Increasing primary antibiotic resistance and ethnic differences in eradication rates of *Helicobacter pylori* infection in New Zealand—a new look at an old enemy

John Hsiang, Sri Selvaratnam, Susan Taylor, Joey Yeoh, Yu-Mwee Tan, Judy Huang, Alasdair Patrick

**Abstract**

**Aims** To determine the current prevalence, primary antibiotic resistance and eradication rate with standard triple therapy of *Helicobacter pylori* (*H. pylori*) infection in South Auckland, New Zealand (NZ).

**Methods** Consecutive patients undergoing gastroscopy in 2012 were prospectively enrolled. The prevalence of primary *H. pylori* infection was determined from all Campylobacter-like organism (CLO) tests performed. Antibiotic susceptibility testing was performed for a range of relevant antibiotics and the success of eradication therapy was determined by stool antigen clearance.

**Results** The prevalence of *H. pylori* infection by ethnic group; European (7.7%), Māori (34.8%), Pacific People (31.3%) and Orientals (23.8%). Metronidazole resistance was found in 49.3% of isolates, clarithromycin resistance in 16.4%, and moxifloxacin resistance in 9.5%. No isolates were resistant to tetracycline. Clarithromycin resistance (≥15%) was prevalent among Māori, Pacific People and Orientals. Metronidazole resistance has increased significantly from 32.7% in 1999 to 49.3% in 2012 (p=0.011), and clarithromycin resistance from 7% in 1999 to 16.4% in 2012 (p=0.021). The eradication rate (intention to treat) with standard omeprazole, amoxicillin and clarithromycin (OAC) therapy in ethnic groups where clarithromycin resistance was <15% was 85.7% versus 64.9% in groups where clarithromycin resistance was ≥15% (p=0.024).

**Conclusion** *H. pylori* infection is very common among certain ethnic groups living in South Auckland. Resistance to clarithromycin and metronidazole have increased significantly among treatment naïve patients compared to historical NZ data. Ethnic groups with clarithromycin resistance of ≥15% were associated with lower eradication rates with OAC therapy. This suggests a need to review the current NZ *H. pylori* eradication guidelines to accommodate ethnic differences in the response to first-line regimens.

It has almost been 30 years since the initial culture and identification of the micro-organism now known as *Helicobacter pylori* (*H. pylori*). There is an increasing body of evidence implicating the role of *H. pylori* in the pathogenesis of chronic gastritis; peptic ulcer disease;¹ mucosal associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma; all of which contribute significantly to healthcare-related costs.²,³

Triple therapy consisting of omeprazole, amoxicillin and clarithromycin (OAC) is commonly recommended as first-line therapy but studies have shown variable
eradication rates of 65–90%. Local data in 1999 suggested that 6.8% of *H. pylori* isolates were resistant to clarithromycin while 32% were resistant to metronidazole. Worldwide clarithromycin resistance rates vary from region to region and range between 5% and 25%.

Recent international data also suggest an emerging primary quinolone resistance in some countries, ranging from 5.7% to 39%. In fact, a recent consensus report has even recommended first-line quadruple therapy instead of proton pump inhibitor (PPI)-based triple therapies in regions with high clarithromycin resistance (≥ 15–20%) due to reported high rates of treatment failure associated with such resistance.

The current eradication rate of *H. pylori* infection with standard OAC therapy in New Zealand (NZ) is unknown. Counties Manukau District Health Board (CMDHB) is a catchment area encompassing a diverse mix of ethnic groups. As seen in other countries, it is highly likely that local primary antibiotic resistance, particularly to clarithromycin, has risen in the intervening years rendering the recommended first-line PPI-based triple therapies inadequate if the goal is to achieve successful (>90%) *H. pylori* eradication. This warranted further scientific examination and underpins the basis of this study.

**Methods**

This is a single centre prospective study of consecutive patients recruited from the CMDHB Endoscopy Service. All patients undergoing gastroscopies (in- and out-patients) between February 2012 and October 2012 were prospectively screened and enrolled. Ethnicity data was ascertained from the hospital computer database. Ethnicity coding reflected that used by the NZ Ministry of Health: NZ-born European, Other European, Māori, Pacific People, Indian, Oriental and ‘Other’. The ‘Other’ ethnic group included African and Middle Eastern ethnicities in this study. This study was further subdivided into three parts to ensure more accurate data collection and to provide separate data subsets.

