many New Zealanders' health needs are still not being met. Recently the New Zealand Health Survey (NZHS) for 2014/15 reported 29% of adults had experienced some form of unmet need for primary care in the previous 12 months.[3] This figure is high even against other countries with comparable health systems, including the UK and Canada (5% and 21% respectively).[4] Furthermore, unmet need is implicated as a significant driver of health inequalities. It is well established that Māori experience unequal access to healthcare at all levels of service provision.[3,5,6] The comparable figure for Māori experiencing unmet primary healthcare need (PHN)—as reported in the above 2014/15 NZHS—was 39% (MOH, 2016).

Unmet need and its unequal burden are a cost to the economy—it does not result in savings but rather shifts costs within, and creates costs outside, the health system. Indeed, there is a strong case to be made that addressing unmet need could result in substantial savings. As Mills and colleagues point out, there are long-term benefits to society of addressing the unmet health needs of Māori children.[7]

So, we have indications that there is significant unmet need as well as growing argument that we need better measurement, particularly within secondary care. The two articles in this issue highlight some of the challenges of both measuring and understanding unmet need. First, Bagshaw and colleagues[8] describe a pilot study conducted in Auckland and Christchurch trialling different methods (GP survey and a population survey involving online, face-to-face or telephone interviews) for undertaking a national survey of unmet secondary healthcare need (SHN) and estimating the prevalence of unmet SHN, to inform sample size calculations. Estimating a prevalence of unmet PHN at 29% and unmet SHN at 9%, the authors suggest an approach similar to that used for the NZHS was most promising in terms of meeting the challenges posed by a survey of this kind. Interestingly, the authors conclude that "asking GPs to record unmet need for secondary health care at clinical presentation was not worthwhile because very few GPs participated" (in this pilot).

The second article by Inglis and colleagues[9] reported a study for determining the 'real' unmet need related to the implementation of a triage system for elective hip and knee referrals in Canterbury. They found that 43% of hip and 54% of knee patients were not able to move beyond the initial triage process, which rations access to specialist appointments. This finding was at odds with MOH figures that show 0.6% of patients are waiting longer than the government target of four months for hip and knee surgery. With an estimate of close

to 50% of unmet in the community, this study suggests that by aiming for the health target through local implementation, the real burden of unmet need is obscured. This is an interesting illustration of how general targets influence actions towards achieving the goal—at the expense of real and more meaningful outcomes. It also shows the diversity of actions that may occur locally, as well as the potential value of having greater local knowledge for improving real health outcomes.

The substance of these two articles raises some important questions for measuring and understanding unmet need including whether there is any real rationale for separating unmet need in primary care from that within secondary care. Health systems are complex systems[10] and integrated care models recognise this implicitly.[11] Unmet need in primary care influences unmet need in secondary care—particularly in respect of increasing health inequalities. The evidence of the critical role of GPs in influencing access to secondary care underscores this, despite their low participation in the Bagshaw et al study[8] alongside the potential for GPs to be reluctant to refer patients due to the high threshold of acceptance for treatment as noted by Inglis et al,[9] as does the increasing evidence of the utility of employing 'navigators' to facilitate greater access to and through the health system for population groups who experience multiple barriers.[12,13]

Here we offer up two—not mutually exclusive—potential ways forward for addressing some of the challenges identified here.

First, is it time that we looked past more traditional measurement methodologies and moved towards those strategies which explicitly attempt to take account of local context—one example being Qualitative Comparative Analysis (QCA).[14] The strength of this approach, and those similar, would be to enable some measure of the burden of unmet need, as well as to gather information on the characteristics of unmet need, in context, that may be amenable to responsive action. The example of the locally implemented triage system in Canterbury[9] illustrates this need to acknowledge the vagaries of local actions.

A second potential way forward is for adaptive processes and practices to become core features of health systems. If we recognise the health system as complex, where the levels of care are interrelated, then the need for health organisations to be forward as learning and adaptive organisations becomes clearer. This would enhance their ability to respond to unmet need through their actions of providing services. Limited examples of these types of adaptations currently occurring in primary care, include PHOs and other providers extending outreach services to homes or other settings, changing hours of practice to accommodate people's employment situations and promoting culturally safe practice.[15,16] Could such adaptive practices be extended, and become commonplace, in primary care? And could secondary care organisations also move in this direction? The coordination and responsiveness of health funding contracts is one mechanism that can encourage adaptation over time, while how health targets are implemented could be another. General targets can be useful for guiding priorities, but their ability to obscure real outcomes needs to be acknowledged.[17] They are useful as long as there is also an ability to learn and adapt where the reality of outcomes misses the target.

We agree with Keene and colleagues that the health system requires greater funding to a level that enables New Zealanders' healthcare needs to be met.[18] However, we would also suggest that some kind of reform is needed towards better integration and greater recognition of the importance of focussing on unmet need. Is it possible to have an adaptive health system that responds to *different* needs *differently* and learns from its past actions? Undoubtedly, more attention must be given to prioritising, measuring and responding to unmet need. There is a moral and equity imperative to ensure this happens.

Competing interests:
Nil.

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Trends in genital warts diagnoses in New Zealand five years following the quadrivalent human papillomavirus vaccine introduction

Jeannie Oliphant, Joanna Stewart, Peter Saxton, Min Lo, Nicky Perkins, Daniel Ward

ABSTRACT

AIM: To investigate whether changes in rates of genital warts diagnosis at Auckland Sexual Health Service (ASHS), pre and post the quadrivalent human papillomavirus (4vHPV) vaccine introduction in late 2008, differed between clients vaccine-eligible and not eligible.

METHOD: All new clients attending ASHS from 2007 to 2013 were categorised as having genital warts or not. Generalised linear mixed models were used to compare differences in rates of change in diagnoses.

RESULTS: Overall, 43,480 were seen with genital warts diagnosed in 13.1%. The difference in rate of change over time in diagnosis pre- to post-vaccine differed in females vaccine-eligible to not (p=0.004). The relative risk of diagnosis per year pre-vaccine was 0.98 (0.84, 1.13) and post-vaccine 0.77 (0.74, 0.81) in those eligible compared to 0.87 (0.80, 0.95) and 0.95 (0.91, 0.98), respectively, in those not eligible.

This difference in change, between vaccine eligible or not, differed between males and females (p=0.02), with males considered eligible if the same aged female would have been. In males, no difference in rate change pre- to post-vaccine could be shown in those eligible or not (p=0.53).

CONCLUSION: In this study a population effect for women of the 4vHPV vaccine was demonstrated.

Since 2007, countries around the world have rolled out vaccination programmes using the quadrivalent human papillomavirus (4vHPV) vaccine. This vaccine provides protection against HPV types 6 and 11, which are responsible for the majority of genital warts, in addition to the oncogenic types 16 and 18 that can cause cervical cancer and penile cancer, respectively, for women and men, and oropharyngeal and anal cancers for both.[1] Genital warts are an early indicator of HPV-related disease, but are not typically notifiable conditions, therefore studies investigating an early population response to the vaccine have examined rates of genital warts diagnoses among sexual health clinic attendees. These have found decreases in genital warts among vaccine-eligible young women in a number of countries, including the UK and Australia,[2] with the latter reporting a 93% reduction over the five years following the introduction of a school-based HPV vaccination programme.[3]

In New Zealand the 4vHPV vaccine (Gardasil®) was made available on 1 September 2008 with the school-based arm of the vaccination programme commencing in February 2009 and an initial catch up programme through to the end of 2010 targeting women before they turned 20 years of age. The ongoing publically funded programme targets girls in year 8 of school (aged about 12 years) although the vaccine

is funded for young women up to the age of 20 years. There has been no publically funded vaccination programme for boys, although it is possible for males to purchase the vaccine privately. From January 2017 the New Zealand government's drug purchasing agency is widening funded access to Gardasil® to both sexes up to and including age 26 years.[4]

A previous New Zealand study that investigated genital warts diagnoses in clients attending the Auckland Sexual Health Service (ASHS) noted a 63% decline in genital warts diagnoses for young women, 18 months into the New Zealand vaccination programme.[5] We sought to update that analysis by examining rates of genital warts diagnoses over time in the same service up to five years after the vaccine introduction.

The aim of the study was to investigate whether the introduction of the 4vHPV vaccine had influenced the rate of genital warts diagnosed in females eligible to receive it, using those not eligible as a comparator. Secondary aims were to investigate whether any effect of the vaccine introduction was comparable in different ethnic groups and whether any effect of vaccine introduction seen in females was paralleled with one in males.

Method

The study setting was the ASHS, which is a regional service covering a large, urban, multicultural population with four clinics across Auckland. Patients access these clinics by self-referral or referral from other health providers and services are free of charge.

A retrospective review was undertaken extracting data on all new clients attending the ASHS between 1 January 2007 and 31 December 2013. For purposes of data extraction a new client was defined as an individual presenting to the service for the first time within the past five years.

The main variable extracted was whether or not there was a diagnosis of genital warts.

Genital warts are not a notifiable infection in New Zealand, but clinicians at the ASHS routinely enter diagnostic codes for each new diagnosis made for each client at each visit.

Demographic data is routinely collected for all new clients. Additional information included was: ethnicity (self-identified)—categorised NZ European, Māori, Pacific Peoples, Other; age—age at presentation; sex; month—time of presentation measured as number of months since January 2007; period—whether the date of presentation was pre- or post-vaccine (the time cut off point for pre- and-post vaccine was taken at the start of 2009 as few could have had full protection for the vaccine prior to this time); eligible—whether they were eligible to receive vaccination (ie, aged less than 20 years of age at the time of the vaccine introduction). Males of the appropriate age were termed eligible if a female of the same age would be eligible.

Statistical analysis

Statistical analysis was performed with SAS (version 9.2) software. Using a generalised linear model assuming a binary distribution and log link, comparison was made between the difference in the rate of change in proportion of visits to the ASHS with a diagnosis of genital warts from pre to post the introduction of the 4vHPV vaccine in females eligible and not eligible for vaccination. The outcome was whether or not there was a diagnosis of genital warts. Explanatory variables included were age, month, period and eligible along with the interactions of eligible, month and period. The relationship of interest was the three-way interaction—ie, whether there was a difference in the change in slope over time from pre- to post-vaccine introduction in the cohort who became eligible for vaccine once released compared to those who were never eligible.

To investigate whether any effects observed differed for different ethnic groups, this analysis (in females) was also run, including ethnicity and its interactions with month, period and eligible with the four-way interaction the relationship of interest. Where a four-way interaction was detected the analysis was run separately for each ethnicity.

To investigate whether any effect of the vaccine introduction observed in females was also reflected in males a further analysis as described above was run,

Table 1: Annual number and proportion of first visit clients diagnosed with genital warts at time of presentation to ASHS.

	2007 *n*=5,648	2008 *n*=6,001	2009 *n*=6,037	2010 *n*=5,351	2011 *n*=6,754	2012 *n*=6,837	2013 *n*=6,852
All	971 (17.2%)	938 (15.6%)	883 (14.6%)	737 (13.8%)	838 (12.4%)	753 (11.0%)	591 (8.6%)

including both males and females, with sex included as an additional explanatory variable, also with its interactions with month, period and eligible. The four-way interaction was the result of interest.

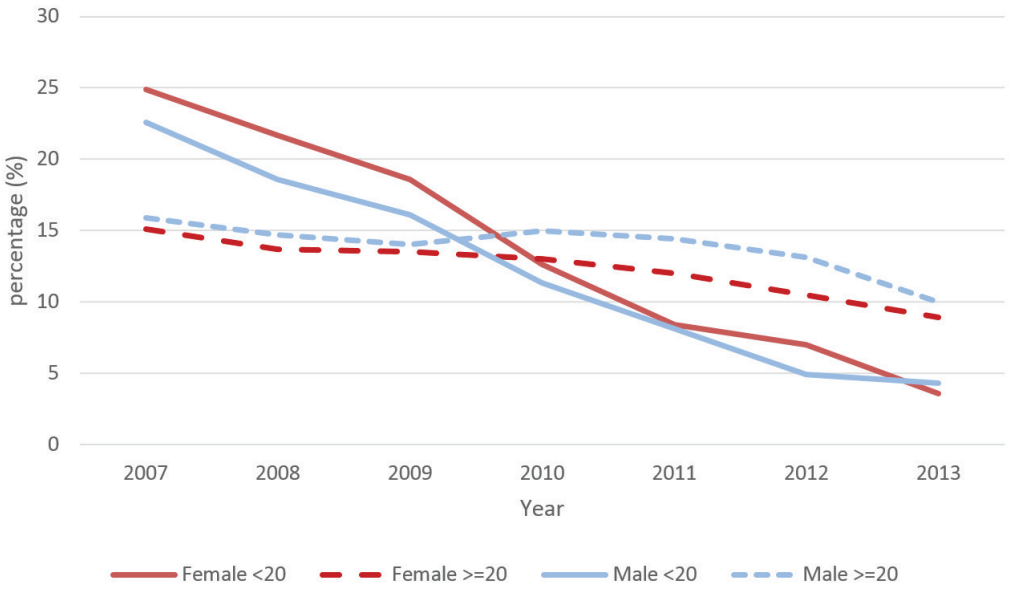
The effect size was assessed by estimating the genital wart diagnosis relative risk and 95% confidence intervals for the change from one year to the next, obtained from the estimates in the model. These relative risks were converted to those for a 12-month change to produce a meaningful estimate, although time was entered into the model as month.

Ethics approval for the study was granted by the Northern B Health and Disability Ethics Committee 15/NTB/71.

Results

Over the study time-period from 01/01/2007 to 31/12/2013, 43,480 new clients were seen at ASHS and genital warts were diagnosed in 5,711 (13.1%). Of the 19,894 female new clients seen, ethnicity was recorded as: NZ European 39.5%, Māori 15.1%, Pacific Peoples 13.0%, Other 32.5%. There were an unknown number of non-residents in the study group with the largest proportion likely to have been in the Other ethnic group. There was a general decrease across time in all groups presenting to ASHS in the diagnoses of genital warts (Table 1). While the graph in Figure 1 shows steady declines, based on the

Figure 1: Proportion of new clients diagnosed with genital warts by sex and age,[1] at time of presentation to ASHS with the Auckland HPV school vaccine programme starting in 2009.



[1]Note from 2009 onwards an increasing proportion of females presenting to ASHS as >=20 years will have been <20 years at the time of the vaccine introduction and so been eligible for funded vaccination. Over time an increasing proportion of the group <20 years presenting to ASHS will have been vaccinated as part of the school programme.

Table 2: Modelled relative risk for change over time in genital warts diagnosis, from one year to the next, for females separated by eligibility for vaccination pre and post the introduction of the vaccine to New Zealand.

	Pre vaccine 2007–2008	**Post vaccine 2009–2013**	***p* value[1]**
Female eligible	0.98 (0.84–1.13)	0.77 (0.74–0.81)	*p*=0.004
Female not eligible	0.87 (0.80–0.95)	0.95 (0.91–0.98)	

[1] the *p* value is testing whether the difference in the slope pre-vaccine compared to post-vaccine is different in those eligible for vaccination compared to those not.

age at presentation to ASHS, further statistical analysis using a model that adjusted for the changing ages of the increasing numbers of those who would have been eligible to receive the funded vaccine over the study time-period provides a more refined estimate of the effect of the vaccine programme in New Zealand (Table 2–4).

Vaccination programme effect in eligible and not eligible females

For females, there was evidence of a difference in the pre- to post-vaccination era in the rate of change of the proportion of genital warts diagnoses in the vaccine-eligible cohort compared to the vaccine-ineligible cohort (*p*=0.004). As

Table 3: Relative risk for genital warts diagnosis from one year to the next for the vaccination eligible and not eligible cohorts for Pacific Peoples, Māori, NZ European and Other females pre and post the introduction of the vaccine to New Zealand.

Female	**Pre vaccine 2007–2008**	**Post vaccine 2009–2013**	***p* value[1]**
Pacific Peoples eligible	1.03 (0.69–1.5)	0.67 (0.58–0.77)	*p*=0.28
Pacific Peoples not eligible	0.97 (0.77–1.23)	0.86 (0.78–0.96)	
Māori eligible	1.00 (0.75–1.32)	0.71 (0.64–0.80)	*p*=0.01
Māori not eligible	0.79 (0.62–1.01)	1.02 (0.92–1.12)	
NZ European eligible	0.99 (0.80–1.24)	0.78 (0.73–0.83)	*p*=0.01
NZ European not eligible	0.83 (0.73–0.94)	0.96 (0.91–1.01)	
Other eligible	0.86 (0.56–1.32)	0.90 (0.81–1.00)	*p*=0.75
Other not eligible	1.00 (0.82–1.2)	0.95 (0.89–1.02)	

[1] the *p* value is testing whether the difference in the slope pre-vaccine compared to post-vaccine is different in those eligible for vaccination compared to those not, within ethnic group.

Table 4: Modelled relative risk for change over time in genital warts diagnosis, from one year to the next, for males separated by eligibility for vaccination pre and post the introduction of the vaccine to New Zealand.

	Pre vaccine 2007–2008	**Post vaccine 2009–2013**	***p* value[1]**
Male eligible[2]	0.93 (0.72–1.19)	0.84 (0.79–0.89)	*p*=0.53
Male not eligible	0.95 (0.88–1.02)	0.96 (0.93–0.98)	

[1] the *p* value is testing whether the difference in the slope pre-vaccine compared to post-vaccine is different in those eligible for vaccination compared to those not.

[2] For males the group 'eligible' were those where a female of the same age would have be eligible.

shown in Table 2, for females the proportion of clients diagnosed with genital warts each year was fairly stable in the vaccine-eligible cohort pre-vaccine (RR=0.98), but has decreased markedly post the introduction of the vaccine (RR=0.77). In comparison the non-eligible females showed a small decrease in proportion of genital warts diagnoses both pre- and post-vaccine (RR=0.87 and RR=0.95, respectively).

Comparison of vaccination programme effect in different ethnic groups in females

There was evidence that the eligibility difference in change of slope pre and post the vaccine introduction differed by ethnic group (*p*=0.02), therefore the analysis was run separately for each ethnic group. A difference in the change in decline in those eligible compared to not eligible was demonstrated in Māori and NZ European. While it could not be demonstrated in Pacific Peoples this was because of a small decrease also occurring in those not eligible. The increase in the decline in genital wart rates from before to after the vaccine introduction was similar in Māori, Pacific Peoples and NZ Europeans. The observed ethnic interactions were largely due to the Other group where the change from pre to post was similar in those eligible and ineligible for vaccination (Table 3). It is likely that this group contained many non- residents who may not have been vaccinated prior to arrival and were not able to access funded vaccination in New Zealand.

Comparison on vaccination programme effect for males and females

When comparing males and females (males defined as eligible for vaccine if a female of the same age would be eligible) there was evidence that the difference in the change over time pre- to post-vaccination in those eligible or not for vaccination differed in males and females (*p*=0.02). The analysis was therefore also run separately for males. For males, although the difference in the estimated rate of decrease of genital warts diagnoses from pre-vaccine introduction to post the introduction of the vaccine was slightly greater in those eligible compared to those not eligible (Table 4), this difference could not be shown to be significant (*p*=0.53).

Discussion

While there were already signs of the rates of diagnosis of genital warts declining prior to the 4vHPV (Gardasil®) vaccine introduction in New Zealand, the speed of decline in females eligible for the vaccine increased more after the vaccine introduction than it did in those not eligible, with the faster decline being consistent with a vaccine effect. A parallel pattern to the female pattern of difference in decline over time in those eligible or not for the vaccine could not be shown in males considered eligible if a female of the same age was eligible. No difference in the pattern in eligible and non-eligible males was able to be shown, and any increase in rates of

decline after vaccine introduction compared to before was small. This would imply that if there were any potential benefits for males under the current vaccination programme in New Zealand, they are small. In the post-vaccination period, declines in genital warts diagnoses among vaccine eligible women were witnessed for all ethnicities with the exception of an "Other" ethnicity, which likely included more non-New Zealand residents.

The major strength of this study was the large data set available for analysis and the availability of data for a period of time before the introduction of the vaccine. While only genital warts diagnoses at sexual health clinics in Auckland were examined, which are not representative of the total New Zealand population, Auckland contributes substantially to the overall population of the country. Data from other sources such as decreasing prescriptions dispensed for imiquimod and podophyllum products in New Zealand[6] support the findings of this study.

This study has several limitations. It is an ecological study so cannot comment on causality of genital wart reduction. The reduction in genital warts diagnoses among young people may also be due to changing patterns of behavior with less school aged youth in New Zealand reporting being sexually active in 2012 compared to five years earlier.[7] Indeed a decline was observed prior to the vaccine introduction. However, statistical analysis demonstrated significantly greater reductions of genital warts diagnoses pre- to post-vaccine introduction in the vaccine-eligible cohort of young women compared to those not eligible, which would tend to support a role for the 4vHPV vaccine.

ASHS clinic data did not include information on the vaccination status of clinic attendees. Future research linking data from the National Immunisation Register (NIR) and diagnostic codes related to National Health Index (NHI) would be of interest. In addition data could not be extracted separately for men who have sex with men (MSM), which may have provided further information.

The 83.4% reduction in genital warts diagnoses, from just prior to the vaccine introduction (2008 to 2013), in New Zealand is less than the 92.6% reduction seen in young women in Australia, five years into their 4vHPV vaccination programme.[3] However, the vaccination coverage in that study was reported as being 73% for 12–13 year olds compared with 56% in Auckland for the 1993 birth cohort.

New Zealand HPV vaccination coverage information is derived from the NIR. Ministry of Health data on the cumulative vaccination coverage from the start of the programme on 1st September 2008 through to 31st December 2013 for each birth cohort was reviewed. Ethnicity in the reports is categorised into Māori, Pacific Peoples or Other, with the denominator figure derived from New Zealand census-estimated population projections in order to assess vaccination coverage. The majority of females in the Other category are of NZ European ethnicity, although in Auckland, Asian young people also make a significant contribution to the population.

Thus in the Auckland region, the birth cohort of young women born in 1993 who were aged between 14 and 20 years over the study period of 2007 to 2013 had a vaccination coverage to the end of 2013 for all three vaccines of 48% for Māori, 68% for Pacific Peoples and 51% for Other. These vaccinations occurred as part of the initial catch up programme. There was a trend for vaccination rates to improve for Māori and Pacific Peoples over time with no change for the category Other. For the birth cohort of young women born in 1999 (turning 14 years in 2013), who would have predominately been vaccinated in year 8 at school, the vaccination coverage was 62% for Māori, 77% for Pacific Peoples and 52% for Other.

It is anticipated that HPV vaccination programmes will have the potential to reduce ethnic and socioeconomic disparities of HPV related disease.[8] In New Zealand cervical cancer incidence rates are higher for Māori women[9] so that it is important that any interventions such as HPV vaccination are effective for this population. Recent modelling showed that HPV vaccination is a pro-equity intervention in New Zealand for Māori women, provided vaccine coverage is not lower for this population group.[8]

In Auckland, HPV vaccination coverage was notably higher for Pacific and Māori young women. While it is difficult to make

any further comment on the basis of this study it is encouraging that Māori and Pacific young women had larger decreases in genital warts diagnoses post-vaccine introduction (93.4% each) followed by NZ European (80.2%), (data not shown).

Vaccine coverage has been shown to be an important predictor of population response in a recent meta-analysis. Only countries with high vaccine coverage for females showed significant reductions in genital warts diagnoses for young men with no evidence of any herd effect in countries with low vaccine coverage.[10–11]

Despite a slightly quicker rate of decline in the rates of genital warts diagnoses over time post-vaccine introduction compared to pre-introduction for young men in this study, the reduction was not shown to be statistically different when compared to older men. While there are other possible explanations to account for this finding, such as changing reasons for young men to present to sexual health clinics over time, it may also be that the vaccination rates across the study population were not high enough to provide more than a small herd immunity effect for young men.

The findings of this study would suggest that publicly funding Gardasil® vaccination for males is needed to ensure equitable prevention of HPV related disease in New Zealand. In particular men who have sex with men, who are at higher risk of HPV related anal cancer,[12] would not have benefited from the current vaccination programme.

The findings of this study support an early and equitable population effect of the HPV vaccination programme for young women in New Zealand. The authors applaud the decision to extend the funded programme to include males and anticipate that this is likely to have a significant impact on continuing to reduce HPV-related disease in New Zealand.

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The diagnostic performance of ultrasound in the detection of ectopic pregnancy

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ABSTRACT

BACKGROUND: Accurate diagnosis of ectopic pregnancy is essential in reducing maternal mortality and morbidity. Transvaginal ultrasound (TVUS) is the accepted imaging modality of choice for the diagnosis of ectopic pregnancy (EP).

AIMS: To assess the effectiveness of transvaginal ultrasound (TVUS) in the detection of EP in consecutive women presenting for ultrasound to a radiology department with a clinical suspicion of EP.

METHODS: Retrospective analysis of 585 women presenting for TVUS over a 2.5-year period was performed. Women were classified as having a confirmed EP on the basis of surgery and histology. Women with a suspected EP who were treated medically or expectantly were also included.

RESULTS: Eighty-seven women had a confirmed EP and 29 women had a suspected EP. The sensitivity and specificity of ultrasound for the detection of confirmed EP was 88.5% and 96.5% on the initial TVUS and 93.1% and 95.7% with an additional rescan.

CONCLUSION: TVUS in the radiology setting of a tertiary hospital has excellent diagnostic performance for the detection of EP.

Accurate and timely diagnosis of ectopic pregnancy is essential in reducing maternal mortality and morbidity in the first trimester. Pain, vaginal bleeding and inappropriately rising βHCG in early pregnancy typically raise suspicion of an underlying EP. In the last two decades, transvaginal ultrasound (TVUS) has become the imaging investigation of choice in patients presenting with suspected EP primarily due to its accessibility, excellent diagnostic performance, safety, repeatability and relatively low cost. Ultrasound, however, is an operator-dependent modality and the success of an ultrasound examination is influenced by many factors including the operator's level of experience.

We assessed the diagnostic performance of ultrasound in the diagnosis of EP in a tertiary hospital in New Zealand (Waikato Hospital, Hamilton). The study was retrospective in nature and the data therefore reflect the normal operating characteristics of ultrasound under common workplace conditions. Examinations were performed by qualified sonographers in the radiology department, rather than by dedicated O&G sonographers working in a subspecialist or research unit. We examined ultrasound performance in patients with a surgically and histologically confirmed EP ("confirmed EP" category) and we also analysed patients who were treated medically or expectantly ("presumed EP" category).

Method

We performed a retrospective audit of all patients who presented for ultrasound at Waikato Hospital (Hamilton, New Zealand) with a clinical suspicion of EP over a two and a half year period between 1 January 2013 and 26 June 2015. The study was approved by the Waikato DHB Research Office in consultation with the Health and

Disability Ethics Committees, Ministry of Health, New Zealand. Patients were referred for ultrasound from the emergency department or from a hospital-based early pregnancy assessment clinic. All patients were scanned in the radiology department by general sonographers with a minimum of postgraduate ultrasound qualification or by trainees or radiology registrars under direct supervision of a sonographer. Patients' electronic and hard-copy records were reviewed, including: ultrasound reports, clinic notes, discharge summaries, surgical reports, histology reports and repeat admissions.

Patients were included in the study if the referral for the ultrasound included any of the following clinical query terms: "ectopic", "pregnancy location" or "PUL". Patients were excluded if they were referred for a scan before a blood pregnancy test was performed and this subsequently proved negative, or if they arrived with a working diagnosis of an EP based on an outpatient scan performed elsewhere.

Classification of ultrasound scan results:

For the purpose of statistical analysis, ultrasound was classified as positive for EP when the conclusion of the ultrasound report contained positive or affirmatory statements such as:

- "consistent with ectopic pregnancy",
- "suspicious for ectopic pregnancy",
- "suggestive of ectopic pregnancy" or
- "ectopic should be considered".

Ultrasound was classified as negative for EP when the conclusion of the report did not mention ectopic pregnancy or contained non-affirmatory statements regarding ectopic pregnancy such as:

- "pregnancy of unknown location",
- "no evidence of ectopic",
- "no convincing features of ectopic" or
- "ectopic pregnancy cannot be excluded".

Classification of clinical outcomes:

The patient's outcome was classified as "confirmed ectopic pregnancy" (confirmed EP) if the patient underwent a diagnostic laparoscopy and an EP was identified and was histologically confirmed. The patient's outcome was classified as "presumed ectopic pregnancy" (presumed EP) if the referring team treated the patient as an ectopic pregnancy medically (methotrexate) or expectantly such as in the context of a clinically stable woman with inappropriately rising βHCG. The confirmed and presumed EPs were also pooled together for analysis.

Results

Over the study period, 585 women met our inclusion criteria. The patient's age ranged between 15 and 47 years with a median age of 28 years. Eighty-seven patients had a surgically and histologically confirmed EP pregnancy (prevalence rate 14.9%) and an additional 29 patients were treated as a presumed EP (prevalence rate 5.0%). In women diagnosed with confirmed EP, 21.8% (19/87) had a previous history of EP.

The majority of the EPs were tubal in location (83/88), of which three were live EPs. Of the tubal EPs, 40 were on the right and 42 on the left. A small number of EPs (5/88, 5.6%) were identified in other locations:

- two cornual EPs
- one ruptured cornual EP in the horn of a bicornuate uterus
- one abdominal EP in in the pouch of Douglas and
- one abdominal EP adherent to the anterior abdominal wall

The sensitivity and specificity of ultrasound in the diagnosis of confirmed and EP was 88.5% and 96.5% on the initial ultrasound. The addition of a second examination increased the sensitivity to 93.1% but did not improve the specificity (95.7%). The addition of a third examination did not substantially improve the diagnostic performance of ultrasound any further with a combined sensitivity of 94.2% and specificity of 95.7%.

All patients in whom an EP was missed on the first ultrasound were initially diagnosed as pregnancies of unknown location (PUL). Of these patients, 80% (8/10) required a second TVUS for further evaluation, of whom 62.5% (5/8) were diagnosed with EP. Only one of the 87 patients with a confirmed ectopic pregnancy escaped detection despite three ultrasound examinations. This patient had three ultrasound examinations over the course of 21 days, all with a diagnosis of PUL, but slowly rising bHCG. Subsequent laparoscopy identified an unruptured right tubal EP.

An additional 29 patients did not have surgery, but were treated by the referring team medically or expectantly as presumed, possible or likely ectopics. We classified these patients as "presumed EPs". While some of these pregnancies probably represent true EPs, others may represent entities such as persisting pregnancies of unknown location (PULs) or failed early pregnancies with an incidental adnexal mass. When the presumed EPs pregnancies were pooled with the confirmed EPs, the sensitivity and specificity of ultrasound decreased, reflecting the diagnostic and clinical uncertainty in these patients. Table 1 summarises the performance of the initial ultrasound and additional follow-up ultrasounds in the detection of EPs.

Overall, the majority of patients in our study (79%) required only one ultrasound examination. A second examination was required in 21% of patients and of these a further 26% required a third examination. When only patients with confirmed EPs were analysed, 82.8% required only one ultrasound examination, 16.0% a second examination and only one patient required a third examination. The median time from the first to the second ultrasound in patients with confirmed ectopic pregnancies was five days.

The distribution of patients' presenting βHCG levels is shown in Table 2. In patients with a confirmed EP, presenting βHCG level at the first ultrasound examination ranged from 70 IU/l to 79,600 IU/l, with a mean value of 4705 IU/l and median value of 1430 IU/l. In our series, 32 confirmed EPs (36%) had a presenting βHCG level was <1000 IU/l units, a level considered discriminatory for the diagnosis of an intrauterine gestational sac in live intrauterine gestations.

Discussion

The diagnosis of EP can be challenging. Women present with variable symptoms, at differing times during early gestation, sometimes not knowing they are pregnant or with uncertain dates making the interpretation of βHCG values in the clinical context difficult.[1–3] Symptomatology of women with EP often overlaps significantly with other early pregnancy complaints such as painful hemorrhagic corpora lutea, implantation bleeding, early pregnancy failure and miscarriage. While some women with EP present with convincing constellation of symptoms and become haemodynamically unstable requiring urgent surgical management, the majority of women present with less convincing

Table 1: The sensitivity and specificity of ultrasound for the detection of ectopic pregnancy.

Initial ultrasound (one scan only)		
	Confirmed EP	*Confirmed and presumed EP pooled*
Sensitivity	88.5%	80.2%
Specificity	96.5%	84.1%
Initial ultrasound + one follow-up ultrasound		
	Confirmed EP	*Confirmed and presumed EP pooled*
Sensitivity	93.1%	87.1%
Specificity	95.7%	82.8%
Initial ultrasound + two follow-up ultrasounds		
	Confirmed EP	*Confirmed and presumed EP pooled*
Sensitivity	94.3%	87.9%
Specificity	95.7%	82.6%

Table 2: Distribution of βHCG levels at presentation in patients with confirmed ectopic pregnancies.

βHCG level (IU/l)	*Number of confirmed EP*	*Percent of confirmed EP*
<250	4	4.6%
250–500	11	12.6%
500–1,000	17	19.5%
1,000–2,000	15	17.2%
2,000–5,000	23	26.4%
5,000–10,000	10	11.5%
>10,000	7	8.0%

clinical signs to their primary care doctors and these patients are then streamlined through regional emergency departments and specialist early pregnancy clinics that heavily rely on diagnostic ultrasound.[1,5–8]

Advances in transvaginal ultrasound over the last 20 years have enabled early and accurate diagnosis of ectopic pregnancy and have contributed to a marked reduction in maternal mortality and morbidity.[9] The prevalence of ectopic pregnancy varies in different patient populations, depending on the population characteristics and study selection criteria.[5–7] In this study, the prevalence of confirmed ectopic pregnancy in patients specifically referred with clinical suspicion of ectopic pregnancy to a tertiary hospital typical of other institutions in Australasia was 15%.

Our results indicate that the diagnostic performance of a single initial transvaginal ultrasound scan performed by general sonographers in a radiology department within a tertiary hospital carries a high sensitivity (88.5%) and specificity (96.5%) for the diagnosis of ectopic pregnancy. Other large prospective studies have shown comparable results with sensitivity ranging from 73.9%–90.9% and specificity 99.8–99.9%.[5–8]

While the vast majority of EPs can be successfully diagnosed by a single initial TVUS, some women will require clinical reassessment, repeat βHCG and a follow-up ultrasound examination.[2–4] Missed cases of EP (false negative ultrasounds) are initially diagnosed as PULs. The addition of a second follow-up ultrasound modestly improves the diagnostic performance of ultrasound. In our series of 87 patients with confirmed ectopic pregnancy, only one evaded detection despite multiple scans. The patient was eventually diagnosed with an unruptured right tubal EP. Overall, 21% of patients presenting to our department with a clinical suspicion of ectopic pregnancy needed a repeat ultrasound examination. The rate of repeat examinations in patients with confirmed ectopics pregnancies was lower (17.1%) and was especially low for third re-examination (1.1% versus 26%). This suggests that patients who harbor an EP are somewhat easier to diagnose than those presenting with other early pregnancy problems such as miscarriage or persisting PUL.

In women with an initial diagnosis of PUL, 7.8% (10/129) were subsequently diagnosed with a confirmed EP. It is likely these EPs were too small to be visualised at the time of the initial TVUS. A further challenge in the diagnosis of small unruptured ectopic pregnancies is the paucity of associated imaging findings that normally suggest the presence of a non-visualised underlying ectopic pregnancy such as free fluid, particulate fluid, organised haematoma or blood clots in the pelvis.

Non-surgical management of ectopic pregnancy in clinically stable patients has become commonplace.[10–12] For this reason, apart from the surgically and histologically diagnosed EPs pregnancies in the confirmed EP category, we also included in our analysis those pregnancies that were treated by the early pregnancy clinic team medically or expectantly "as if" they harbored an unruptured EP (presumed EP category). While some of these pregnancies do represent true ectopics, others may represent other entities such as persisting PULs or failed

early pregnancies with an incidental adnexal mass. There is no way to know how many presumed EPs were in fact true EPs pregnancies and how many represented other entities. Given that ultrasound has a very high sensitivity for the detection of EP in patients proven to harbor an EP, it is reasonable to suppose that the vast majority of the women in the presumed EP category did indeed harbor an EP.

A common clinical dilemma in the early pregnancy clinic involves patients who are symptomatic but stable and in whom an initial ultrasound is inconclusive (PUL).

In our analysis, we pooled patients from the confirmed EP and presumed EP category to help answer a useful clinical question: "if there is anything that the clinicians need to worry about in terms of surgery, methotrexate or at least expectant management of an underlying ectopic pregnancy, what is the probability that an ultrasound scan will identify it?"

When the presumed EPs were pooled with the confirmed EPs, the sensitivity and specificity of ultrasound reduced. This reduction in apparent performance is not unexpected and does not necessarily reflect underperformance of ultrasound in these patients, but rather, it highlights the lack of observable findings, diagnostic uncertainty and the lack of a gold standard.

The diagnosis of EP can be particularly challenging when the βHCG level is <1000 IU/l. This is because the non-visualization of an intrauterine gestational sac at this level does not exclude an early intrauterine pregnancy. In our series, over a third (36.7%) of the patients with confirmed EP presented for the initial ultrasound with β<1000 IU/l. The lowest βHCG level at which an ectopic pregnancy was successfully diagnosed by TVUS was only 79 IU/l.

This study has several limitations. Firstly, our patient population was pre-selected based on the geographical location of our centre and the level of service (tertiary teaching hospital). Secondly, in order for patients' radiology reports to be statistically analysed, we needed to classify the terminology used in radiology reports as positive or negative for EP even though the reports sometimes did not provide such a clear binary distinction. We encountered a wide range of reporting styles with varying levels of diagnostic certainty and diagnostic hedging. The reports did not conform to the recently published concensus statements on the nomenclature and definitions in pregnancies of unknown location.[13] Even though we applied strict criteria, process of classifying radiology reports may have introduced unexpected biases. Thirdly, the sonographers who performed the scans were not blinded to the patient's clinical information, blood test results and patients' symptomatology. Instead, the sonographers and radiologists considered each case in its clinical context and used all available clinical information to assist them in the formulation of a diagnostic impression. It should therefore be acknowledged that this study did not evaluate the standalone performance of sonography in the diagnosis of ectopic pregnancy, but rather, the performance of ultrasound combined with clinical information, symptomatology, bHCG as well as the expertise and clinical judgment of the sonographer. Finally, we considered the retrospective nature of this study an advantage. This is because our study reflects the standard operating characteristics of a normal busy radiology department rather than the stringent parameters associated with a prospective study performed by subspecialist experts in a research unit. The sonographers who assessed the patients in our study did not know their performance was going to be scrutinised in the future.

Conclusion

Ectopic pregnancy continues to present a clinical and imaging challenge. The performance of ultrasound in the diagnosis of EP in the setting of a general radiology department within a tertiary hospital in New Zealand is excellent and on a par with international literature. The vast majority of patients can be successfully diagnosed on the first examination with a small number of patients requiring further reassessment with modest diagnostic delays. The likelihood that a clinically significant EP will escape detection on repeat ultrasound examinations is very low.

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Nil.

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Pilot study of methods for assessing unmet secondary health care need in New Zealand

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ABSTRACT

AIMS: In this pilot study, the primary aim was to compare four potential methods for undertaking a national survey of unmet secondary healthcare need in New Zealand (one collecting data from GPs, and three from community surveys). The secondary aim was to obtain an estimate of the prevalence of unmet secondary healthcare need, to inform sample size calculations for a national survey.

METHODS: An electronic system was set up for GPs in Christchurch (Pegasus PHO) and Auckland (Auckland PHO) to record cases of unmet need as encountered in clinics. For the community surveys, a questionnaire developed by the authors was administered to people from the same electoral wards as the GP clinics. Three modes of questionnaire administration were trialled: online, telephone and face-to-face interview. Random population sampling from the Māori and General Electoral Rolls was used to identify eligible survey participants until there were approximately 200 respondents for each method in each city. Data collection took place from November 2015 to February 2016.

RESULTS: GP reports: Pegasus PHO: 8/78 eligible practices recorded 28 cases of unmet secondary healthcare need in 10 weeks. Auckland PHO: 3/26 practices participated and recorded no cases in three weeks.

Surveys: 1,277 interviews were completed (online 428, telephone 447, face-to-face 402).