**Part I Methods: Prevalence**—Point prevalence of treatment naïve *H. pylori* infection was determined by prospectively collecting positive CLO test results over a 4-month period.

**Part II Methods: Antibiotic susceptibility testing**—During gastroscopy, four gastric biopsies from the antrum and the body of the stomach were obtained for CLO testing and two further gastric biopsies were performed for culture and placed into 1 ml of brain-heart infusion (BHI) broth. The culture specimens were immediately refrigerated and sent to the on-site microbiology department if the CLO test was positive within 24 hours. 100 CLO positive cases were prospectively collected in this manner. The culture samples were macerated using a sterile scalpel blade and inoculated onto two *Brucella* agar plates of 5% sheep blood (Fort Richard Laboratories). The inoculated plates were then incubated at 37°C in microaerophilic conditions using a CampyGen generator (Oxoid) and examined for typical colonies on days 3 and 7.

Susceptibility testing was performed on any identified curved gram negative bacilli that was both oxidase and urease positive. Minimum inhibitory concentrations (MIC) of amoxicillin, clarithromycin, tetracycline, metronidazole and moxifloxacin were performed by E-test. A suspension of organism was prepared in saline to a two MacFarland standard density. This suspension was used to inoculate Mueller Hinton 5% sheep blood agar plates (Fort Richard Laboratories). One E-test was applied per plate and incubated at 37°C for 72 hours in microaerophilic conditions before reading the MIC. Moxifloxacin was chosen as the representative quinolone since this antibiotic is available in NZ in contrast to levofloxacin which is not. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used to interpret all the MIC results. Levofloxacin breakpoints were used to interpret the Moxifloxacin MIC results. Resistance patterns were then compared to historical data from a similar cohort.

**Part III Methods: Treatment efficacy**—Two cohorts were used for the third part of the study: the 100 patients who underwent *in vitro* *H. pylori* antibiotic susceptibility testing and the 40 random patients from the Part I: Prevalence study who did not consent for antibiotic susceptibility testing. The
two cohorts were used to minimise any selection bias that may occur from being followed up in the Part II: Antibiotic susceptibility testing study.

When a CLO test was positive a notification letter recommending NZ Guideline Group (NZGG) based standard OAC therapy (Omeprazole 20 mg, Amoxicillin 1 gram and Clarithromycin 500 mg twice daily for 7 days)\(^1\) was sent to both the general practitioner (GP) and the patient, informing them of the positive \(H. pylori\) status. Penicillin allergic patients would be substituted with Omeprazole 20 mg, Clarithromycin 500 mg and Metronidazole 400 mg (OCM) twice daily (BiD) for 7 days as per NZGG guidelines. A follow-up stool antigen test was performed 6–10 weeks after completion of antibiotic therapy (minimum of 4 weeks after the eradication therapy and 2 weeks off PPI therapy).

All patients for follow-up were contacted by phone within three months of completion of eradication therapy and data on treatment compliance, side effects and smoking status were obtained. A further notification letter was sent if there was no response from the patient after a period of 6 weeks. Data on the specific antibiotic regimen, duration of regimen and date of GP prescription were obtained from the regional pharmacy dispensary (TestSafe) database which is updated weekly. Exclusion criteria—Patients with a history of previous \(H. pylori\) infection or previous positive rapid urease test (CLO test) as determined via the regional hospital computer database (linked to the regional community laboratory database) were excluded. Patients with severe cognitive impairment and patients who were unwilling or unable to provide written consent for antibiotic susceptibility testing were also excluded, as were patients who were deemed by the endoscopist to be at high risk of bleeding as a result of gastric biopsies. Patients who were subsequently diagnosed with metastatic malignancy of any kind or considered to have less than 6 months estimated survival due to newly diagnosed chronic disease or malignancy were excluded from treatment and subsequent follow-up stool antigen testing since the benefits of \(H. pylori\) eradication are unproven in these instances. Data analysis and ethics—Treatment success (eradication rate) was ascertained utilising Clarithromycin and Metronidazole resistance data. The eradication rates and their respective 95% confidence intervals (CI) for both intention to treat (ITT) and per protocol (PP) analysis were calculated. The difference in eradication rates between ethnic groups was analysed utilising the Fisher’s exact test and a p-value of <0.05 was considered significant. This study was approved by the NZ Northern X Regional Ethics Committee.

Results

Part I: Prevalence—592 patients were tested for \(H. pylori\) infection (CLO test) during upper endoscopy over the 4-month period. The proportion of male and female patients were equal (50% each) and the median age was 60.6 years (range 16–90.4 years). The overall prevalence of \(H. pylori\) infection in patients undergoing endoscopy was 18.6% (110 of 592 patients). Forty of the 110 with \(H. pylori\) infection during this period who did not have isolates for antibiotic susceptibility testing were included in the study cohort for Part III: Treatment efficacy.

Europeans (both NZ and overseas born) had a low prevalence of \(H. pylori\) infection at 7.7% while the prevalence was highest in Māori (34.9%) followed by Pacific People (29.6%), Oriental (23.8%) and Indian (19.2%).

Part II: Antibiotic susceptibility testing—A total of 593 patients were enrolled and consented for endoscopic gastric biopsy, culture and antibiotic susceptibility testing. Of these, 100 patients who were CLO test positive had biopsies obtained for culture. The CLO positive cohort consisted of 19% Māori, 6% NZ European, 30% Pacific People, 17% Indian, 14% Oriental, 9% Other European and 5% Other; 48% were male, 52% were female and the median age was 59.8 years (range 22–93.5 years). Seventy-three out of the 100 CLO positive patients were subsequently culture positive.
The overall resistance rates were; amoxicillin 5.5% (4 of 73 patients), tetracycline 0%, metronidazole 49.3% (36 patients), clarithromycin 16.4% (12 patients) and moxifloxacin 9.5% (6 of 63 patients). Ten patients did not have quinolone susceptibility testing performed due to unavailability of moxifloxacin E-tests when the study first commenced and these patients were therefore excluded from analysis involving the prevalence of moxifloxacin resistance.

The prevalence of any two antibiotic resistance was 12.7% (8 of 63 patients) and 6.5% (4 of 63 patients) for triple antibiotic resistance. Metronidazole and clarithromycin dual resistance was 8.2% (6 of 73 patients).

Table 1. Pattern and prevalence of *H. pylori* dual and triple antibiotic resistance

<table>
<thead>
<tr>
<th>Antibiotic resistance</th>
<th>Dual resistance</th>
<th>Triple resistance</th>
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<tbody>
<tr>
<td></td>
<td>AMO and MET</td>
<td>AMO and CLA</td>
</tr>
<tr>
<td>Case/Total</td>
<td>1/73</td>
<td>0/73</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>1.4</td>
<td>0</td>
</tr>
</tbody>
</table>

AMO, amoxicillin; MET, metronidazole; CLA, clarithromycin; MOX, moxifloxacin.

Amoxicillin-resistant or moxifloxacin-resistant *H. pylori* strains were only isolated from patients born overseas and were not present in the NZ-born cohort. However due to relatively small numbers, this finding was not significant (p>0.05).

The four patients with amoxicillin-resistant strains were Oriental (1), Other (1) and Pacific People (2). The 6 moxifloxacin resistant strains were seen in Pacific People (2), Other (1), Other European (1) and Indian (2). Three out of four (75%) amoxicillin-resistant strains were resistant to at least two other antibiotics. Moxifloxacin-resistant strains were also resistant to at least two other antibiotics. Moxifloxacin resistance was a predictor of resistance to two or more antibiotics (OR 10.4, 95%CI 1.64–65.79, p=0.046).

The overall primary metronidazole resistance was 49.3% (95%CI 37.8–60.8%). There was no significant difference in metronidazole resistance between ethnic groups or by birthplace (Figure 1).