For primary healthcare, 211/1,277 (16.5%) had missed a GP visit because of cost (online 25.0%, telephone 11.6%, face-to-face 12.9%). For secondary healthcare, 119/1,277 (9.3%) reported unmet healthcare need that had been identified by a health professional (online 11.2%; telephone 9.2%; face-to-face 7.5%). Of these, 75/119 (63.0%) required a consultation, and 47/119 (39.5%) required a procedure.

Completed interview rates as a percentage of names on the Electoral Roll were low (online 8.8%, telephone 15.4%, face-to-face 13.9%), affected by changed addresses and lack of listed telephone numbers. The response rate for those with valid phone numbers was 47.6%, and for those with valid addresses was 31.5%.

CONCLUSIONS: Using the Electoral Rolls to identify respondents is problematic. For a national survey, random population sampling by address, similar to the method employed for the New Zealand Health Survey, but giving respondents a choice between face-to-face and phone interviews, is proposed. Asking GPs to record data on unmet need for secondary care was not successful. Our pilot study suggests there is sufficient unmet secondary healthcare need in New Zealand to merit a national survey.

Universal healthcare was adopted, by consensus, as a global objective by the United Nations General Assembly in 2012.[1] However, even in countries with state-funded health systems, there is evidence of unmet need and inequitable access to health care services.[2,3] Both 'need' and 'unmet need' for healthcare can be difficult to define and measure.[4,5] However, both are key indicators of the effectiveness of a health system, so surveys of unmet need, including questions in international health surveys, have been carried out in many countries.[6–9]

Methods for estimating the prevalence of unmet need for healthcare in other countries have ranged from questions in large-scale surveys such as the EU Survey of Income and Living Conditions (EU-SILC) and the

Canadian Community Health Survey (CCHS), to computer-assisted telephone interviews of random samples of adults[8] and household surveys.[10,11] In the EU-SILC, nationally representative probability sampling and personal interviews were used for the section of the survey that includes questions on unmet need.[12] The CCHS used multi-stage stratified cluster sampling of households, with random selection of an adult from each household to be interviewed in person (86%) or by telephone.[13] Surveys in Thailand and in Sierra Leone were undertaken by field workers or trained medical and nursing students respectively, who visited households and carried out face-to-face interviews.[10,11] A 2013 survey of adults in 11 countries used computer-assisted telephone interviews, including mobile phone numbers as well as landline numbers.[8]

In Europe, estimates of the prevalence of unmet need for healthcare (primary and secondary healthcare) have ranged from low prevalence of 0.4% in Switzerland, 1.2% in Spain and 1.6% in Sweden to high prevalence of 15.6% in Turkey, 19.7% in Russia and 24.8% in Ukraine.[2] The prevalence of unmet healthcare need in Thailand was estimated at 1.4% for outpatient and 0.4% for inpatient services respectively,[10] while the prevalence of untreated surgical conditions in Sierra Leone was 25%.[11] In Canada the prevalence of unmet health care need in the previous 12 months was 13.2%.[14] Comparisons between countries are limited by differences in the definitions used, types of unmet need measured and differences in survey methods. The New Zealand Health Survey (NZHS), undertaken by the Ministry of Health, "focuses on health service utilisation and patient experience" and provides the only comprehensive source of New Zealand data on unmet need.[15] It collects data on unmet primary healthcare need (PHN) by asking if people have missed out on primary care consultations, after-hours care, dental care or prescriptions because of cost or because of difficulties with transport.

Some studies have reported on deficiencies in specific medical, surgical and mental secondary healthcare services in New Zealand.[16–18] However, unmet secondary healthcare need (SHN) is not routinely measured in this country. The New Zealand Ministry of Health states that information on the use of secondary services can be captured from administrative databases;[15] however, only about 50% of private hospital discharges are recorded, and there are only limited data available on patients in need who are not referred.[19,20]

Because a national survey of unmet need for secondary care has never been undertaken in New Zealand, prior to planning a national study, we sought to establish a reliable and efficient method of measuring unmet SHN in New Zealand with a pilot study. A system of routine notification from GP practices had potential to provide an efficient and effective method for estimating the prevalence of unmet need for secondary care, including patients who were not referred for secondary care, but crucial information such as the acceptability and uptake of this method were unknown. A population survey using the methodology of the New Zealand Health Survey would be expensive, and whether alternative methods could provide equivalent prevalence estimates for the New Zealand population, was unknown. Thus, the primary aim of the pilot study was to: test the possibility of using anonymous data downloaded from general practice patient management software (PMS), similar to the routine notification system used by the New Zealand Ministry of Health as part of the National Patient Flow programme,[21] and trial a population questionnaire comparing three survey methods (online, face-to-face and telephone interviews). The secondary aim was to provide an indication of the approximate prevalence of unmet SHN and the sample size required to estimate it with acceptable precision. The pilot was located in Christchurch and Auckland with the assistance of Pegasus and Auckland Primary Health Organisations (PHOs).

Key information to be delivered from the pilot study was:

- whether face-to-face interviews result in a higher response proportion than telephone contacts
- whether the high cost of face-to-face interviews is justified
- whether inexpensive electronic surveys generate adequate response proportions
- to what extent GP recording of unmet need (anonymous data downloaded from practice management software)

compares with need as reported by survey

- An indication of the approximate prevalence of unmet need and the sample size required to estimate it.

To our knowledge, these four methods for estimating the prevalence of unmet SHN have not been compared before.

Methods

GP survey arm

The authors consulted with a range of general practitioners (N=190) in Christchurch and Auckland and asked them whether they could identify areas of unmet need for secondary health care; no restriction was placed on the number of examples of unmet need each GP could list. Most felt that there was significant unmet SHN. On average, each GP identified three areas of need in which supply was inadequate, with 8% of GPs listing six or more areas of need.

Software tools that allowed GPs to record instances of unmet SHN were developed and installed at Pegasus and Auckland PHO practices. Pegasus practices used a PMS screening entry and Auckland practices used an electronic advanced form. These allowed GPs to classify a patient's unmet SHN and to indicate why the need was unmet. Participating GPs were asked to record instances of patients' unmet SHN as they were encountered in consultations. Data were extractable centrally and anonymously from participating practices' PMS by both PHOs.

Eight types of unmet SHN could be entered in pre-determined categories (colonoscopy, counselling, cholecystectomy, gastroscopy, hernia, joint replacement, dental care, varicose veins); these were selected from the findings of the consultation with GPs mentioned above, conducted in 2015, where participants were asked to list "areas of unmet secondary healthcare need that affect your patients and/or interfere with your capacity to provide desirable care." Other types of unmet need could be entered in an 'other' category.

In Pegasus PHO the unmet SHN recording tool was automatically installed at all practices using the appropriate PMS configuration. Data were collected at Pegasus practices for ten weeks between January and March 2016.

In Auckland PHO, the unmet SHN recording tool was installed at practices that indicated willingness to be involved in the study. Data were collected at Auckland practices for three weeks between February and March 2016.

GPs in Pegasus and Auckland PHOs were informed about the study by their PHO practice facilitators, and were encouraged to participate by their PHOs. Pegasus GPs also received two emails from a member of the study team outlining the study and encouraging participation.

When data collection ceased, a non-responder survey was conducted. Twenty non-responding practices were randomly selected. A GP at each practice was contacted by phone or email and asked whether they had been aware of the unmet need survey, whether they had encountered instances of unmet SHN among their patients in the previous three months and, if so, what had prevented them from recording unmet SHN during the data collection period.

Population survey arm

The population survey was undertaken by the company *Research First* (http://www.researchfirst.co.nz/) from November 2015 to February 2016 (letters were sent in November 2015). The online survey was open from 5 November to 30 November, telephone interviewing took place between 15 November and 7 December 2015 and face-to-face interviewing took place between 15 November 2015 and 3 February 2016. A computer-generated random sample was drawn from the Māori and General Electoral Rolls (from Electoral Roll data provided by the Electoral Commission in July 2015).

The random sample was drawn from all electoral wards in Christchurch; Auckland PHO has a majority of its patients in only six electoral wards and, to improve comparability, the sample was drawn only from these. Addresses that were outside the areas covered by the PHOs were excluded. The target population was the usually resident, non-institutionalised population of New Zealand aged 18 years and over, residing in permanent private dwellings. People living in non-private dwellings, rest homes, hospitals and psychiatric institutions, and penal institutions were excluded. Participants were randomly allocated to three groups. For each city, based on the

experience of the research company with likely contact and response rates for each method, 2,500 people were selected for the online survey arm, 1,500 for the phone arm and 1,500 for the face-to-face arm, giving a sample of 11,000. Sample size calculations had suggested that, for a reliable prevalence estimate (95% confidence interval <+/- 5%), 200 informants for each survey method in each city would be needed; recruitment continued until approximately this number had been reached.

An invitation letter and an information sheet were mailed to all those sampled; these explained the purpose of the study and gave potential respondents the opportunity to opt-out.

Those selected for the online approach were given a link, a code and a password. Those selected for the telephone approach were informed that they could expect a call (both landlines and mobiles were called, if they were listed numbers); up to six call-backs were made. Those selected for a face-to-face interview were informed they could expect a visit. Homes were visited up to seven times (the initial call, plus up to six call-backs) in order to make contact with the potential respondent.

Telephone calls and face-to-face interviews were distributed across all days of the week and occurred between 9.30am and 8.30pm on weekdays and from 10am to 5pm on weekends.

Using a questionnaire developed by the authors (Appendix 1), respondents were asked about missing any of three aspects of primary care because of cost and about missing primary care for any reason in the last 12 months. The questions were based on those used internationally, (EU-SILC, and CCHS) or were similar to those used by the NZHS. Because the New Zealand Health Survey includes questions on unmet need for primary care, but not for secondary care, questions on unmet need for primary care were included in the pilot questionnaire so we could compare our estimates of the prevalence of unmet need for primary care with the population estimates from the New Zealand Health Survey. We also included questions about unmet PHN (such as the cost of seeing a GP) that impact on SHN. We developed question 8 based on the feedback we received from Pegasus GPs (the examples of operations/healthcare were the ones identified by GPs as areas of unmet need). Question 13 is a health status question used in many surveys—a similar question is used in the New Zealand Health Survey. Questions 16–20 were derived from the New Zealand Census, so we could compare our respondents with the wider New Zealand population.

Respondents were asked whether they had not received secondary health care that had been recommended by a doctor or other health professional in the previous five years, and another question asked about the nature of the most recent secondary care that had been missed. Respondents who had missed primary or secondary care were asked why the care had not been received and what impact this had had on their life.

The research was approved by the Human Ethics Committee of the University of Canterbury on 14 May 2015 – Reference HEC 2015 / 20 / LR – PS.

Results

GP survey arm

Seventy-eight of Pegasus PHO's 109 practices had a PMS that was configured to allow installation of the software tool used for data collection, which made them eligible to participate in the study. However, despite encouragement from their PHOs, only eight practices responded and only three responded out of the 26 practices in Auckland PHO.

Twenty-eight cases of unmet SHN were recorded from the eight Pegasus PHO practices across a diverse range of health procedures. Only six cases were in the named eight categories (two colonoscopies, one gastroscopy, two hernias and one varicose veins). There were six cases of musculoskeletal problems and three cases of radiology. The most common referral issue was "did not meet DHB criteria" (eight cases) followed by "previously referred to public service and declined for assessment" (six cases). No reports of unmet SHN were received from any of the Auckland PHO practices.

One GP from each of 20 randomly selected non-responding practices was contacted. Of these GPs, 14 (70%) were aware of the study, and 19 (95%) had seen

patients with unmet SHN in the last three months. Non-responders were asked to give reasons for their non-response and four key themes were identified: the GP was unaware of, or had misunderstood the instructions for, the survey;[6] the GP was too busy;[6] the GPs were completing another study examining unmet need;[3] and no patients with unmet SHN were seen.[1] Because of the sparse nature of the GP responses, no comparison was made with the results of the population survey.

Population survey arm

For each survey type; online, face-to-face and telephone, sampling continued until there were 400 participants (approximately 200 participants in each city). Table 1 shows the numbers approached in order to achieve this. For the online survey this was achieved without any reminder.

The online arm of the pilot required the highest number of initial letters to be mailed in order to achieve the required sample size. The completion rate was the lowest at 8.8%; a few letters were returned and some refusals were received, but there was no information from the other 91.2% who were mailed. Some may no longer be at the mailed address, others might not have had access to a computer. Therefore it is not

Table 1: Sampling yields and completion rates (as percent of those mailed).

	Online		
	Christchurch	**Auckland**	**Both**
Total sample (mailed)	2,446	2,426	4,872
Mail returned	75	61	136
Refusal	60	28	88
Completions	248	180	428
Completion rate	10.1%	7.4%	8.8%
	Telephone		
	Christchurch	**Auckland**	**Both**
Total sample (mailed)	1,459	1,452	2,911
Available phone number	557	438	995
Disconnected	30	26	56
Refusal	262	159	421
Completions	232	215	447
Completion rate	15.9%	14.8%	15.4%
	Face-to-face		
	Christchurch	**Auckland**	**Both**
Total sample (mailed)	1,451	1,447	2,898
Address visited*	868	892	1760
No longer resident/inaccessible	237	246	483
Not available	272	292	564
Refusal	148	154	302
Completions	202	200	402
Completion rate	13.9%	13.8%	13.9%

*Not all addresses needed to be visited once the required quota had been achieved.

Table 2: Gender profile of respondents by survey method.

Methodology	Total		Online		Telephone		Face-to-face	
Total number	N=1,277	%	n=428	%	n=447	%	N=402	%
Male	548	43%	158	37%	199	45%	191	48%
Female	729	57%	270	63%	248	55%	211	52%

possible to calculate a response rate from those eligible to respond to the online arm of the study.

For the telephone arm of the study, only 34.2% of the original sample had valid listed phone numbers. The response rate among those with valid phone numbers was 47.6%.

For the face-to-face arm, 27.4% of those visited could not be reached because they had moved and the response rate for the remainder was 31.5%.

The three methods differed in cost—the estimated cost per completed interview was approximately $31 for online, $41 for telephone and $73 for face-to-face administration of the questionnaire.

Characteristics of respondents

The characteristics of the respondents across survey method and cities were compared. The mean age of the respondents was 54.4 years. Differences in age across sites and methods were relatively minor; the mean age of those responding by phone was slightly less than the other two methods. Almost 57% of respondents were women.

The commonest reported ethnicity was European, 80% of respondents (87% in Christchurch and 72% in Auckland). Māori were significantly under-represented with only 2.6% of respondents (2.3% in Christchurch and 2.9% in Auckland); 3% reported as Pacific peoples; almost all were in the Auckland sample; 7% reported as Asian (3% and 13%).

Other characteristics of those responding included that 77% rated their health as good or better; the equivalent figure from the NZHS was 89%.[15] Respondents in Auckland and Christchurch had the same chance of being employed (60%) but those in Auckland were more likely to have private health insurance: 56% vs 41%. Auckland respondents were more likely to be in households with incomes over $150k (20.6%) than were Christchurch respondents (6.9%).

The online sampling yielded the least representative sample. Sixty-three percent were women (Table 2). It had the highest percentage reporting as European (85% compared to 82% for telephone and 72% for face-to-face); and the lowest percentage as Asian (4% compared to 5% for telephone and 14% for face-to-face).

Estimate of unmet need for primary and secondary health care

Primary—Of the 1,277 respondents, 367 (28.7%) reported one or more unmet PHN (Table 3). Reasons for unmet PHN included missing a GP visit due to cost: 211 (16.5%); missed filling a prescription due to cost: 63 (4.9%); and missed a test, treatment or follow-up due to cost: 146 (11.4%). GP help had been missed "for any reason" by 199 (15.6%).

Table 3: Reasons for unmet primary healthcare need in last 12 months.

Methodology	Total		Online		Telephone		Face-to-face	
Total number	N=1277	%	n=428	%	n=447	%	N=402	%
Didn't visit doctor because of cost	211	16.5%	107	25.0%	52	11.6%	52	12.9%
Missed script/meds because of cost	63	4.9%	27	6.3%	16	3.6%	20	5.0%
Missed test, Rx, FU because of cost	146	11.4%	76	17.8%	30	6.7%	40	10.0%
Missed GP help, any reason	199	15.6%	82	19.2%	65	14.5%	52	12.9%
Any of the answers combined	367	28.7%	161	37.6%	108	24.2%	98	24.4%

Table 4: Types of unmet secondary healthcare need in last five years.

	All	Online	Telephone	Face-to-face
Number of respondents	1,277	428	447	402
Number with any need	119	48	41	30
Total needs	132	57	42	33
Needs per person	1.11	1.19	1.02	1.10
Percentage with any need	9.3%	11.2%	9.2%	7.5%
Specific needs (% of those with any needs)				
Orthopaedic operations	15.1%	14.6%	19.5%	10.0%
General surgical operations	12.6%	10.4%	12.2%	16.7%
Endoscopy	9.2%	12.5%	4.9%	10.0%
Other procedures	2.5%	4.2%	0.0%	3.3%
Surgical consults	15.1%	10.4%	26.8%	6.7%
Medical consults	31.1%	35.4%	22.0%	36.7%
Dental consults	11.8%	12.5%	9.8%	13.3%
Psyche consults	5.0%	8.3%	4.9%	0.0%
Non-specific	8.4%	10.4%	2.4%	13.3%
Any procedure	**39.5%**	**41.7%**	**36.6%**	**40.0%**
Any non-procedure	**71.4%**	**77.1%**	**65.9%**	**70.0%**

Unmet PHN for the online survey was 50% higher than for face-to-face or telephone interviews.

Secondary—Of 1,277 respondents, 119 (9.3%) mentioned an unmet SHN that had been identified by a doctor or other health professional in the last five years (Table 4). Thirty-nine percent of this unmet need occurred within the last year and a total of 63% within two years. A number of people mentioned two or more issues for a total of 132 issues. Of the 119 respondents mentioning any unmet SHN, procedures were said to be required by 47 (39.5%); the largest numbers were in orthopaedics 18 (15.1%), general surgery 15 (12.6%) and endoscopy 11 (9.2%). Consultations were required by 75 (63.0%) of the 119; these were classified as medical 37 (31.1%), surgical 18 (15.1%), dental surgery 14 (11.8%) and psychiatry/counselling 6 (5.0%).

The prevalence of unmet SHN was higher in the online sample (11.2%), intermediate in the telephone (9.2%) and lowest in the face-to-face (7.5%) sample.

Those who mentioned unmet PHN or SHN were asked how their life had been affected by not getting the help they needed (Table 5). An answer was available from 213 of those with an unmet PHN and from all the 119 with an unmet SHN. The commonest positive response was "pain or other symptoms" and was given by 46/213 (21.6%) relating to unmet PHN and by 50/119 (42.0%) relating to unmet SHN. The second commonest response was "worry, anxiety and stress" and was given by 36/213 (16.9%) relating to unmet PHN and by 19/119 (16.0%) relating to unmet SHN.

Primary and secondary unmet need

The prevalence of unmet PHN and SHN were examined. The following list summarises the key findings:

1. The prevalence of both unmet PHN and SHN was higher among those responding to the online survey (refer Tables 3 and 4), but this difference was statistically significant only for

Table 5: Impact of unmet need.

(% of those with any needs)	Primary		Secondary	
Worry, anxiety, stress	36	16.9%	19	16.0%
Worry or stress for family or friends	1	0.5%	1	0.8%
Pain or other symptoms	46	21.6%	50	42.0%
Problems with activities of daily living	9	4.2%	13	10.9%
Loss of work	6	2.8%	7	5.9%
Loss of income	3	1.4%	0	0.0%
Increased dependence	2	0.9%	1	0.8%
Increased use of over-the-counter drugs	4	1.9%	2	1.7%
Overall health deteriorated, condition got worse	16	7.5%	12	10.1%
Health problem improved	4	1.9%	2	1.7%
Personal relationships suffered	2	0.9%	3	2.5%
Unable to do (or do as much) child care	1	0.5%	1	0.8%
Increased cost	10	4.7%	0	0.0%
Care unsatisfactory	14	6.6%	3	2.5%
Other	32	15.0%	13	10.9%
No impact	43	20.2%	21	17.6%
Not answered/declined/don't know	10	4.7%	6	5.0%
Total number of items	**239**	**112.2%**	**154**	**129.4%**
Total number of respondents	**213**	**100.0%**	**119**	**100.0%**

unmet PHN (χ^2=24.7 p<0.001, and χ^2=2.7 p=0.1 respectively).