The overall primary clarithromycin resistance was 16.4% (95%CI 7.9–24.9%). No clarithromycin resistance was detected in NZ-born Europeans, however clarithromycin resistance was seen in 25% of NZ-born indigenous Māori. The prevalence of primary clarithromycin resistance was ≥15% in Māori, Orientals and Pacific People.

There has been an apparent significant increase in the prevalence of primary metronidazole and clarithromycin resistance in the Auckland region since the 1990s. Indeed, clarithromycin resistance has more than doubled and there has been a smaller increase in metronidazole resistance as well (Table 2).
Figure 1. Primary *H. pylori* metronidazole and clarithromycin resistance rates according to ethnicity

![Primary H. pylori metronidazole and clarithromycin resistance rates according to ethnicity](image)

MET, metronidazole; CLA, clarithromycin.
Other Euro, Europeans born overseas; Other: includes African, Middle Eastern people.

Table 2. Proportion of primary antibiotic resistance of *H. pylori* infection between 1993–2012 in the Auckland region of New Zealand

<table>
<thead>
<tr>
<th>Antibiotic resistance</th>
<th>1999*</th>
<th>2012</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole resistance</td>
<td>84/257 (32.7%)</td>
<td>36/73 (49.3%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Clarithromycin resistance</td>
<td>18/257 (7%)</td>
<td>12/73 (16.4%)</td>
<td>0.032</td>
</tr>
<tr>
<td>Metronidazole + clarithromycin resistance</td>
<td>8/257 (3.1%)</td>
<td>6/73 (8.2%)**</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* Includes two triple resistance strains [amoxicillin (1) and moxifloxacin (1)].

Part III: Treatment efficacy—The overall combined first-line treatment (OAC, OCM, and OAM) eradication success was 84.8% (89 out of 105 patients). The overall all-treatment compliance was 98.1% (103 out of 105). 16.2% (17) suffered side effects from eradication therapy. These were mainly gastrointestinal (GI) symptoms such as nausea, diarrhoea and abdominal discomfort (12), parageusia (4), and dizziness (1).
7.6% (8 of 105) patients were actively smoking and all but one of these patients had successful eradication. Only 4 patients (3 OAC and 1 OCM) in total were prescribed a 10-day treatment course whereas the rest were prescribed the standard 7-day course.

In total, there were 9 patients receiving non-standard under-dosing of the triple therapy and 2 of these patients had subsequent persistent *H. pylori* infection. Although 13 patients were prescribed non-penicillin based therapy, only 4 patients had documented penicillin allergy or penicillin intolerance and none had documented allergies or intolerances to macrolides.

In patients with available susceptibility data and who received clarithromycin-based eradication therapy (OAC or OCM), the eradication rate was 33.3% (95%CI: 2.5–64.1%) for those with clarithromycin-resistant strains, while the eradication rate was 95.2% (95%CI: 88.8–100%) for clarithromycin susceptible strains (p<0.001).

The difference in eradication success remained significant even when only OAC therapy was analysed (Figure 3). Although metronidazole resistance data was available, the total number of patients taking metronidazole-based (OCM, OAM) therapy was small (13 patients). Therefore the efficacy of metronidazole-based therapy could not be adequately assessed.

Ethnic subgroup analysis identified ethnic groups with low and high resistance to clarithromycin (Figure 1). Therefore the cohort was further stratified into two groups (Group A and B), by low (<15%) and high (15%) prevalence of clarithromycin resistance to further examine the efficacy of clarithromycin-based therapy; Group A (NZ Europeans, Indian, Other) and Group B (Māori, Pacific People, Oriental, Other European).
Figure 2. Flow diagram depicting number of patients initially identified, excluded, lost to follow-up and those who were finally followed-up with stool antigen testing providing data on eradication rates with three different eradication regimens used in the community.

OAC: omeprazole, amoxicillin, clarithromycin.
OCM: omeprazole, clarithromycin, metronidazole.
OAM: omeprazole, amoxicillin, metronidazole.
Figure 3. Impact of clarithromycin-resistant *H. pylori* strains on the efficacy of OAC therapy (numerical values represent ratio of successful eradication to total number treated)

![Figure 3](image)

OAC: omeprazole, amoxicillin, clarithromycin.

OCM: omeprazole, amoxicillin, metronidazole.

Figure 4. Efficacy of OAC therapy among treatment naïve patients with low and high prevalence of clarithromycin resistance (numerical values represent ratio of successful eradication to total number treated)

![Figure 4](image)

ITT, intention to treat; PP, per protocol; OAC: omeprazole, amoxicillin, clarithromycin.
The eradication rate of OAC therapy among treatment naïve patients with *H. pylori* infection was significantly higher in Group A (ITT: 85.7%, 95%CI: 75.1–96.3%) compared to Group B (ITT: 63.9%, 95%CI: 52.8–75%), see Figure 4.

When the minor ethnic groups (Other European, n=6; African and Middle Eastern, n=7) were removed from analysis, the difference in eradication success remained significant; 88.9% (95%CI: 78.6–99.2%) in Group A and 63.2% (95%CI: 51.7–74.7%) in Group B (ITT analysis, *p*=0.008) and 100% in Group A and 81.1% (95%CI: 70.6–91.7%) in Group B (PP analysis, *p*=0.012).

**Discussion**

The efficacy of *H. pylori* eradication therapy is dependent upon the prevalence of local antibiotic resistance. PPI-based triple therapy of 7 to 10 day duration has been the foundation of eradication therapy for many years and is the recommended first-line treatment in NZ and also the Asia-Pacific region.14,17

Alternative strategies recommended in NZ and in international guidelines13,14,17 include OCM (in penicillin allergic patients) therapy as well as bismuth-based quadruple therapy.4,12,14 However bismuth compounds and Tetracycline are not readily available in NZ and are expensive to purchase without subsidy.

Without current knowledge of the local prevalence of *H. pylori* antibiotic resistance and the efficacy of standard OAC therapy, there is a risk of treatment failure and development of multi-resistant strains.18 Infection due to resistant strains would increase the subsequent risk of failing second-line and third-line eradication regimens. In contrast to successful early eradication, those with refractory *H. pylori* infections would continue to be at risk of gastric cancer and peptic ulcer disease.19

This study identified several significant findings via the careful administration of its three parts; prevalence, antibiotic susceptibility testing and treatment efficacy. Firstly, treatment naïve *H. pylori* infection is very common among Māori (~30%) and also immigrants from the Asia-Pacific region, similar to a previous study in 1999 by Fraser AG, et al.5 Importantly, ethnic groups with high *H. pylori* prevalence have also been associated with higher incidence of gastric cancer locally.20,21

Secondly, study data suggests that there is an apparent increase in metronidazole resistance to almost 50% and a doubling in clarithromycin resistance to 16.4% in the Auckland region over the last decade alone. Our study used a different method of resistance testing (MIC testing rather than disc diffusion method5 in the 1999 study) but we do not believe that this changed our finding.

The increasing prevalence of clarithromycin resistance is a concern and is reflected in the relatively poor eradication rate with OAC therapy (<90%). This is consistent with trends seen overseas over time.15,22 Moxifloxacin resistance is a predictor of multi-resistant *H. pylori* in this study.

Moxifloxacin use in NZ is tightly regulated and would rarely be available for general use in the community setting. However other second-generation quinolones such as norfloxacin and ciprofloxacin are commonly prescribed and may potentially
contribute to \textit{H. pylori} cross-quinolone resistance. Indeed, a recent study found a significant association between outpatient quinolone and long-acting macrolide use and levofloxacin and clarithromycin resistance.\textsuperscript{22}

Finally, OAC therapy exhibits poor eradication rates in our region among those with a high prevalence of clarithromycin resistance ($\geq 15\%$). In the multi-ethnic cohort in this study, the primary clarithromycin resistance varied among the different ethnic groups and this was reflected in the significantly different eradication rates between Groups A and B receiving OAC therapy. OAC therapy may still offer effective \textit{H. pylori} eradication in certain ethnic groups such as NZ Europeans and Indians where primary clarithromycin-resistant strains are not common.