2. People reporting unmet PHN were more likely to report unmet SHN; 64 of 367 (17.4%) with PHN had unmet SHN, compared to 55 of 908 (6.1%) without PHN (χ^2=40, p<.001).

Reasons healthcare was not received

Respondents who had not received help from a GP for unmet PHN were asked to give reasons. A total of 226 items were recorded from 212 respondents. The most common reasons were: 'Too expensive'—given by 52 (24.5%) of respondents; 'Could not take time'—by 28 (13.2%); and 'Waiting list too long'—by 24 (11.3%). It is likely that the last response indicates an inability to get an appointment within a reasonable time (GPs do not usually have formal waiting lists).

Similarly, respondents were asked why they had not received needed secondary care. A total of 124 reasons were recorded from 119 respondents. The most common reasons were 'Not available at public hospital/below public hospital threshold'—given by 53 (44.5%), and 'Could not afford to pay for operation/procedure/ healthcare'—given by 32 (26.9%). Eleven (9.2%) were currently on a waiting list.

Discussion

GP survey arm

Of the 81 participating practices, reports came from just eight Pegasus PHO practices; the majority of GPs who could have recorded data did not do so. Our non-responder survey showed that while the majority of GPs were aware of the survey and had encountered instances of unmet SHN during the study period, most did not use the study software tools to record these instances. For some GPs, recording unmet SHN was simply forgotten while others

gave pressure of workload as a reason for non-completion. Only 28 instances of unmet SHN were recorded from the eight practices that reported. In summary, recording unmet SHN in primary care was not found to be a reliable means of collecting these data, though potentially it could be made more effective by providing primary care with dedicated resources to undertake data collection. It cannot, however, record unmet SHN in that section of the population which is unable to access GP care and secondary healthcare referral because of financial or other reasons. Other studies have shown cost to be a barrier to accessing GP care,[8,22] and this in turn is likely to have a negative impact on access to secondary care.

Population survey arm

None of the three survey techniques we piloted approached the capacity of the method used for the NZHS, to obtain a representative sample. Because we used the Electoral Roll as the initial sampling frame, all three methods were disadvantaged by inaccurate addresses related to the high mobility of New Zealanders (nearly a third of those on the Electoral Roll no longer lived at the listed address). The online methodology was the least expensive but generated the least representative sample, in part because nearly a quarter of New Zealanders do not have access to the internet at home.[23] Because we had no access to email addresses, respondents had to copy the link to the survey website from the invitation letter and enter it, rather than clicking on it, which complicated the process. Those with good computer skills and people who had experienced unmet need may have been more likely to respond. The telephone methodology was hampered by difficulty accessing telephone numbers in addition to housing mobility. Landline use has declined in New Zealand as the use of mobile phones has increased.[23] The face-to-face methodology although also limited by incorrect addresses on the Electoral Roll, mitigated some of the described shortcomings of the other two sampling methods; it was, however, the most expensive. The Auckland sampling area was limited to the Electoral wards served by the Auckland PHO, so that a comparison could be made between the population survey and the GP survey. This comparison did not take place, because the pilot study demonstrated that an online GP survey was inappropriate. This was an important finding of the pilot study; leading us to conclude that population sampling would be the most appropriate method for a national survey of unmet SHN.

About 29% of our respondents reported unmet PHN. The NZHS 2015 Summary of Results reported that 27.1% of the New Zealand adult population have unmet PHN;[15] this figure combines data from five questions covering a range of issues similar to those reported here. The similarity in results suggests the prevalence estimates from our pilot study are valid. Across the EU, where primary care is typically free, the average prevalence of unmet PHN is 2.5%.[6] The Commonwealth Fund reports the prevalence of missed primary health care for those with above average and below average income; only the US (24% and 49%) has higher values than New Zealand (19% and 29%).[7]

About 9% of our respondents reported unmet SHN. There do not appear to be any comparable international data specifically restricted to such unmet SHN. Studies by the Health Funds Association of New Zealand and New Zealand Private Surgical Hospitals, in 2013 and 2016,[19,20] surveyed 1,830 and 1,800 adults respectively and calculated the prevalence of unmet need for elective surgery at 5% on both occasions. It is unclear if endoscopies or dental surgery were included, and the need for consultation was not assessed. Taking this into consideration, their findings are broadly similar to those reported here.

We conclude from these preliminary pilot data that: (i) unmet PHN is likely to be present among at least 25% of the adult population, and (ii) 9% is a reasonable estimate of the prevalence of unmet SHN for the purposes of predicting the required sample size for a national population survey.

Assuming a prevalence of unmet PHN and unmet SHN of approximately 29% and 9% respectively, a responding sample of 500 would be needed for each group of interest (eg 10,000 for 20 DHBs) to generate an estimate of the prevalence of unmet need, with a 95% confidence interval of plus or minus approximately 4% and 2.5% respectively.

The pilot study allowed us to determine that:

- None of the piloted population survey methods had the capacity of the method used for the NZHS, to generate a representative sample
- GP recording of unmet need is not recommended as a method to estimate the prevalence of unmet need for secondary health care, because very few GPs participated
- Despite their limitations, all the piloted survey methods identified some unmet need for secondary health care. The pilot survey and the New Zealand Health Survey produced similar estimates of the prevalence of unmet PHN, which suggests that our estimate of the prevalence of unmet SHN is adequate to calculate the sample size required to estimate the prevalence of unmet SHN in a national study.

Proposed methodology for a national survey

In the pilot study, potential respondents were identified from the Electoral Roll. Our findings indicated that this document ages rapidly and a significant number of people were no longer at the address given; further, listed landline and mobile phone numbers were often not available. These problems contributed to the low contact rates in the pilot study. Although it is more expensive, a future national survey of unmet SHN should use an approach similar to that used for the NZHS in order to obtain an adequate representative response proportion. The NZHS, using household visits followed by face-to-face interviews, obtains a response proportion of 79% after excluding ineligible households (vacant sections, vacant dwellings and non-residential dwellings) but allows up to 10 call backs (visits) to secure an interview. In order to reduce costs, we propose household contacts followed by face-to-face interviews or telephone interviews. (We have the option of offering a telephone interview because, unlike the NZHS, we would not need to take measurements such as height, weight and blood pressure from participants). Two previous national surveys have offered the option of face-to-face or telephone interviews.[13,24] As in the NZHS, over-sampling of Māori will be undertaken so that Māori-specific prevalence estimates of unmet SHN can be made.[25]

Surveys may find it difficult to recruit Māori participants, so the recruitment approach for this survey will be designed to maximise Māori participation.[26] This will involve testing the survey materials to ensure they are appropriate for Māori participants, ensuring relevant Māori organisations are aware when the survey is being conducted in their area, having Māori interviewers, and prioritising resources to achieve an adequate number of Māori participants.

Conclusions

For the estimation of the prevalence of unmet SHN, random population sampling by address should be used and respondents could be offered a choice between face-to-face and phone interviews. Asking GPs to record unmet need for secondary health care at clinical presentation was not worthwhile because very few GPs participated. Investigation of ways to increase GP participation in routine recording of unmet need may be worthwhile, however this would not capture unmet need in people who cannot afford to access primary care. The pilot survey indicates that there is unmet SHN (as well as PHN) in New Zealand, which impacts individuals' well-being and productivity. A national survey of unmet SHN would be a valuable contribution to service assessment and planning in New Zealand.

Competing interests:
Prof Hornblow reports personal fees from Pegasus Health (Charitable) Ltd during the conduct of the study and outside the submitted work.

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Appendix

Questionnaire—pilot study of unmet secondary healthcare need

1. During the last 12 months, was there a time when you had a medical problem but did not visit a doctor because of the cost?
   - ☐ Yes
   - ☐ No
   - ☐ [*Do not read*] Not applicable
   - ☐ [*Do not read*] Not sure
   - ☐ [*Do not read*] Decline to answer
2. During the last 12 months, was there a time when you did not collect a prescription, or you skipped doses of your medicine because of the cost?
   - ☐ Yes
   - ☐ No
   - ☐ [*Do not read*] Not applicable
   - ☐ [*Do not read*] Not sure
   - ☐ [*Do not read*] Decline to answer
3. During the last 12 months, was there a time when you skipped a medical test, treatment or follow up that was recommended by a doctor because of the cost?
   - ☐ Yes
   - ☐ No
   - ☐ [*Do not read*] Not applicable
   - ☐ [*Do not read*] Not sure
   - ☐ [*Do not read*] Decline to answer
4. During the last 12 months, was there ever a time when you felt that you needed the help from a GP but you did not receive it for any reason?
   - ☐ No—**If no,** please go to question 7
   - ☐ Yes—**If yes,** please go to question 5
5. Thinking of the most recent time, why didn't you get this health care?

   Verbatim response:

   [*Classify response—more than one reason can be identified*]
   - a. ☐ Could not afford to (too expensive)
   - b. ☐ Waiting list too long
   - c. ☐ Could not take time off because of work, caring for children or others
   - d. ☐ Too far to travel/no means of transport
   - e. ☐ Fear of doctor/hospitals/examination/treatment
   - f. ☐ Wanted to wait and see if the problem got better on its own
   - g. ☐ Did not know any good doctor or specialist
   - h. ☐ Other (*Specify*) _____
6. How was your life affected as a result of not getting help from your GP?

   Verbatim response:

(Classify responses—more than one response may be identified)

a. ☐ Worry, anxiety, stress
b. ☐ Worry or stress for family or friends
c. ☐ Pain or other symptoms
d. ☐ Problems with activities of daily living (eg dressing, driving)
e. ☐ Loss of work
f. ☐ Loss of income
g. ☐ Increased dependence (on relatives, friends)
h. ☐ Increased use of over-the-counter drugs
i. ☐ Overall health deteriorated, condition got worse
j. ☐ Health problem improved
k. ☐ Personal relationships suffered
l. ☐ Unable to do (or do as much) voluntary work
m. ☐ Unable to do (or do as much) child care
n. ☐ Other (*Specify*) _____

7. In the last five years, have you ever been told by a doctor or other health professional that you needed hospital or specialist care, but you have not received it?

☐ No— **If no**, please go to question 11
☐ Yes—**If yes**, please go to question 8

8. Thinking of the most recent time what was the hospital or specialist care that you did not receive? (*Tick the appropriate box*)

a. ☐ Hernia operation
b. ☐ Varicose veins operation
c. ☐ Gall bladder operation
d. ☐ Joint replacement operation
e. ☐ Colonoscopy
f. ☐ Gastroscopy
g. ☐ Tooth extraction or other dental care
h. ☐ Counselling
i. ☐ Other
    i. ☐ Other medical consultation
    ii. ☐ Other surgical consultation
    iii. ☐ Other (*Specify*) _____

9. What year was this? (*Year*) _____

10. What were the reasons for not getting the hospital or specialist care?

Verbatim response:

(*Classify response—several responses may be identified*)

a. ☐ Not available at a public hospital
b. ☐ Currently on a waiting list
c. ☐ Could not take time off because of work, caring for children or others
d. ☐ Too far to travel
e. ☐ Fear of operation/procedure
f. ☐ Problem got better on its own
g. ☐ Could not afford to pay for operation/procedure/healthcare
h. ☐ Other (*Specify*) _____

11. How was your life affected as a result of not getting the operation(s) or other hospital health care?

Verbatim response:

(Classify responses—more than one response may be identified)

a. ☐ Worry, anxiety, stress
b. ☐ Worry or stress for family or friends
c. ☐ Pain or other symptoms
d. ☐ Problems with activities of daily living (eg dressing, driving)
e. ☐ Loss of work
f. ☐ Loss of income
g. ☐ Increased dependence (on relatives, friends)
h. ☐ Increased use of over-the-counter drugs
i. ☐ Overall health deteriorated, condition got worse
j. ☐ Health problem improved
k. ☐ Personal relationships suffered
l. ☐ Unable to do (or do as much) voluntary work
m. ☐ Unable to do (or do as much) child care
n. ☐ Other (*Specify*) _____

12. Sometimes people have a condition and do not know if it could be improved with medical treatment or surgery. Examples could be varicose veins, a small hernia or frequent stomach aches. Do you have anything like this?

☐ No—**If no**, please go to question 13
☐ Yes—**If yes**, please describe…

13. In general would you say your health is… (*tick one response only*)

a. ☐ Very good
b. ☐ Good
c. ☐ Fair
d. ☐ Bad
e. ☐ Very bad
f. ☐ Don't know

14. What is your date of birth? (*day/month/year*)

☐☐/☐☐/☐☐☐☐

15. Which best describes you?

☐ Single
☐ Couple

[*Insert gender*] ☐ Male ☐ Female

16. Which ethnic group or groups do you belong to? (*include as many as given*)

a. ☐ New Zealand European
b. ☐ Māori
c. ☐ Samoan
d. ☐ Cook Island Māori
e. ☐ Tongan
f. ☐ Niuean
g. ☐ Chinese
h. ☐ Indian
i. ☐ Other such as DUTCH, JAPANESE, TOKELAUAN. Please state:

17. Are you in the paid workforce?
    ☐ No—**If no**, please go to question 19
    ☐ Yes—**If yes**, please go to question 18
18. What is your main occupation? (for example PRIMARY SCHOOL TEACHER, CLOTHING MACHINIST, MOTEL MANAGER, RECEPTIONIST etc. *Please list if respondent has more than one main occupation*)

19. If you are retired or not in the paid workforce, what was your main occupation? (*Please list if respondent had more than one main occupation*)

20. From all your sources of income, what was the total income that you (and your partner (*if there is one*)) got before tax or anything was taken out of it in the last year?
    a. ☐ Loss
    b. ☐ Zero income
    c. ☐ $1–$10,000
    d. ☐ $10,001–$30,000
    e. ☐ $30,001–$50,000
    f. ☐ $50,001–$100,000
    g. ☐ $100,001–$150,000
    h. ☐ $150,001 or more
    i. ☐ Don't know *If respondent knows his/her <u>after tax income</u>, please write here:*
    j. _____ ☐ Declines (*do not read out*)
21. Are you covered by any health or medical insurance?
    a. ☐ Yes—**If yes,** please go to question 23
    b. ☐ No—**If no**, please go to question 22
    c. ☐ Don't know—please go to question 22
22. Did you have health or medical insurance in the past?
    d. ☐ Yes *Why did you stop having this insurance?*
    Verbatim response:

    e. ☐ No
    f. ☐ Don't know
23. Do you have any comments on the adequacy of the New Zealand health system?
    Verbatim response:

    Interviewer's comments:

Rationing of hip and knee referrals in the public hospital: the true unmet need

Tom Inglis, Paul Armour, Graehame Inglis, Gary Hooper

ABSTRACT

AIM: The aim of this paper is to outline the development of a triage system for elective hip and knee referrals to the Orthopaedic Department of the Canterbury District Health Board (CDHB), and to determine the unmet need within this population for accessing first specialist assessment (FSA).

METHODS: Between 1 August 2015 and 31 March 2016 data was collected from all elective hip and knee referrals that underwent triage for a FSA. The number of outpatient appointments available according to the government four-month waiting time is set by the CDHB. Patients were triaged by two consultant surgeons on the basis of their referral letter and radiological imaging into one of five categories: accepted for FSA, insufficient information, no capacity, low priority or direct entry to waiting list (if already seen by a specialist). Those not accepted for an FSA were returned to general practitioner (GP) care.

RESULTS: During the study period there were 1,733 referrals (838 hip related referrals and 895 knee related referrals) to the orthopaedic department with a request for FSA. All patients had failed conservative management. Of these referrals 43% of hip and 54% of knee related referrals could not be offered an FSA and were returned, following triage, to general practitioner care unseen. Only 8% and 9% respectively were declined for insufficient information in the referral letter or lack of need.

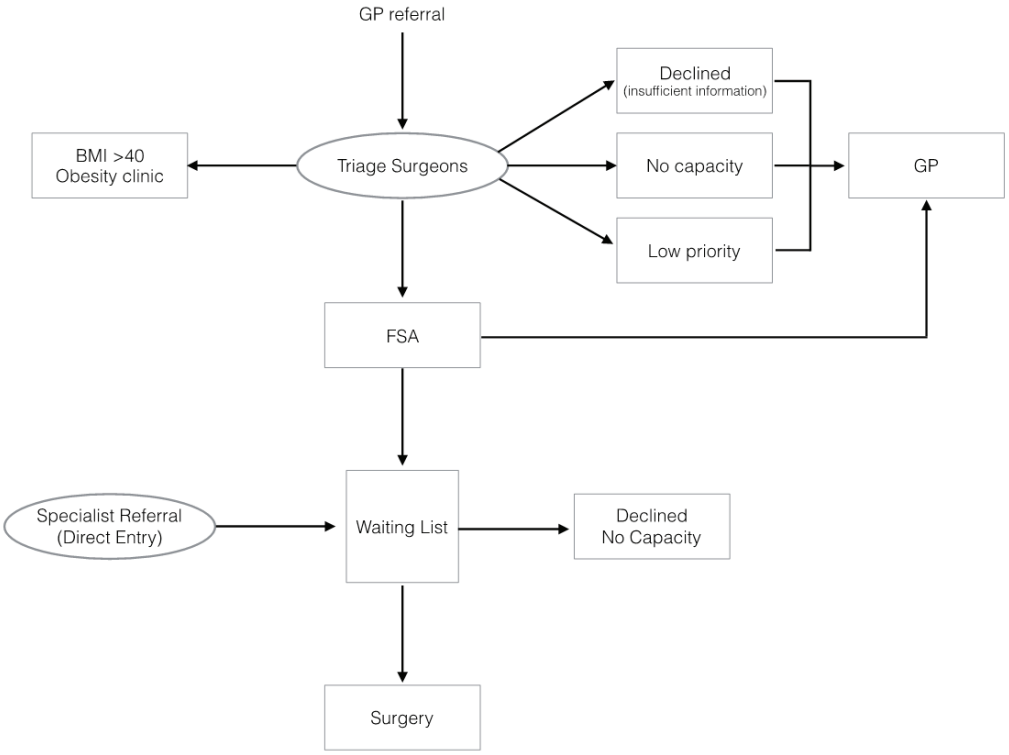
CONCLUSION: This study details the implementation of a triage system for elective hip and knee referrals to the CDHB and with accurate data we have been able to determine the large number of patients unable to access a specialist opinion. These patients represent the unmet need within our community and highlights the degree of rationing taking place within the public hospital.

New Zealand's public health system is under increasing pressure in terms of service delivery, particularly with regard to the provision of elective surgery. In Canterbury the reasons for this include: an increasing population, high patient expectations, restriction of resources and limitations on funding. Within the Canterbury District Health Board (CDHB), orthopaedic surgical services are particularly strained due to the increasing Canterbury population and added responsibility for surgical services in both the Chatham Islands and the West Coast District Health Board. This has resulted in an added demand on resources, increasing the difficulty of the CDHB to meet the orthopaedic needs of the community.

The population in New Zealand is ageing rapidly with predictions this will increase the requirement for orthopaedic surgery. Elective hip and knee replacements alone are predicted to increase by 84% and 183% respectively by 2026.[1] US data suggests demand for elective hip and knee replacements will increase by 174% and 673% respectively by 2030.[2] This inevitable growth in demand needs to be matched by a similar growth in resource.

In an attempt to improve surgical service delivery, within the public system, the Government has insisted on achieving a first specialist assessment (FSA) and, if indicated, a surgical procedure within mandated time frames.[3] An FSA must be provided within

Figure 1: Flowchart of triage process.



four months, and if indicated, a surgical procedure performed within a further four months. Failure to meet these targets results in a significant financial penalty for the district health board (DHB), further reducing valuable resource and limiting service delivery. As well as these service targets, the Ministry of Health sets total surgical volumes for the year with the anticipation that each DHB will manage these appropriately. Failure to do so results in further financial penalties and reduction in volumes for subsequent years. These restrictions place a considerable responsibility on DHBs and individual departments to manage their service within the constraints imposed.

In order to comply with these time restrictions, the number of patients accepted for an FSA needs to be closely monitored. It is also imperative that those considered to require a surgical procedure do not exceed departmental resources and can be adequately managed to comply with the mandated Ministry of Health four-month time frames. In reality this means that patients need to be triaged prior to accessing an FSA.

Triage as defined by the Merriam-Webster Dictionary is: "The sorting of patients according to the urgency of their need for care". However, reviewing the literature, there is no consensus in the methodology of selecting patients most in need of surgical care and thereby providing reliable triage.[4]

Within the CDHB Orthopaedic Department a triage system has been implemented to manage this surgical workload for patients presenting with elective hip or knee problems. This paper outlines the development of this system and reports the first eight months results with the specific aim of determining the number of patients who miss out on an FSA, and it additionally assesses the unmet need within the community.

Method

Two orthopaedic surgeons with a combined experience of 60 years practice in orthopaedic surgery were tasked to develop a process to triage all elective hip and knee referrals that were likely to benefit from surgery. Triage is dependent on the quality of the referral letter provided, so a protocol was developed informing general practitioners (GPs) and specialists alike of the information required to facilitate an accurate assessment. This protocol was communicated to all GPs in Canterbury by

Table 1: Triage categories.

Insufficient information	Referral letters in this category did not comply with the requested information on the triage protocol, and GP' and specialists were requested to resubmit the referral when the requested data was provided.
No capacity	These patients were denied access to orthopaedic surgical services even if they had pathology that would benefit from an operative procedure.
Low priority	Patients who were considered to have pathology that caused a lesser degree of disability than the majority of referred patients were returned to general practitioner care.
Direct entry to waiting list	Patients that had already been seen by a surgeon and triaged were deemed to have had an FSA and gained a direct access to the waiting list.
Accepted for FSA	These patients fulfilled the criteria for access.

hard copy and was posted on the GP website (ERMS). Workshops were then conducted by orthopaedic surgeons to ensure understanding of the triage process and the importance of detailed information in the referral letter. (Appendix 1) The functional limitation and pain highlighted in this referral letter was predominantly used to determine the requirement for an FSA.

In addition to the requested clinical information in the referral letter, standard radiographs (no older than six months) were required. These radiographs were then assessed to confirm the clinical diagnosis and the degree of disease severity (Kellgren and Lawrence and Ahlback Classification). As over 90% of the patients undergoing triage were for arthritic joint problems, this formed an important part of the assessment process. Patients were then triaged, based on the information in the referral letter and their radiology, according to clinical severity (Figure 1). Failure to comply with the protocol in terms of the requested clinical information and radiological views resulted in a return of the referral letter with an invitation to re-submit when the requested documentation was provided.

In order to comply with Ministry of Health directives the number of patients able to be accepted onto the waiting list following FSA was constantly monitored, with the number of FSAs performed adjusted accordingly. In reality the triage process developed into a 'virtual FSA'. Patients with a high likelihood of surgery were then moved on to a 'real FSA'.

Data was collected from the triage process between 1 August 2015 and 31 March 2016 and information was obtained under five different categories for patients referred with hip and knee pathology (Table 1). Those who were not accepted for an FSA or did not gain direct entry to the waiting list were referred back to their GP. It was confirmed that all referrals were deemed to have failed conservative treatment.

Early in the study, patients who were seen privately by an orthopaedic surgeon and assessed as requiring surgery were admitted to the waiting list without triage. However, because of concerns related to equity of access to public hospital treatment, patients seen privately were required to go through the same triage procedure. If they were accepted for progression to an FSA they were then placed on the waiting list without further assessment.

Results

In the eight-month study period there were 1,733 hip and knee referrals to the CDHB Orthopaedic Department for an FSA. Over 90% of the referrals were for arthritis; the remainder were a mixture of non-traumatic complaints. Traumatic conditions were rarely referred to the public hospital and were assessed separately under ACC. Of these, 838 referrals were for patients with hip pathology (Table 1). This included 87 (10%) referrals from orthopaedic surgeons, which following triage were passed directly through to the waiting list as they were felt to have had an FSA, and to be assessed again

Figure 2: Result of referral letter triage for hip patients.

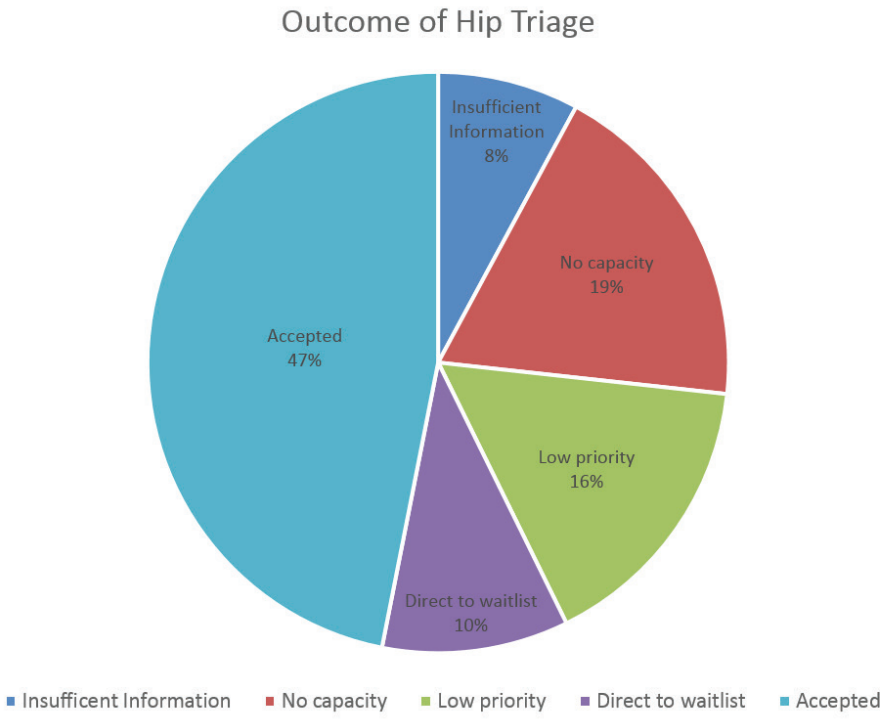
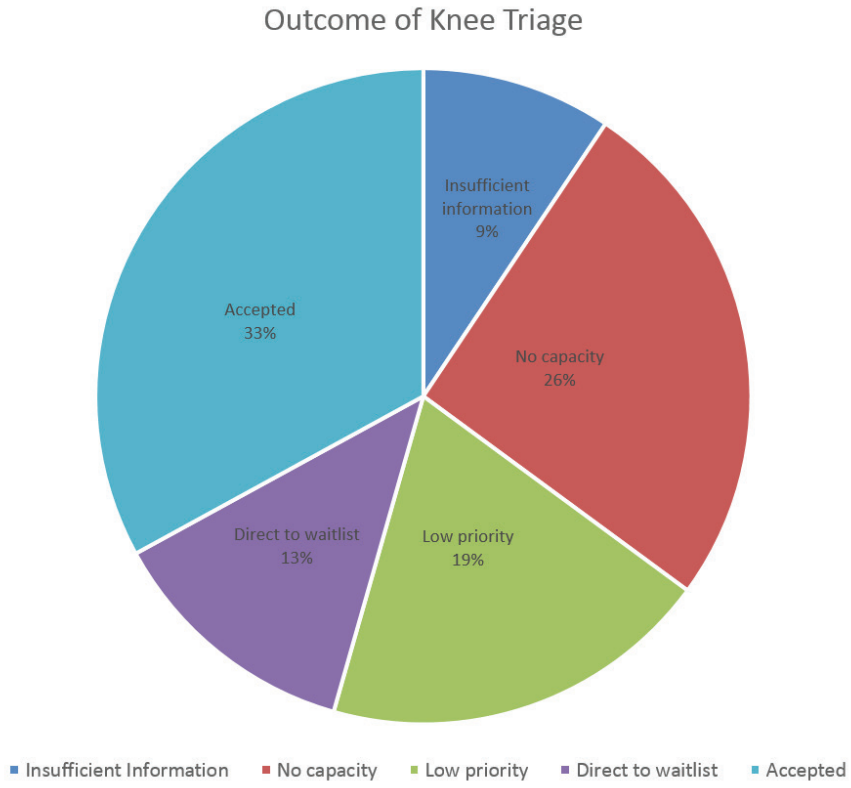


Figure 3: Result of referral letter triage for knee patients.



would be an unwise use of resources. Of the remaining hip referrals, 393 (47%) were accepted for FSA after triage; 66 patients (8%) were declined an FSA as there was insufficient information in the referral letter. There were 134 (16%) patients not seen as they were felt to have a condition of lower priority when compared with other patients referred, and 158 (19%) patients were not seen due to the fact there was not enough capacity within the service even though they had pathology that would have benefited from an operative procedure.

There were 895 referrals for knee pathology during the study period (Figure 2), of which 113 (13%) were from orthopaedic surgeons and following triage were sent directly to waiting list. Only 295 referrals (33%) were able to be accepted for an FSA following triage, with 84 declined (9%) due to insufficient information in the referral letter. This left 45% who were unable to be given an FSA with 173 referrals deemed low priority (19%) and 230 due to no capacity (26%) despite having a condition that would benefit from surgery.

In total there were 43% of hip and 54% of knee problems that were denied access for an FSA, most of whom were returned to their GP.

The predictive accuracy of the triage process in assessing patients who would be subsequently placed on the waiting list was >90%.

Discussion

This paper describes a consultant-led triage process whereby the referred clinical data (history, examination and past treatment) was assessed with the relevant radiological data, and a decision made as to whether the patient was likely to benefit from a surgical intervention and therefore proceed to an FSA. The triage process was influenced by the surgical capacity of the department and its ability to remain compliant with a maximal four-month waiting time requirement as determined by the Ministry of Health.

The triage process could be criticised because of the lack of objective scoring. The process relied on a clinical assessment from two experienced surgeons following a full functional and symptomatic history from the GP, which was supported by radiological changes. However it soon became apparent that this process was a "virtual FSA", with those patients progressing to FSA almost always being placed on the waiting list (>90% predicted accuracy). Over the time course of this study the triage process was refined, and in particular the standard of the GP referral letters improved so that towards the end of the eight months very few letters were being rejected because of lack of information.

The purpose of this study was to accurately report the number of patients who fail to receive an FSA for elective hip and knee problems within the orthopaedic department of the CDHB. Our data clearly show that for hip and knee problems, 43% and 54% respectively of referred patients are not accessing further assessment. These results do not match the recently reported figures released by the Ministry of Health,[5] which show for the CDHB in June 2016, that only 0.6% of patients waited longer than the required timeframe for their FSA. This metric is misleading and implies that only 0.6% of patients miss out on an FSA and that this represents the unmet need. In fact, the metric is actually measuring those patients that have been accepted for an FSA and as shown by this study, patients must first pass through the triage process before accessing this FSA. The triage process rations access so that the true unmet need is closer to 50% for those patients referred. It is acknowledged that this may not necessarily be the total unmet need, as GPs may be reluctant to refer patients because of the high threshold for acceptance and progression of treatment. In the last year 14.3% of the Canterbury population has not accessed GP care due to cost, and they too are therefore unable to access specialist care and will not be represented in our figures.[7]

It seems unlikely that this unmet need within our community for these elective procedures is isolated to Canterbury. Gwynne-Jones et al[6] reviewed the Otago shortfall, where 241 patients requiring joint replacement in 2014 were returned to their GP while 367 (60%) patients underwent surgery. Blacket et al found a similar situation when exploring the effect of the introduction of a six-month waiting time in Whangerei and Hawkes Bay hospitals, with

up to 36% of people being declined surgery for hip and knee osteoarthritis.[8]

This current study has concentrated on hip and knee pathology, which is overwhelmingly that of osteoarthritis, and it is acknowledged that because of previous hip and knee initiatives, this group of patients have had better access to treatment within the public hospital than those presenting with other orthopaedic disorders. Patients with non-arthritic problems are likely to have reduced access to an FSA and subsequent surgery, resulting in an even greater percentage of unmet need. Inglis et al reported on the access for spinal disorders within the CDHB and confirmed that the unmet need was considerably higher than hip and knee problems, with 74% unable to access an outpatient appointment.[9]

This problem may not be limited to the specialty of orthopaedics, with a recent health survey showing a significant unmet need for surgical healthcare in general in New Zealand, with 170,000 people being told they would benefit from publicly-funded surgery but not formally placed on a waiting list.[10]

Remaining compliant and avoiding financial penalties is clearly one of the driving forces in limiting the number of FSAs. This reduction in waiting times for both an FSA and subsequent surgery, although well intentioned, has let to deleterious consequences. Patients with a surgically treatable problem are failing to be assessed and offered a surgical option. At least prior to the introduction of minimum waiting times, patients were able to have an assessment and reach a decision as to whether surgery was an option. Admittedly, waiting times often were excessive, but at least patients had assurance that they were on a waiting list and had a diagnosis that was confirmed. The FSA is important in maintaining ongoing patient assessment and management. The request for an FSA is an indication from the GP that help is required either for patients who have exhausted conservative care or to establish a diagnosis to enable a reliable management plan. The failure of GPs to gain this FSA creates a serious deficiency in our historical referral process, leaving GPs isolated and patients vulnerable.

The Ministry of Health has funded a trial of further non-operative treatment with the engagement of dietitians, physiotherapists and GPs to deal with the large number of arthritic patients who fail to gain access to the waiting list. This may be of some benefit to a few, but is unlikely to help the majority of patients with end-stage osteoarthritis in whom the only viable option is joint replacement. This approach should be questioned as the patients have already been subjected to a comprehensive conservative management approach demanded by the' Hip and Knee Arthritis Protocol,' (Appendix 1) a necessity before even being considered for the triage process.

Numerous scoring tools have been used to try and improve the access to surgery for those with musculoskeletal disability[11–17], but none of these have been validated for this purpose and there is no standardisation between institutions.[4] Currently a new tool (CPAC) has been developed to help prioritise a patient's access to the waiting list and this tool may be helpful in comparing different DHBs. However, it is being implemented after triage has been undertaken and is therefore of debatable value. With 97% of patients who pass to FSA being placed on the waiting list for surgery and most progressing within four months, there seems little need to re-prioritise these patients. The current problem is lack of resource, not how a patient is prioritised for the waiting list: it matters little to the patient what score they achieve on an assessment tool if they can't access surgery.

Increasing surgical resource is a complex problem, and increasing current outputs is not just a function of increased health expenditure. We have already highlighted the expansion of joint replacement surgery alone, whereby servicing the projected increase by 2026 is likely to require up to 80 additional surgeons in New Zealand if current working practices continue.[1] This surgical training requires 6–7 years of time investment and is not something that can be turned on and off with impunity. Likewise, training other members of the surgical team (anaesthetists, theatre nurses, anaesthetic technicians, etc) requires time and educative commitment. Hospitals need to have the infrastructure to accommodate this increasing requirement for elective surgery,

including operating theatres and wards, and enough staff to deal with the "flow-on" effect of patient care following surgery. To plan for this expansion of orthopaedic services within the public hospital, rigorous data must be used to substantiate change. In the past there has been significant criticism of data released by the Ministry of Health, in particular its assessment of unmet need. We believe that the data in this study is 100% accurate, and as such shows that the true referred unmet need within our community for hip and knee problems is likely to be closer to 50%.

The cost to the country of failing to offer appropriate treatment for patients who have failed conservative management is significant. It was estimated in 2010[18] that 530,000 New Zealanders suffered from arthritis. Of this number 57.8% were female and 54% were of working age. These numbers are estimated to grow to 650,000 by 2020. The total financial cost of arthritis in New Zealand in 2010 was $3.2 billion. With 50% of patients in Canterbury unable to access an FSA for hip and knee pathology and potential surgery, the cost to the community in terms of lost productivity and added support services is likely to be significant, and in our opinion is unacceptable. If the treatment options available had marginal efficacy then a conservative non-operative approach could be argued for. Hip and knee arthroplasty, however, are regarded internationally to be at the top of the most clinically successful and cost-effective procedures across all surgical disciplines.[19]

In summary, the strength of this study was in the experience of the triage surgeons. They are likely responsible for the high surgical acceptance levels. With the now excellent referral information, the result of an education programme and the insistence of up-to-date x-rays, it has been possible to accurately assess and prioritise the need for surgery. We have accurately documented the large number of patients unable to obtain a specialist opinion within the public hospital in the Canterbury region for hip and knee problems. These data are at considerable variance to that published by the Ministry of Health. We believe that an unmet need of 50% for these common problems requires urgent attention with a coordinated plan involving the CDHB, Orthopaedic Department, New Zealand Orthopaedic Association and the Ministry of Health.

Competing interests:
All authors work within the orthopaedic department of the Canterbury District Health Board.

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Appendix

GP HIP/KNEE ARTHRITIS REFERRAL GUIDELINES

Referral letters should be written using the following guidelines and format.

SYMPTOMS

Pain - document the following:

- Anatomical location of the pain and its radiation
- Pain onset i.e. gradual / acute
- Exacerbating factors, e.g. weight bearing, twisting, impact landing etc
- Relieving factors, e.g. rest etc
- Duration of pain, e.g. intermittent/constant
- Intensity of the pain: Use an analogue scale from 0 - 5 to indicate severity. Compare with the worst lifetime pain the patient has experienced.

Functional Limitations - describe and document:

- Walking distance in metres and time
- Restrictions of activities of daily living e.g. putting on shoes/socks, getting in/out of car
- Knees only:
  Locking or instability symptoms

Treatments to Date- document the use of:

- Regular Analgesia:
  Paracetamol
  NSAIDS
  Tramadol
  Codeine
- Walking aids
- Paramedical treatment:
  Physiotherapy
  Acupuncture

INTERCURRENT MEDICAL PROBLEMS

Document all current medical and surgical problems with particular reference to:

- Peripheral Vascular Disease
- History of bleeding disorders
- History of VTE
- Anticoagulant therapy
- BPH/urinary retention
- Active oral infection
- Open Wounds/Ulcers
- BMI >/= 40
- Active medical issues must be completed prior to referral and if necessary specialist referral completed, to ensure patient is fit for surgery if indicated.

EXAMINATION

HIP

- Limp : antalgic |Trendelenburg
- Pain on palpation
- ROM: flexion / extension / adduction / abduction : internal/external/rotation

KNEE

- Limp :
  antalgic |Trendelenburg
- Pain on palpation
  ROM: flexion/ extension
- Deformity: varus / valgus / flexion contract

GP HIP/KNEE ARTHRITIS REFERRAL GUIDELINES

MANDATORY RADIOLOGY FOR HIP/KNEE

- Osteoarthritis Hip/knee Series

INDICATIONS FOR REFERRAL

- Severe pain and functional limitations
- Patient ready to proceed to surgery if offered, and willing to accept risk of complications
- Patient not prepared to continue in current painful and restricted state

CONTRAINDICATIONS FOR REFERRAL

- Any infective focus e.g. urinary tract infection, respiratory infection
- Open wounds or ulcers
- Active/chronic oral infection
- BMI >/= 40
- Failure to exhaust all non-operative treatment options

OTHER MINIMUM PREREFERRAL INVESTIGATIONS REQUIRED

FBC,ESR, CRP
U&Es
MSU

POTENTIAL SURGICAL COMPLICATIONS

- **MEDICAL:**

Stroke
Delirium (confusion)
Myocardial infarction/cardiac arrhythmias
Respiratory difficulties
Renal:
    urinary retention
    renal failure

- **SURGICAL:**

Scar
Pain
Bleeding
DVT/PE
Infection
Intra operative fracture
Leg length discrepancy
Nerve injury
Dislocation
Loosening / wear of implant requiring revision surgery

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

Refining metformin prescribing in New Zealand

Sisira Jayathissa, Paul Dixon, Raymond Bruce, David Reith

ABSTRACT

Metformin is the mainstay of treatment of type 2 diabetes. However, there has been significant concern on prescribing metformin in patients with renal impairment as a result of metformin-associated lactic acidosis (MALA). Recent studies have cast doubt on the existence of MALA purely related to metformin use. Medsafe recently initiated changes to datasheet so lower doses of metformin could be used in patients with GFR down to 15ml/min. In this paper we outline the context and implications of this change.

For many years metformin has been the mainstay of pharmacological treatment of patients with type 2 diabetes. The International Diabetes Federation,[1] the American Diabetes Association[2] and European Association for the Study of Diabetes[3] recommend that metformin be commenced as the first-line treatment in all newly diagnosed patients, regardless of age.

The discovery of metformin can be traced back to the pioneering work with extracts of the herb Galega officinalis in early 20th century, which led to the characterisation of the blood-lowering effects of an active ingredient named galegine.[4] Metformin has a significant effect on blood glucose levels and reduces mortality compared to other therapeutic modalities and the risk of cardiovascular disease.[5,6] Based on medium-sized cohort study with 10-year follow-up, metformin may be associated with a reduction in cancer risk.[6,7] It helps in weight reduction and seems to prolong survival in experimental models,[8] and will be tested for anti-aging effect in humans.[9]

In general, metformin is well tolerated, although may cause nausea, vomiting or diarrhoea in some patients, especially if introduced at a high dose or taken on an empty stomach. Vitamin B12 deficiency is a less common side effect, and occasional measurement of Vitamin B12 levels in patients on long-term metformin therapy is prudent.[10] Lactic acidosis is a spectre that has hung over metformin ever since its introduction because other biguanides, phenformin and buformin (long since withdrawn from the market) were clearly associated with an increased rate of lactic acidosis. This association has resulted in application of restrictions on use of metformin, not taking into account the different pharmacokinetics. The question arises as to whether metformin can induce lactic acidosis on its own, and in the normal course of events the answer is probably no, or if it does, it is exceedingly rare. However, metformin is known to raise lactate levels in humans but magnitude of this increase is small. Overdose of metformin can result in raised lactic acid levels and in serious overdose, lactic acidosis may occur even in healthy individuals.[11] In animals and humans, metformin administration is associated with an increase in blood lactate levels. The increase in plasma lactate concentration with therapeutic doses of metformin is small, usually <2mmol/L, although higher levels may occur.[12] In patients with lactic acidosis, lactate levels are usually raised above 5mmol/L. Lactic acidosis is most commonly associated with tissue ischaemia such as in septic shock, burns, limb ischaemia, seizures, trauma, severe dehydration, cardiac arrest or cardiogenic shock, and may be aggravated by hepatic and renal dysfunction, alcohol, respiratory insufficiency and elevated levels of metformin. It is likely that in most cases of lactic acidosis occurring in patients taking metformin, other causes have been major contributors. Metformin-associated lactic acidosis (MALA) has a high mortality, but the rates have decreased from 50% to 25% in recent studies.[13]

A Cochrane review[14] failed to identify any cases of lactic acidosis in patients taking metformin. However, a Dutch observational study found an incidence of 47 cases of metformin-associated lactic acidosis per 100,000 patient years, but the outcome of MALA was determined by the severity of the underlying disease rather than by metformin itself.[15] However, in other studies the highest estimates are ≤10 events per 100,000 patient-years of exposure.[11] Even though large-case series have given polar opposite results, cases of lactic acidosis associated with metformin use have been reported regularly. There may be a link between metformin use and lactic acidosis, though a systematic review suggested that other factors may be implicated.[16]

Renal impairment is a particular risk in patients with type 2 diabetes, in part because of the incidence of diabetic nephropathy, but they are also usually in an older age group and they may have co-morbidities, such as hypertension, that may play an aetiological role in renal damage. Metformin is not metabolised in the body, but transported through the body by transporters and is actively excreted unchanged by the kidneys. Reduction in glomerular filtration rate reduces active excretion of metformin and can be associated with an increase in plasma concentration of the drug. It is considered that a plasma metformin level of <5mg/L is safe and does not carry any significant risk of lactic acidosis.[11,17] Previous advice has been that metformin was contraindicated in patients with a creatinine clearance <60mL/min. However, some health authorities have reset the contraindication at 30ml/min.[11]

Recently an Australian group has studied pharmacokinetics of metformin, both normal and sustained release preparations in healthy subjects and patients. The group assessed dose-response curves of metformin in healthy subjects and patients with type 2 diabetes, and then by modelling have developed maximum metformin doses in relation to creatinine clearance that will maintain plasma metformin levels <5mg/L.[17] Medsafe has evaluated this data and have now made changes to the New Zealand data sheet for metformin, incorporating the information from this paper. These recommendations are shown in Table 1.

In practice GFR is often estimated using alternative methods to Cockroft Gault, such as the MDRD or CKD-EPI equations, and also adjusted to a surface area of 1.73m^2. All these equations produce an acceptable estimation of GFR, although in patients with lower GFR, the MDRD and CKD-EPI equations have higher accuracy compared to the Cockroft-Gault.[18] The CKD-EPI equation was developed using measured GFR that was adjusted for surface area (ref Levey et al 2009).[19] When using GFR expressed as mL/min/1.73m^2 to adjust dose, patients who have a low surface area may as a result be overdosed, and patients with a high surface area may be underdosed.[20] Hence, at extremes of body size it would be advisable to base the dose adjustment on total GFR, expressed in mL/min, instead of GFR adjusted for surface area, expressed as mL/min/1.73m^2. The conversion can be performed by multiplying the estimate of GFR expressed as mL/min/1.73m^2 by the patients surface area divided by 1.73m^2.

Metformin dose reduction has been recommended by Medsafe below eGFR 60mL/minute. However, NICE guidelines[21] suggest review of dose of metformin if eGFR is below 45mL/min, and stopping metformin at GFR below 30ml/minute. Australian guidelines suggest reduction of metformin dose to 1,500mg daily between eGFR 45–60mL/minute and maximum of 850mg daily if eGFR is between 30–45ml/minute.[22] According to Lipska, there is clear recognition that renal failure may be a risk factor for adverse events with metformin use, but

Table 1: Recommendation of metformin dose based on creatinine clearance (Doung et al).[16]

Creatinine clearance	Maximum daily dose of metformin
15–30mL/min	500mg
30–60mL/min	1000mg
60–120mL/min	2000mg

there is significant divergence in opinion across the globe regarding the optimal definition of safety.[23] All guidelines concur about the need for review and reduce some of the higher doses (2.5–3.0g daily) encountered in clinical practice when GFR is lower.

The main message to practitioners is to consider progressive dose reduction and monitoring in renal impairment, while maintaining the pharmacological benefits of therapy down to a GFR as low as 15mL/min based on current Medsafe recommendations. Therefore patients may not need to change to other medication early, which could be less desirable and also not available under New Zealand pharmaceutical benefits scheme. It is likely that higher dosage of metformin has been continued in many patients with moderate renal failure without appropriate guidance or dose adjustment, which perhaps contributed to some cases of lactic acidosis, so using lower doses may lead to safer use of metformin.

However, there are some unresolved issues. These recommendations are not based on randomised controlled trial data or chronic treatment pharmacokinetics, and this need to be addressed by long-term studies. It is equally important to conduct further research into therapeutic efficacy of metformin in patients with normal renal functions to identify maximum effective and safe dose and its relationship to metformin levels. Efficacy of metformin at lower doses in patients with renal failure has also been questioned by some[11] and needs to be studied further. In addition, according to Medsafe guidance, highest recommended daily dose in patients with normal renal functions is two grams, less than the commonly used daily dose of up to three grams, and it is not clear that dose reduction may lead to loss of therapeutic efficacy and practitioners need to be vigilant about this potential. It is well known that lower doses of metformin work in early type 2 diabetes, and so it is likely to be effective in patients with renal impairment. There may be a case for metformin measurements when used in patients with very low GFR,[4] but the assay is not routinely available in New Zealand. Measurement of venous lactate levels may be a potential alternative in high-risk situations.

Metformin should not be used when the GFR is <15mL/min. Adam et al predicted plasma metformin level of 4.4mg/litre at GFR of 10mL/min when 500mg/day metformin dose was used.[24] Although the risk of MALA does not seem to be increased, and the progression to end-stage renal disease is significantly lower, patients on metformin at this level of renal function have significantly higher all-cause mortality.[25]

Like many other medicines, prescribers need to be vigilant for side effects and adjust the dose of metformin accordingly, but unfortunately this is often forgotten. Renal function should be checked regularly in patients on metformin. We suggest renal function testing annually for patients with creatinine clearance >80mL/min, six monthly for patients 30–80mL/min and three monthly for patients <30mL/min or more frequently in patients at particular risk of renal function deterioration, eg commencement of ACE inhibitors or NSAIDs. Metformin doses should be adjusted according to the eGFR.

Medsafe is to be congratulated for their initiation of these changes for metformin in the context of renal impairment. This is unusual, where the regulatory agency takes an active step in improving dosing recommendations. Suggested changes should allow continuation of this valuable medication at a lower dose in patients with type 2 diabetes, despite declining renal function. Several authors have advocated the liberalisation of metformin therapy in the context of renal impairment.[26,27] Patients should be warned to discontinue metformin during serious acute illness especially leading to dehydration and serious infections to minimise any aggravation of the risks for lactic acidosis. Insulin can always be used as a short-term substitute for glycaemic control. Question of maximum effective dose in patients with normal renal functions need to be clarified with further research. Prescribers should be vigilant in monitoring side effects and reporting them to CARM (Centre for Adverse Reaction Monitoring), especially when used in patients with moderate to severe renal impairment. These reports can be made electronically through the CARM website.

Competing interests:
Dr Jayathissa is a member of Medicine Adverse Reaction Committee (MARC), a ministerial advisory committee for Medsafe. MARC committee endorsed Medsafe changes to metformin data sheet. Associate Professor David Reith is chair of the MARC committee.

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Getting the foundations right for the measurement of medication safety: the need for a meaningful conceptual frame

Jerome Ng, Shane Scahill, Jeff Harrison

ABSTRACT

A number of initiatives aimed at improving medication safety in and across New Zealand public hospitals have been introduced over recent years. Clinicians, policymakers and patients now want to know whether patients are safer today from medicine use than they have been in the past. The challenge has been determining exactly what should be measured. In this viewpoint, we critically examine the suitability of adverse drug events (ADE) as a primary metric for assessing the progress of medication safety improvement. We provide an overview of contemporary dialogue on medication safety measurement and highlight the emergent challenges. Finally, we reflect on how New Zealand has approached medication safety measurement so far and argue the need for a multi-stakeholder informed conceptual framework with a view to further enhancing meaningful assessment of medication safety.

Research shows that patients admitted into New Zealand public hospitals are harmed by the medical care intended to help them.[1–7] Since the publication of the *New Zealand Quality in Healthcare Study* (NZQHS) a number of initiatives aimed at improving patient safety, in particular safety associated with medication use, have been introduced.[8,9] Clinicians, policymakers and patients now want to know whether patients are safer today than they have been in the past, and whether medication safety across hospitals has improved.[10–13] To track progress and inform improvement, the assessment of medication safety has mainly focused on detecting and measuring medication error and more recently, harm.[14,15]

In this article, we discuss important but commonly missed limitations of using medication-related harm as the primary metric for assessing progress around medication safety. We explore contemporary dialogue on medication safety measurement and the challenges involved with operationalising this construct. Finally, we outline our observations on local medication safety measurement activity and argue that a key practice and research gap has been the lack of a common understanding of medication safety by stakeholders and the absence of a framework for measurement. We propose that the way forward is to develop a locally agreed multi-stakeholder derived conceptual framework which can be used to guide and inform the meaningful measurement of medication safety across New Zealand public hospitals.

Preventable harm as a primary metric for assessing medication safety progress

A large proportion of iatrogenic harm (up to 38%) relates to medications.[16] Such injuries are known as adverse drug events (ADE). Most ADEs are expected to occur despite appropriate and error-free care because the use of medicines to derive benefit carries with it an intrinsic risk of injury.[17] Up to 47% of ADEs, however, could be prevented through the implementation

of safer medication practices, and it is this type of harm that national improvement programmes have tended to target.[16,18–21] A number of measurement techniques and indicators have been developed to assess the progress of medication safety, focusing on total ADEs or subsets thereof as the primary safety metric.[14,16,19,21–35]

If medication-related harm is the primary metric used to determine progress then has medication safety across hospitals improved? In New Zealand and countries such as the UK and the US, the answer is unknown. No national longitudinal studies have been conducted and no ADE reporting rate appears to exist.[36–38] Where large scale longitudinal studies have been conducted, for example in the Netherlands, preventable harm rates have remained relatively stable.[39,40] One possible interpretation is that national medication safety improvement programmes have been ineffective. Other interpretations, which are more likely in our view, are that ADEs as a primary metric are neither sensitive nor reliably measured enough to demonstrate progress, even if programmes are successful at making medication use safer for patients.

There are pragmatic, methodological and conceptual reasons why ADEs may not be suitable as a single primary metric for monitoring medication safety and progress over time. From a pragmatic perspective, because different types of ADEs are detected by different tools, the resource required to reliably and accurately measure changes over time is challenging to undertake in practice, on a regular basis.[25,27,28,41] From a methodological perspective, the relative rarity and heterogeneity in types of ADEs means that any single intervention may not affect the total harm rate in a significant enough manner for a change to be detected.[42–44] Advances in medical knowledge and technology can change how harm and the degree of preventability are classified, so rates may appear to be unchanged.[38,42–50] As the sensitivity of ADE detection techniques and surveillance systems improve, the rate of harm may appear to increase, which misrepresents the true state of affairs.

From a conceptual perspective, ADEs only represent the visible consequences of unsafe medicines use. In most instances, medication use can be erroneous and unsafe with no visible or consequential injury.[16,51] An acute and unexpected drug shortage which necessitates the use of alternative medications and strengths, for example, may mean that the potential for error and harm is higher today compared to yesterday.[52] The resulting change in the state of safety from moment to moment, however, will not be indicated by ADEs as a metric. If ADEs are solely used for monitoring, the apparent lack of safety present in a system may be invisible and go undetected. Furthermore, ADEs can only be measured after the fact so it can only provide an indication of how safe the medication system has been in the past but does not inform whether it is safe in the present, or likely to be in the future.

The measurement of ADEs is still an important facet of medication safety assessment because ADEs highlight the types and relative frequency of some safety problems that may occur. The major limitation of ADEs as a primary safety metric is that they only provide part of the overall picture in determining whether patients are safer now than they have historically been.[12,43,44,50,53,54]

Contemporary views on medication safety measurement and its challenges

There is a shift to widening how medication safety measurement should be thought about. In parallel with increasing knowledge on the factors associated with unsafe medication systems, and the characteristics which contribute to making them safer;[16,20,23,55–63] the scope of medication safety measurement has broadened (see Table 1 for an overview of existing medication safety measures and their foci).[55,64]

As can be seen from Table 1, assessment now includes, for example, determining whether safe practices are in place and working as expected. If they are, then one could assume that the likelihood of adverse outcomes would be reduced.[12,13,55,64] Reliable clinical systems and organisations which learn from, and respond to, safety incidents are other examples of the key characteristics thought to influence and contribute to safer hospitals.[75] And so, when such facets of medication safety are concurrently

Table 1: Existing medication safety assessment measures, tools and their foci.

Category of measure types	Description and focus of assessment (example)	Metric sets and tools examples
Structure based	Assess the attributes of the settings in which medicines use occurs. Can be related to:[65] **Material resources** (eg necessary equipment available? Adequate lighting in drug preparation room?); **Human resources** (eg adequate staffing?) and; **Organisational structures** (eg medicines governance group and systems in place and its robustness?)	Assessment frames (eg Medication safety-self assessment (MSSA) tool)[66,67] Hospital certification standards[68,69] Quality Safety marker[70]
Process based	Assesses the actions or steps of medicines use (eg % of patients initiated on warfarin who are counselled before discharge, administration error rates).	Indicator sets[24,32,71] Observation[72]
Outcome based	Determines the effects of medicine use on the health status of patients (eg harm, patient experience): focus has been on undesired consequences (ie ADEs) rather than effectiveness.	ADE detection (eg trigger tools, record review and others)[25,28,29]
Characteristics and principles based	Assesses medicines use related organisational traits, attitudes, mind-sets and behaviours of organisations and its members (eg safety culture, learning environment, reliability, resiliency, mindfulness).	Safety culture[73,74] May include other measures from above

measured and monitored over time, they provide a more holistic and balanced view of medication safety than harm rates alone could ever provide.

The increase in the number of assessment frames, measure sets and tools has not, however, been without its own challenges. It is now unclear exactly which assessment frame or set of metrics should be used to measure medication safety in its entirety. Even though some overlap exists between assessment frames and metrics, there are differences between them, and research has not been undertaken to determine whether one is superior to another, and if so, on what grounds.

A single conceptual frame which synthesises the breadth of scientific knowledge on what constitutes a safe medication system is needed in order to provide a coherent, balanced and cohesive structure for organising and informing subsequent medication safety measurement.[12,13,76–80] The process of canvassing stakeholders' preferences then incorporating them within the developed framework increases the likelihood of the data obtained being meaningful[81–83] and used.[87,84–89] Standardised and longitudinal measurement and monitoring based on the elements incorporated within the framework can then be used to ascertain whether medication safety has improved or not, across a broad range of facets.

Observations on the New Zealand approach to assessment and a way forward

A review of New Zealand research and practice suggests that, similar to the international literature, ADEs have been focused upon as the primary metric for monitoring medication safety.[1–7] Reports commissioned by the Health Quality and Safety Commission (HQSC) to measure and evaluate the national medication safety programme, for example, have focused on tools designed to measure harm.[38,90,91] These efforts should be congratulated and continued because enhanced detection of ADEs and standardised national taxonomies to classify identified harm can help New Zealand better understand the types of medication related problems that occur in hospitals.

In this viewpoint we have argued that to more holistically measure and monitor medication safety, there is a need to expand beyond ADEs as the primary metric. This change in thinking appears to have been reflected in recent measurement related activity in New Zealand. The HQSC, for example, have proposed a quality safety marker (QSM) relating to whether electronic medicines reconciliation (eMR) has been implemented.[70] Because eMR is a process which may help reduce the risk of harm from errors resulting from unintended medication discrepancies, its implementation may suggest safer hospital practices.[92,93] More comprehensive assessment, which includes medicines reconciliation but importantly extends to other medication safety considerations, have also recently been trialled at a district health board (DHB).[22]

The acknowledgement for the need to broaden the scope of medication safety measurement and monitoring in New Zealand and the beginning of efforts is heartening. The absence of a single conceptual framework for measurement which establishes a common understanding of medication safety among its stakeholders, however, is sub-optimal. There is certainly no shortage of measures and tools which can be used to help assess medication safety, but until there is a locally agreed conceptual framework to guide medication safety measurement and monitoring, New Zealand faces the possibility of piecemeal, *ad hoc*, inconsistent and unreliable medication safety measurement, which can mean that results cannot easily be summated into anything useful.

Proposed approach to developing a conceptual framework

A multi-stakeholder informed conceptual framework for measurement is the most appropriate route to take when making sense of what is important to include.[94] We propose the development of a locally agreed multi-stakeholder derived conceptual framework which can be used to guide and inform the meaningful measurement of medication safety across New Zealand public hospitals. This needs to be founded on what key stakeholders value and find meaningful.

The relevant stakeholders for medication safety measurement include three key groups. Firstly, government and local management bodies who make policy and funding decisions. Secondly, clinicians, researchers and managers who have expert knowledge of the medication process and are likely to be involved in advocating for and implementing the framework as well as subsequent changes to practice. Thirdly are the consumers, patients and family members who are the service end-users and the ones most impacted by system change. Engagement of relevant stakeholders at the outset would not only increase the face validity of the conceptual framework but would also increase the likelihood of its use in practice settings.[95]

Final thoughts

Contemporary research suggests that in order to comprehensively and holistically assess whether medication safety has improved, it is no longer enough to measure the occurrence of harm. We believe the development of a conceptual framework for medication safety measurement informed by input from multiple stakeholder groupings provides a platform to begin developing the right metrics in order to conduct longitudinal studies and determine whether systems are safer over time. Until there is a clear understanding of what it means to be "safe" in this context it will not be possible to measure it. The development of a multi-stakeholder informed conceptual framework is expected to provide a meaningful, clear and comprehensive approach to progressing the sound measurement of medication safety.

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Household transmission of NDM-producing *E. coli* in New Zealand

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ABSTRACT

This report describes the introduction of an extensively antibiotic-resistant carbapenemase-producing *Escherichia coli* into a hospital in Auckland, New Zealand, by a patient who was a household contact of recent travellers to the Indian subcontinent. The carbapenemase was identified as New Delhi metallo-β-lactamase (NDM) and reflects probable household transmission in the context of a recent upsurge in NDM-producing *Enterobacteriaceae* isolation in New Zealand. The observations in this report suggest that hospital screening practices to identify carbapenemase-producing *Enterobacteriaceae* (CPE) colonised patients may need to be extended to include travellers to high-risk countries who were not hospitalised during their trip, and possibly also their close contacts.

New Delhi metallo-β-lactamase (NDM)-producing *Enterobacteriaceae* (NDM-PE) are a particular type of carbapenemase-producing *Enterobacteriaceae* (CPE) that have been circulating in India since circa 2006. NDM-PE are now widespread in both hospitals and the community in the Indian subcontinent and are spreading globally. Local and global dissemination has been facilitated by promiscuous inter-strain and inter-species transfer of the bla_{NDM} gene as well as human factors, such as poor sanitation, environmental contamination and extensive international travel.[1,2] In New Zealand, NDM-PE were first identified in 2009.[3] Since then NDM-PE have been isolated only sporadically, primarily from patients with a history of hospitalisation in the Indian subcontinent.[3,4] Hospital outbreaks have been reported in non-endemic countries, but community spread appears to be rare.[1] For these reasons, active screening for NDM-PE in New Zealand hospitals has targeted patients with previous hospitalisation in high-risk countries. Active screening involves culturing rectal swabs or stool to determine whether a patient is a carrier of NDM-PE, allowing for appropriately stringent infection control precautions to be implemented. This communication describes the chance identification of an NDM-producing *Escherichia coli* in December 2015 from a patient in Auckland with no known risk factors for CPE acquisition. Informed consent of the individual and local institutional approval were obtained.

The patient was a New Zealand-born Māori woman in her early twenties admitted to an Auckland hospital with trauma-associated injuries. She had no history of recent hospitalisation, chronic medical conditions, regular medications or recent antibiotic use, and no prior international travel. In the absence of any risk factors, CPE screening was not performed on admission. After 13 days in hospital the patient transferred to a rehabilitation facility where their routine screening identified a NDM-producing *E. coli* in faeces. The isolate was identified as *E. coli* by MALDI-TOF mass spectrometry (bioMerieux, Marcy-I'Etoile, France) and the presence of bla_{NDM} determined with the Xpert Carba-R (Cepheid, CA, USA) real-time PCR assay. Antimicrobial susceptibility testing was performed using the Vitek 2 GN AST card (bioMerieux) and interpreted according to Clinical Laboratory Standards Institute (CLSI) criteria. The isolate was resistant to amoxicillin, amoxicillin-clavulanate, piperacillin-tazobactam, extended-spectrum cephalosporins, cefoxitin, aztreonam, meropenem, quinolones and cotrimoxazole, but remained susceptible to aminoglycosides.

Susceptibility to colistin and tigecycline was determined by Etest (bioMerieux) with minimum inhibitory concentrations of 1mg/L and 0.5mg/L, respectively. The isolate underwent whole genome sequencing, which showed the *E. coli* multi-locus sequence type (*adk*, *fumC*, *gyrB*, *icd*, *mdh*, *purA,* and *recA* loci) to be ST69 and the NDM type to be NDM-5.

CPE screening of remaining patients on the hospital ward identified no further cases. There were no other known NDM-PE carriers in the hospital, and only two cases had been identified in the preceding 24 months (both imported). Extended background history revealed the case patient resided in a household with two family members who 3–4 months before her admission had spent five weeks in India visiting family and friends. These family members had no healthcare contact in India. No CPE screening was performed on the family members, however, on the balance of probability this case appears to represent household transmission of an NDM-producing *E. coli* initially acquired by travellers to India. This case represents the first documented episode of presumed household transmission of NDM-PE in New Zealand. Intra-familial (mother to child) transmission of a NDM-producing isolate post-travel has also been recently described in Australia.[5] These cases are unlikely to be isolated events, but represent instances of transmission captured by chance detection.

Over the past two years New Zealand has experienced a notable increase in the number of importations of NDM-PE and other CPE, predominantly from the Indian subcontinent.[4] The current emergence of NDM-PE in New Zealand draws many parallels with the emergence in the early to mid-2000s of CTX-M-15 extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*. CTX-M-15 ESBL also originated in the Indian subcontinent. In 2008, community-onset CTX-M-15-producing *E. coli* infection in New Zealand was highly associated with a history of travel to the Indian subcontinent.[6] In addition, both CTX-M-15 ESBLs and NDM carbapenemases are frequently found in association with both *E. coli* and *Klebsiella pneumoniae*.[4,7] It is notable that CTX-M-15 spread in the community in New Zealand was primarily associated with *E. coli* rather than *K. pneumoniae*.[8] This suggests that in non-endemic countries such as New Zealand there is a potentially heightened risk for similar community transmission of NDM-producing *E. coli* compared to carbapenemases primarily associated with *K. pneumoniae*.

Appropriate empiric treatment of infections with multi-drug resistant CPE is often delayed, and definitive treatment options are severely limited. Therefore, substantial efforts are required to prevent the transmission of CPE to vulnerable patients in the hospital environment. In non-endemic areas, infection prevention measures, such as active screening and preemptive isolation, tend to be targeted at particularly high-risk individuals with a history of hospitalisation in endemic countries.[9,10] However, increasing CPE acquisition by non-hospitalised travellers, and this report of probable secondary spread to a household member on return to New Zealand, suggest that broadening screening criteria to include recent travel exposure alone, or even recent travel exposure among household members, may be justified and should be considered.

Competing interests:
Nil.

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Poststreptococcal episcleritis

Nicholas Young

ABSTRACT

This report describes the case of a patient presenting with an unusual poststreptococcal syndrome that featured episcleritis as a prominent manifestation. To my knowledge, this is the first time that poststreptococcal episcleritis has been described in the literature.

A 51-year-old Samoan woman presented to hospital due to pain in her left knee of 24 hours duration. Preceding this was a six-day history of sore throat and fever, for which she had consulted her general practitioner and had been treated with ibuprofen. A throat swab taken by her GP at this time subsequently grew *Streptococcus pyogenes*.

On examination, she was afebrile. Her tonsils were erythematous without exudate. Her left knee had restricted range of motion with a small joint effusion. Cardiorespiratory examination was normal and there was no erythema marginatum rash, subcutaneous nodules or choreiform movements.

Her bloods showed neutrophilia of 14.98×10^9 and CRP of 209mg/L. Her midstream urine was bland and renal function was normal. A knee aspirate yielded 5ml of bloodstained fluid, which was unsuitable for cell count, with no crystals and sterile cultures. Her ECG showed normal sinus rhythm, and transthoracic echocardiogram demonstrated no valvular lesions.

Rheumatic fever was thought unlikely due to the patient's age and the short time course. Due to the culture proven antecedent *S. pyogenes* infection, she was diagnosed with poststreptococcal reactive arthritis, and treatment was commenced with penicillin on day six of her illness to eradicate persisting *S. pyogenes* carriage.

On day 11, she reported discomfort in her left eye without photophobia or visual disturbance. Examination revealed temporal episcleral injection and a non-tender globe. Visual acuity was 6/5 in the affected left eye, and 6/12 in the right. There was no relative afferent pupillary defect, and the anterior chambers were quiet. B-scan ultrasonography did not demonstrate posterior scleritis. Blanching was seen with topical phenylephrine, leading to a diagnosis of episcleritis.

Investigations for other causes of episcleritis yielded normal titres for antinuclear, anti-double-stranded DNA, rheumatoid factor and anti-cyclic citrullunated protein antibodies, and negative C and P-ANCA.

Her episcleritis was managed with lubricating eye drops, topical corticosteroids and oral naproxen, and she completed 14 days of penicillin. Three weeks later, all her symptoms had resolved.

Discussion

Group A streptococcal (GAS) infections have been associated with a range of poststreptococcal syndromes, including poststreptococcal glomerulonephritis, rheumatic fever, reactive arthritis and paediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS). These are thought to be caused by molecular mimicry, where antibodies directed against GAS antigens cross-react with antigens in host tissues.

This report describes a patient who developed episcleritis on day 11 following the onset of GAS pharyngitis. This time course is typical for poststreptococcal syndromes.[1] While other ocular sequelae of GAS infection have been previously described, this is the first reported case of poststreptococcal episcleritis to my knowledge.

Ocular sequelae of GAS infection are rare. Of these, uveitis is the most well

described, predominantly in children and young adults.[2] As with rheumatic fever, these cases appear to follow GAS pharyngitis or tonsillitis; cases following GAS skin infection have not been clearly documented. Uveitis was accompanied by scleritis in only two reported cases.[3,4] Conjunctival disease appears rarer still, with one report of a poststreptococcal syndrome mimicking conjunctival lymphoma.[5] The only reported case of isolated poststreptococcal scleritis describes a 60-year-old woman who developed bilateral scleritis, 10 days following commencement of amoxicillin for GAS pharyngitis.[1] Similarly, the patient in our report developed episcleritis five days following commencement of penicillin. Together, these reports suggest that GAS infection should be considered as a rare aetiology of episcleritis and scleritis (along with other well-described causes such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and vasculitis). These observations also suggest that antibiotics may not be preventative in the development of these poststreptococcal complications, in contrast with their established role in preventing acute rheumatic fever.

Competing interests:
Nil.

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Clostridium difficile infections in patients with inflammatory bowel disease

Michael Chieng

ABSTRACT

Case report of a 23-year-old male presenting with a severe flare of Crohn's disease, exacerbated by community-acquired infection with *Clostridium difficile*. This case outlines the association between *C. difficile* infection and inflammatory bowel disease, as both a mimic and a precipitant of flares. The discussion concerns the latest literature consensus on assessment and management of *Clostridium difficile* infection in patients with inflammatory bowel disease.

A 23-year-old man was diagnosed with Crohn's disease three months previously. At the time of diagnosis, active inflammation was observed for 10cm in the terminal ileum, and treatment with tapering prednisolone was commenced. After several weeks, inflammatory symptoms recurred while on a dose of 20mg prednisolone. Therefore, 40mg tapering corticosteroid was recommenced with the addition of 50mg azathioprine.

Two weeks later, he presented to the emergency department with severe abdominal pain, 15 episodes of bilious vomiting and five episodes of watery diarrhoea over a 24-hour period. This occurred in the context of treatment with 50mg azathioprine and 30mg prednisolone. Examination revealed tachycardia (114 bpm), fever (38 degrees C) and right lower quadrant abdominal tenderness. Laboratory investigations suggested a significant inflammatory process with a neutrophilic leukocytosis—neutrophils 18.2 (normal range 2–8x10^9/L), and C-reactive protein 153 (normal range 0–5mg/L). A stool specimen tested positive for *Clostridium difficile* antigen, confirmed by PCR, and treatment with oral metronidazole was commenced. This infection was presumed to be community acquired.

A colonoscopy was performed, with findings of altered vascularity, oedema, erythema and granularity throughout the colon, sparing the sigmoid and rectum. This was a technically limited study as the endoscope could not be advanced past the ileocaecal valve due to swelling. An MRI study of the bowel was undertaken, which revealed an ileal stricture, active inflammatory terminal ileitis and caecitis with involvement of the proximal ascending colon.

This episode was the first flare of Crohn's requiring hospitalisation in this gentleman's history, and represented a significant event with extensive bowel disease associated with *C. difficile* infection. A full recovery was made after treatment with intravenous hydrocortisone and metronidazole.

Discussion

The incidence of *C. difficile* infection (CDI) has been increasing in North America, Europe and Australasia.[1,2] While previously considered a major nosocomial infection, community infection is now being increasingly recognised.[3] Patients with inflammatory bowel disease (IBD) are known to be at a two to four-fold increased risk of developing CDI,[4] and CDI can be difficult to distinguish from flares.[4,5] IBD patients with CDI often present with more severe infections and experience poorer outcomes, including prolonged hospital stay, increased rates of colectomy and higher mortality.[4,6,7]

Due to the high prevalence of *C. difficile* in IBD patients and the difficulty in discerning between IBD flare and infection,[6,8] the *American College of Gastroenterology (ACG) CDI Guidelines Task Force* currently recommends routine testing for CDI in all IBD patients hospitalised with a disease flare.[6] This is particularly important in IBD patients presenting with symptoms of diarrhoea. In patients without significant diarrhoea, the clinical utility of testing for CDI may be limited.[9] This is because asymptomatic *C. difficile* carriage is relatively common in IBD patients.[6,9] Routine testing may result in an increased number of false positives and possibly excessive treatment. Eradication of asymptomatic *C. difficile* is also not without risk. Incomplete treatment, re-colonisation with new strains and increased shedding of *C. difficile* spores have all been described in the general population.[9]

Risk factors for CDI in the general population include recent antibiotic use, hospitalisation, age >65 and significant comorbidity.[2,5,7,8] However, IBD patients tend to be younger, and commonly present with community-acquired infections.[6,8,9] They have the additional risk factors of steroid use, recurrent hospitalisations and treatment with immune-modulating therapies.[2,8] Antibiotic use does not appear to play such a major role in the development of CDI in patients with IBD,[5,6] possibly due to pre-existing altered microbiota in these individuals.[8]

Special consideration should be taken when making decisions about immune-modulating and biologic agents during active treatment of CDI.[4,6,8] In these instances, ACG guidelines suggest that baseline therapy should be maintained at existing doses[9] and escalation of immunosuppressive therapy should not be undertaken in the first 72 hours of treating CDI.[4,9] This is a conditional recommendation based on low-quality evidence, and is associated with poorer outcomes in IBD patients treated with concurrent immunosuppressive and antibiotic therapies.[9] Currently there is a paucity of international evidence concerning safety of changes in immune-modulating therapy while on antibiotic treatment for CDI.[2,8]

In the general population, oral metronidazole is commonly used as the first-line antibiotic for mild-moderate CDI, with vancomycin reserved for severe, recurrent or refractory infections.[1] In adults with IBD, however, those treated with vancomycin had a shortened hospital stay, fewer readmissions and a significantly reduced colectomy rate compared to metronidazole.[4] In the first instance, supportive measures should be introduced for all patients affected by CDI, including rehydration, infective-isolation and rigorous handwashing with soap and water, which is more effective than alcohol-based hand gels in eradicating *C. difficile* spores.[6,8,9]

Newer treatments utilising faecal microbiota transplantation (FMT) in IBD patients have shown promising results with high cure rates detected in recurrent CDI, and with no adverse events yet reported in the literature.[4,9] FMT should be considered for IBD patients with ≥3 recurrences.[9]

In conclusion, this patient suffered from a severe flare of Crohn's disease while on oral corticosteroid treatment. The potential role of *C. difficile* infection in this case is difficult to categorise as a causative or exacerbating factor, and this represents an ongoing challenge for the medical profession. The testing and subsequent treatment of CDI was indicated in this case, given the severity of symptoms and the presence of diarrhoea on presentation. Intravenous vancomycin may have been a better choice of antibiotic because of its improved outcomes in severe infections. Emerging evidence for faecal microbiota transplantation, new antibiotics and new immune-modulating therapies may alter current treatment practices.

Competing interests:
Nil.

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Pick a bogus treatment...

Mark Honeychurch

At the Society for Science Based Healthcare, we spend a lot of time looking at dodgy therapeutic claims. Most of these claims are made by practitioners of alternative therapies. A few months ago Mark Hanna, a colleague of mine at SBH, messaged me with a curious thought:

"Pick a bogus treatment. Now pick a condition. Someone in New Zealand probably advocates for that."

This was an interesting idea—that there is so much misinformation about healthcare these days, there's a high likelihood that someone in New Zealand is claiming their chosen "alternative" therapy can treat pretty much any condition you can think of.

An easy starting place to look for people making claims is online, and there's a nice feature in Google's search facility where you can restrict the search to certain domain names. Mark had already tested out a combination of treatment and condition before challenging me—*chiropractic* and *psoriasis*. For this pairing, the Google search to use would be:

chiropractic psoriasis site:nz

The "site:nz" part of the search restricts the search to only websites whose domain names end in .nz—it's an easy way to restrict the search to sites that are likely to be New Zealand based.

With the above search terms, Mark had found an Auckland chiropractor who has a lengthy testimonial on their website describing the use of chiropractic for treating psoriasis.

It was my turn. I picked *homeopathy* and *bursitis*. Surely nobody's claiming that sugar pills can treat joint issues? After less than a minute of searching, I found a homeopath in Northland who claims that for bursitis and other joint pain, homeopathy can "treat the whole person" and "fit your specific set of symptoms", whereas conventional medicines "can have undesirable side effects, and can also suppress symptoms to the extent that healing is hindered". Damn!

Mark Hanna's next duo was *acupuncture* and *pneumonia*. He found a Christchurch acupuncturist who is claiming to be able to treat "common cold and flu, bronchitis, pneumonia, asthma, sinusitis, hay-fever".

At this point I declared the challenge to be "outright depressing", so I tried to cheer myself up with a more humorous pairing—*aromatherapy* and *flatulence*. It turns out that (at least according to an online naturopathic health store) Oil of Orange Blossom can treat "indigestion, diarrhoea, flatulence and stomach cramps".

Mark Hanna upped the ante with *Rolfing* and *headaches*—for those not in the know, Rolfing is "soft tissue manipulation and movement education". It turns out there's a Rolfing practitioner in Whangarei who can treat "arthritis, colds, depression, fatigue, headaches, [and] insomnia".

My response to Mark's Rolfing was to go for some New Age energy weirdness—*orgone* and *cramps*. Orgone energy is usually accessed using a colourful resin pyramid with a copper coil embedded in it, although back in the 50's you were expected to sit in a small layered wood and metal box. This one was more difficult to find, but within a couple of minutes I'd uncovered a New Zealand based online shop that sells orgone devices, and has a testimonial where menstrual cramps had apparently been alleviated by an "orgone zapper".

Mark Hanna announced he was going "weirder" with *Reiki* and *ulcers*, but this was disappointingly easy to find—there is an online national health practitioner directory in New Zealand where it is claimed that Reiki may be able to help with, among many other serious conditions, "ulcers, immune system disorders, heart problems, paralysis and depression". Remember as you read that list that Reiki is a channeling of the "universal life force" through the palms of the practitioner into the patient. Often Reiki practitioners don't even touch their patients, but merely move

their hands a few inches over them as the patient lies on a massage table.

Our challenge finally came to a halt when I chose *Romi Romi massage* and *bunions*. Romi Romi is "traditional Māori massage", and it's a fairly niche therapy. Hah! I'd found a dud. The unlikeliness of massage helping with bunions, paired with a paucity of websites offering Romi Romi, meant that I'd found a combination that does not appear to be advocated for in New Zealand—at least online.

This fun exchange reminded me of a more serious point I think is very important to keep in mind when considering alternative therapies. Unlike conventional therapies, which have a limited scope, there is a tendency for the practitioners of alternative therapies to advertise their services as something of a panacea. No matter the therapy, there will be people claiming it can treat all conditions—up to and including cancer. Many of these claims are repeated by official industry bodies, despite a lack of evidence. These kinds of claims are likely breaching the Medicines Act, but they have become so prevalent in the last few years that enforcement of our current regulation in New Zealand is failing to keep up with this tidal wave of misleading medical advertising.

Competing interests:
Nil.

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Edwin "Ted" Richard Nye

June 22 1926–1 February 2017

Dunedin doctor Ted Nye could best be described as a polymath or Renaissance man—"a great scholar and person of much, varied learning".

The 90-year-old retired physician, scholar, teacher, friend, activist and man of great humanity and humility died suddenly at his Dunedin home on February 1. Primarily a medical practitioner throughout his long life, first in the United Kingdom then in New Zealand, Dr Nye had a huge and varied range of interests.

From a young age he was fascinated by natural history, particularly entomology and, over the years, built up an extensive mosquito collection. He gained a PhD in tropical medicine from the London School of Hygiene and Tropical Medicine, was an accomplished fencer, mastered the Swedish language, which he also taught for many years, was a pioneering heart physician, helped establish the Antipodean Sherlock Holmes Society and set up the New Zealand division of the International Physicians Against Nuclear War. During his 25-year "retirement", he continued working in the cardiology department, as a physician at Dunedin Hospital, at the Otago Community Hospice and with friend and colleague Dr Jim Mann.

In a formal tribute at Dr Nye's funeral, Dr Mann said it was hardly surprising some of Dr Nye's contributions had been recognised by several honours. He was appointed Officer of the New Zealand Order of Merit in 2003 for services to medicine and the community, and his contributions to Swedish culture were marked by the awarding of Knight of the Swedish Order of the Polar Star. However, Dr Mann said he was confident Dr Nye took on the things he did because he identified an unfulfilled need or felt something was inherently interesting and worthwhile, rather than because

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of a desire for recognition. "He was known to walk away from some of the creations before they had been fully acknowledged if the job seemed to have been done."

Born on June 22, 1926, in Liege, Belgium, where his father was working for a British company, Dr Nye was the eldest of three sons of Edwin and Hortencia Nye. The middle brother, Donald, died when only a few months old, but Richard—younger than Dr Nye by exactly 11 years—still lives in the UK. The Nye family moved to Paris when Edwin was six, returning to England in 1936. With the outbreak of World War 2 and evacuation to Devon, Dr Nye mastered probably his first science, astronomy, assuring local villagers a bright light they had spotted on the skyline towards the coast was not, as some of them believed, German spies signalling to Uboats, but the planet Venus.

As a schoolboy, back in London after the Blitz, he was interested in biology, particularly butterflies, and his intellectual pursuits already extended beyond science to reading Plato. He left school at age 16 and began paid employment, but continued studying for his matriculation so he could enter university. On his 18th birthday, the already confirmed pacifist was called to the army and began his military training at Canterbury. He and his contemporaries never had to go into battle, but after his training he was sent to India via Sardinia then to the Malay peninsula and Singapore just before the handback to the British. He drove buses when Singapore Traction Company drivers were on strike, relying on the passengers to tell him where to go. The rigours of army life apparently did not preclude some of his other interests. With another naturalist, Russell Walker, he hunted local butterflies and succeeded in breeding them. At night, he and Mr Walker played music on a gramophone, using an unlimited supply of needles in the form of thorns from a nearby bush. Their only two records were some music by Delibes and "The Entry of the Nobles" from Wagner's Tannhauser. Dr Nye was later involved with the Wagner Society in Dunedin.

After leaving the army in 1947, his years were filled with completing matriculation papers, gaining a BSc degree, working as a laboratory assistant at London's Archway Hospital, taking up fencing, buying—for a pound—a book about mosquitoes and finally being accepted as a medical student at St Bartholomew's Hospital. During his medical student years, he achieved academic distinction, gained anatomy and physiology prizes and a fencing blue. He continued his fascination with natural history, acquired an interest in guinea pigs and learned to pull teeth.

After graduating MB in 1956, Dr Nye held several junior hospital appointments before applying for a post as junior lecturer in entomology at the London School of Hygiene and Tropical Medicine. He successfully completed his PhD and maintained his clinical skills but decided he did not wish to remain in Britain or pursue a career in tropical medicine. Instead, he followed a lead from a contact and wrote to the Otago Medical School, where he took up a position as medical research officer to Sir Horace Smirk, an internationally known researcher in the field of hypertension. After working with Sir Horace for a short time he was offered a job with John Hunter, who was later to become Professor of Medicine. For that role, Dr Nye had to extend his knowledge of lipids and lipoproteins, which he decided to study with Prof Lars Carlson in Stockholm. Thus began the Swedish connection, which subsequently played such an important role in his life.

A mutual Swedish friend, Prof Stephan Rossner of Stockholm, wrote of the great respect in which Dr Nye was held for his research, his fencing and his masterly knowledge of the Swedish language. His translations of playwright August Strindberg (regarded as the father of modern Swedish literature) were regarded as exceptional. He also wrote his own poetry in Swedish and produced a Swedish-English dictionary of medical terminology.

Dr Nye's work in Dunedin as a physician was "legendary", Dr Mann said. Having inherited many of his patients, he knew how much they loved and respected him, as did all of his colleagues, but his most noteworthy wider medical contributions were in the fields of cardiac rehabilitation and preventive cardiology in which he, Prof Hunter and other Dunedin doctors became interested in the late 1960s. In 1967, he established the Phoenix Club, a pioneering New Zealand heart-health club focused on

the importance of exercise therapy for heart attack patients, an approach which at the time was viewed worldwide as highly novel.

Dr Nye was a life member of the New Zealand Heart Foundation and remained an advocate for the Otago Therapeutic Pool (the physio pool), which played an integral part in the Phoenix Club's approach. He was involved in research related to the prevention of heart disease by treating cholesterol and other risk factors and participated in some of the first trials of statin drugs. He established what was probably the first register in the world of people with inherited cholesterol problems, although that was never able to fulfil its full research potential because the funding was discontinued. He recognised the phenomenon of the clustering of risk factors, now known as metabolic syndrome, and wrote a paper on the subject.

After his "so-called retirement", Dr Nye continued working in the cardiology department, as a physician in Dunedin Hospital and in the hospice, later re-inventing himself as a part-time haematologist and, more recently, as a clinical triallist in the field of obesity, working with Patrick Manning. He retained his strong interest in entomology, co-authoring in 1997 the biography of Nobel Prize-winning malariologist Sir Ronald Ross, and was a moving force behind an undergraduate module on tropical and travel medicine at the Dunedin School of Medicine. Several years ago, he gave his 400-specimen mosquito collection to the Otago Museum where he was an honorary curator.

A champion fencer with a passion for the sport, which he had practised since his student days in London, Dr Nye represented Otago-Southland teams for several years and competed for New Zealand against Australia in 1969. The Ted Nye Trophy, contested annually, was established to raise funds for the Otago Community Hospice with which Dr Nye was involved for many years. He was still enjoying fencing well into his 80s and had "an alarming collection of ancient swords", one of which he used to cut his 90th birthday cake last June.

Stepdaughter Kathryn Fitzpatrick spoke of Dr Nye's love for and enjoyment of family. She recalled the "massive beam on his face" in a photo of him holding his new grandson, Jaz, in 1991, and she treasured the time her own two sons had spent with him and her mother over the years.

Dr Nye is survived by his son Bruce and grandchildren Jaz and Phoebe from his 1956 marriage to Pauline Mahalski, who died in 2015, and by his second wife, Jeanette Leigh, whom he married in Dunedin in 1984, her two daughters, Kathryn and Joanna, and Kathryn's two sons, Daniel and Reuben.

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Fulvestrant 500mg versus anastrozole 1mg for hormone receptor-positive advanced breast cancer

In hormone receptor-positive disease, third-generation aromatase inhibitors have increased efficacy compared with tamoxifen in terms of time to progression. In this trial fulvestrant, a selective oestrogen receptor degrader is compared with a third generation aromatose inhibitor, anastrozole.

Four hundred and sixty-two patients were randomised to receive fulvestrant or anastrozole. Progression-free survival was significantly better in the fulvestrant cohort. Arthralgia and hot flushes were the commonest adverse events with both treatments. Seven percent of the fulvestrant patients and 5% of the anastrozole patients discontinued treatment because of adverse events.

The authors of the paper suggest "These findings consolidate the known clinical effectiveness of fulvestrant and support the use of fulvestrant monotherapy in endocrine-naïve patients with hormone receptor-positive advanced breast cancer".

***Lancet* 2016; 388:2997–3005**

Use of palliative chemotherapy in patients aged 80 years and over with incurable cancer

Treating octogenarians with cancer presents unique challenges because of a decline in organ function and physiological reserve. There is a paucity of data on how chemotherapy is tolerated in this age group. This study aims to throw light on this issue.

Of 420 eligible patients, 100 (24%) started chemotherapy. Forty-one percent received a full dose for the first cycle. Fifty-four percent experienced toxicity necessitating dose reduction, delay or omission. Thirty-two percent required hospitalisation.

The researchers concluded that a quarter of patients 80 years and older received first-line palliative chemotherapy. Despite most receiving a modified dose, one-third were hospitalised during treatment. These findings highlight the need for careful clinical assessment and selection of older cancer patients for chemotherapy.

Internal Medicine Journal 2017; 47:75–81

Ticagrelor versus clopidogrel in symptomatic peripheral artery disease

Data from previous trials on such patients suggest that clopidogrel is superior to aspirin in the prevention of cardiovascular events. This report is of a trial in which ticagrelor, a potent antiplatelet agent is compared with clopidogrel.

The trialists randomly assigned 13,885 patients with symptomatic peripheral artery disease to receive monotherapy with ticagrelor (90mg twice daily) or clopidogrel (75mg once daily). The efficacy end-point was a composite of cardiovascular death, myocardial infarction or ischaemic stroke. At a median follow-up at 30 months there was no difference in efficacy between the two groups.

These results demonstrate that in patients with symptomatic peripheral artery disease, ticagrelor was not shown to be superior to clopidogrel for the reduction of cardiovascular events. Major bleeding occurred at similar rates among the patients in the two trial groups.

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Medical Students and the War Call

April 1917

At the opening of the Medical School, Dr. Ferguson, Dean of the Medical Faculty, replied to statements made by the Hon. G. W. Russell in reference to medical students and enlistments. After stating that the matter was purely a military one and had nothing to do with the Public Health Department, Dr. Ferguson said that students refrained from enlisting on Surgeon-General Henderson advising them to stick to their studies. Some twenty-four students were brought back from the war last year. The Government was instrumental in securing the release of Dr. Drennan from the Imperial authorities to come out and teach the third-year class in which were seven men who had been brought half round the world by the Government for tuition. He thought they were justified in inferring till a month ago that the Prime Minister, the Defence Minister, the Minister of Munitions, the Director-General of Medical Services. the Commandant, and the Imperial authorities agreed on the necessity of keeping the school going.

The Officers' Training Corps must automatically cease if Mr. Russell's views were given effect to. He contradicted the insinuation that students sheltered behind the school to avoid military service. The school was the only source of supply for house surgeons for hospitals, and last September it sent twelve or fourteen fifth year students as acting house surgeons to replace qualified men. Similar arrangements could be made this year, but if the present third-year class was sent into the firing-line this expedient cannot be adopted at the end of next year, and in February, 1920, the graduation class will comprise merely a few girls and such men as have been declared medically unfit. If they had thirty graduates they could all be placed in civil life. Of seventeen graduates, four had been drawn in the ballot and five had volunteered, leaving eight to fill twenty vacancies for house surgeons. If the war continued till 1920 the supply of young men that military service had been getting would cease absolutely.

The Chancellor (Rev. Cameron) suggested that students should not enlist till the University Council received an answer from the Health Department to a request for a conference with Dr. Valintine and Surgeon-General Henderson.

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Comparison of immune cell infiltrate between subcutaneous melanoma and colon carcinoma mouse models

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Cancer vaccines modulate the host's anti-tumour immune response and represent an area of emerging immunotherapy research for the treatment of cancer, including colorectal cancer (CRC). Murine subcutaneous injections of tumour cell lines are used to test cancer vaccines for the treatment of CRC. We aimed to determine the baseline immune response to subcutaneous injection of a colorectal cell line, CT26, compared to a melanoma cell line, B16-OVA, to investigate whether the tumour cell type would affect local and systemic immune responses.

CT26 adenocarcinoma cells were subcutaneously injected into mice. Control mice received B16-OVA melanoma cells or saline. The immune cells: dendritic cells, macrophages, T cells, (CD4+ and CD8+) and B cells were identified via flow cytometry at the tumour site (local immune response) and in the spleen (systemic immune response).

The systemic immune response to CT26 tumours was characterised by a higher frequency of dendritic cells, a lower frequency of T cells and twice the proportion of CD4+ to CD8+ T cells, compared to mice given B16-OVA tumours (n=14 (mice given B16-OVA tumours)-15 (mice given CT26 tumours), Mann Whitney, P=0.0016, P=0.0366, P=0.0001). The intra-tumoural immune response to CT26 tumours had a reduced macrophage and T cell infiltrate compared to B16-OVA tumours (n=14, Mann Whitney, P=0.0233, P=0.0185).

These data represent a baseline immune response to B16-OVA and CT26 tumours that will be used to investigate modulation caused by a therapeutic CRC vaccine. We have also identified immune cell populations likely to be involved in CRC compared to melanoma; these cells have also been shown to be important in human CRC. This work will help link animal models and human data, and help translate cancer therapeutics into treatments for human patients.

Does the subarachnoid space extend into the eye?

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Intracranial hypertension is a neurological disorder characterised by an increase in intracranial pressure (ICP) within the subarachnoid space (SAS). Considered as an extension of the brain, intraocular pressure (IOP) in the eye has been used to estimate ICP. However, recent evidence indicated that although there was a significant correlation between the IOP and ICP, changes in IOP were poor predictor of changes in ICP. The existence of physiological and pathophysiological relationships between them is still elusive. Anatomically, the optic nerve is divided into intraocular, intraorbital, intracanalicular and intracranial segments. The intracanalicular segment is the point where the SAS surrounds the optic nerve and extends into the eye, and thus may provide direct pressure transmission between the ICP and IOP. The aim of this study was to investigate the anatomical configuration of the optic nerve sheath in the optic canal.

A total of nine cadavers were examined in this study. Arachnoid mater of three cadavers were stained with haematoxylin via SAS perfusion. The specimens were prepared as sets of serial plastinated sections with a thickness of 2.5mm or 0.3mm and examined under a stereomicroscope and a confocal microscope.

The results showed that:

1. the dura mater continued the periosteum of the optic canal and joined with the tendinous fibers of the eye muscles giving rise to the optic nerve sheath (n=3), and
2. in the specimens with a SAS staining, the SAS followed the optic nerve and entered the optic canal but terminated at the midpoint within the canal (n=3). However, in specimens without staining the SAS could not be traced. Thus, the observations were not quantified.

This study concludes that the SAS is not continuous throughout the optic nerve sheath, suggesting that there is no anatomical basis to support mechanism of direct pressure transmission between the ICP and IOP.

IGF-R1 pathway in crizotinib-resistance in ALK-positive non-small cell lung cancer

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Non-small cell lung cancers (NSCLCs) account for approximately 85% of all lung cancer-related deaths worldwide. About 4% of NSCLCs contain rearrangements in the EML4 - ALK genes, which encode a fusion protein that drives cancer development. Crizotinib, an ALK inhibitor, gained fast-tracked approval from the Food and Drug Administration in 2011 on the back of unprecedented responses in clinical trials. Unfortunately, resistance to crizotinib invariably develops within two years through a variety of mechanisms. One of the major mechanisms of resistance is the activation of alternative cell signalling pathways, including the insulin-like growth factor receptor-1 (IGF-R1) pathway. This study aimed to investigate the role of the IGF-R1 pathway in crizotinib resistance and whether the combination of crizotinib with an IGF-R1 inhibitor may delay the development of resistance *in vitro*.

To model innate resistance, the established ALK-positive NSCLC cell line, NCI- H3122, was exposed to high dose crizotinib (10μM) for 24 hours. The drug was removed and cells were maintained for 12 days. In order to develop a crizotinib- resistant cell line (C.R-H3122), NCI-H3122 cells were maintained in crizotinib (0.8μM; the steady state plasma concentration in mice) for 114 days.

The IC50 of crizotinib in a model of innate resistance increased in treated cells (0.163μM) compared to non-treated cells (0.071μM). Chronic exposure to crizotinib led to the development of a crizotinib-resistant cell line (C.R-H3122) with an IC50 of 2.082μM, 20.8-fold higher than control. Cytotoxicity testing of an IGF-R1 inhibitor, NVP-AEW541 (NVP) revealed a lower IC50 in the C.R-H3122 cells (2.205μM) compared to control (2.994μM). Moreover, combination treatment indicated the C.R-H3122 cells are sensitised to NVP.

These results suggest the IGF-R1 pathway plays a role in two models of crizotinib resistance, suggesting the combination of crizotinib with NVP may be particularly effective in crizotinib-naïve patients.

Protein modeling of nonsynonymous SNPs in apolipoprotein(a)

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Cardiovascular disease (CVD) is New Zealand's leading cause of death. Elevated plasma lipoprotein(a) [Lp(a)] is a strong risk factor for CVD. Lp(a) is a low-density lipoprotein (LDL) analogue comprised of Apolipoprotein B covalently linked to a unique glycoprotein apolipoprotein(a), which is transcribed from the LPA gene. Lp(a) bears significant homology to plasminogen with repeating kringle structure. This study aimed to model possible effects of nonsynonymous single nucleotide polymorphisms (SNPs) associated with altered plasma Lp(a) on 3D protein structures of apo(a) domains.

Thirty nonsynonymous SNPs were presented from a next-generation sequencing study that sequenced the LPA gene of 48 individuals. The population consisted of individuals with high, medium and low plasma Lp(a). Online protein prediction programs SIFT and PolyPhen-2 to were used to indicate if SNPs were damaging to structure. There was general concordance between the two programs, and ten SNPs were strongly predicted to be damaging to protein structure, others were either possibly damaging or benign. 3D protein structures for four available kringle domains were downloaded from the Protein Databank. Four of the apo(a) kringle domains and the protease domain were unavailable and thus homology models based on the closest available apo(a) kringle structure (or the plasminogen protease domain) were generated using the FFAS Burnham server. The structures were opened in PYMOL and amino acid changes modeled using the mutagenesis wizard tool.

The SNPs R990Q and R1771C are associated with lowered Lp(a) levels and were shown to ablate polar contacts within their respective domains (KIV-4 and KV). Superimposition of the structures showed they are analogous arginine residues in different kringle domains. This indicates that apo(a) kringle structure may be perturbed by these changes. Functional studies in tissue culture are now underway to further elucidate their effects.

Evaluation of plasma cell-free DNA stability and preservation in Roche Cell- Free DNA Collection Tubes and Streck Cell-Free DNA BCT over a 14-day period

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Circulating tumour DNA (ctDNA), a blood based biomarker has the potential to diagnose early stage cancer, monitor treatment response and identify metastatic relapse. This study aimed to compare two commercially available Cell Free DNA Blood Collection tubes for the stability and preservation of plasma cfDNA for 14 days post-collection.

Twenty healthy volunteers had blood drawn via venipuncture into five Streck and

five Roche Cell-Free Blood Collection tubes. Samples were stored at 22°C and processed on 0, 4, 7,10 and 14 days post-collection. cfDNA was extracted from 4mL of plasma using the Qiagen QIAamp→ Circulating Nucleic Acid Kit to a final elution of 35µL. The cfDNA concentration was measured using 2µL of elution with the Quibit→ 2.0 Fluorometer using the Quibit→ dsDNA HS Assay Kit (ng/mL). Pair-wise student t-test was conducted to determine whether there were any differences in the preservation capability of the two tubes.

The results indicated a significant difference of the initial cfDNA reading between the two tubes on day 0 (mean Streck 6.58ng/mL ± 3.55, Roche 5.67ng/mL ± 3.31, P=0.038). However, no significant differences were found between the two tubes for samples processed on days 4,7,10 and 14 (P>0.05).

The findings of the study indicate that either Streck or Roche tubes are suitable for clinical sample collection as neither were significantly better in terms of preservation as measured from day 4 onwards. The initial cfDNA reading on day 0 was significantly different, however, this may be due to sub-standard venipuncture technique resulting in cellular lysis and genomic DNA release. Hence after consideration of price (per 100 tubes) and availability in New Zealand, the Roche tubes have been selected for developing ctDNA as a cancer surveillance assay in the clinical phase.

Rotator cuff-related pain: participants' understanding and experiences

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Persistent rotator cuff-related pain is common in the middle-aged and elderly. A psychosocial approach to treatment indicates individuals' beliefs, and experiences need to be considered in the management of this pain. While extensive research has explored beliefs of individuals with spinal pain, less is known about individuals' beliefs regarding shoulder pain. This qualitative study aimed to explore beliefs about the cause of pain in individuals with persistent rotator cuff-related pain and their experiences of the effect of pain on their daily lives.

Five men and five women, aged 47–68 years, with shoulder pain for more than three months were recruited from the local community via newspaper advertisements and flyers displayed at sporting facilities, physiotherapy and general practitioner clinics. Individual semi-structured interviews were audio-recorded, transcribed in verbatim and analysed using the general inductive approach.

Four key themes emerged following analysis: 'Understanding the pain'; 'It affects everything'; 'Pain-associated behaviours'; and 'Emotions, thoughts, and the future'. The cause of pain, 'Understanding the pain', was described in terms of anatomical factors within the context of the participants' lives. The pain impacted all areas of life, with participants reporting, 'It affects everything'. Participants responded to their pain by adopting certain, 'Pain-associated behaviours' and sought information for general management and exercise prescription, 'Emotions, thoughts, and the future'.

The participants with persistent rotator cuff-related pain believed the cause of their pain to be local to the shoulder. Participants also described various work, sports and family related stressors in their lives. Such stressors can be pain-associated, however, the participants rarely considered these as being contributors. Rehabilitation may need to include educating individuals, expanding their understanding regarding pain mechanisms and addressing certain pain-related beliefs. The pain affected many parts of these participants' lives and the unique experiences shared highlight the need for tailored treatment based on individual goal setting.

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