In another recent antibiotic susceptibility study performed in NZ in early 2000, metronidazole resistance was low (around 20\%) and no resistance to clarithromycin was detected. However in that study, there were 62\% NZ Europeans compared to only 6\% NZ Europeans in our cohort.\textsuperscript{23} Furthermore, there was only a small proportion of Māori, Pacific People and Oriental patients (personal communication from authors of that study). The absence of clarithromycin resistance and disproportionally low metronidazole resistance likely reflected the regional ethnic composition where the study was conducted.

In groups with a high prevalence of clarithromycin resistance (Group B), alternative treatment is required to improve the overall first-line eradication rate especially since extending the duration of OAC therapy from 7 to 14 days has not conclusively shown better eradication rates.\textsuperscript{24,25} Regions with high metronidazole and clarithromycin resistance can utilize non-bismuth quadruple therapy; including sequential, concomitant or hybrid therapy. In a meta-analysis of 15 randomised controlled trials (RCTs), sequential therapy outperformed standard PPI-based triple therapies (91.7\% versus 76.7\%, ITT analysis) even in countries with high Clarithromycin resistance.\textsuperscript{26,27}

Concomitant therapy consisting of a PPI and three antibiotics produced a reported eradication rate of $>90\%$ by ITT analysis in a Greek study where clarithromycin and metronidazole resistance was high ($>20\%$ and $>40\%$ respectively).\textsuperscript{28} A RCT from Taiwan comparing sequential therapy with concomitant therapy found comparable eradication rates of 92.3\% and 93.0\% respectively (ITT analysis).\textsuperscript{29}

Hybrid (modified sequential) therapy consisting of 7 days of dual therapy with PPI and amoxicillin BiD followed by 7 days of quadruple therapy with PPI, amoxicillin, clarithromycin and metronidazole BiD produced eradication rates of $>95\%$. However studies based on hybrid therapy remain limited.

Bismuth-based quadruple therapy containing tetracycline, PPI, metronidazole and bismuth (De-Nol) can also be considered as a first-line therapy in NZ, specifically for patients of Group B ethnicities or penicillin-allergic patients. This study did not demonstrate any resistance to tetracycline but tetracycline is not readily available in many other countries.

Bismuth compounds and tetracycline have only recently been approved for use in NZ for \textit{H. pylori} eradication by Special Hospital Authority request (Note 1). Doxycycline, the readily available alternative, does not have comparable efficacy to tetracycline (eradication rate of 65\% for doxycycline versus 92\% for tetracycline).\textsuperscript{30}
Although metronidazole resistance was associated with a 37.7% (95%CI: 29.6–45.7%) reduction in the efficacy of metronidazole-based triple therapy according to a meta-analysis, there is some evidence that in vitro metronidazole resistance can be overcome by increasing the duration and dose of treatment.\textsuperscript{31,32}

In addition, in ethnic groups with high metronidazole and clarithromycin resistance, OCM eradication therapy may not represent an effective strategy. Although patients on OCM regimen in this study were too few in number to make conclusions with statistical significance, a prior meta-analysis in 2004 had reported somewhat disappointing eradication rates with OCM therapy; 50% overall for metronidazole-susceptible and clarithromycin-resistant strains, 72.6% overall for metronidazole-resistant and clarithromycin-susceptible strains and 0% for dual resistant strains.\textsuperscript{4}

There are also several limitations to this study; the first being that this was a single-centre study. However, this study involved an ethnically diverse cohort represented by the major ethnic groups in NZ, making study results applicable to the NZ population in general which has similar characteristics. Secondly, the number of culture-positive isolates were relatively small (less than 100 samples) but it has been shown, using available antibiotic-resistance data, that there are ethnic differences in antibiotic resistance rates directly contributing to observed eradication rates.

**Conclusion**

The observed eradication rates with current recommended OAC therapy is falling and is therefore unsatisfactory as first-line therapy in South Auckland, especially with the likely emergence of metronidazole and clarithromycin resistant *H. pylori* strains among specific ethnic groups. This trend is likely to continue over time.

Standard PPI-based triple therapy can no longer be recommended as an empiric first-line eradication therapy for ethnic groups with high clarithromycin resistance (≥ 15%) such as Māori, Pacific People and Orientals. Therefore, more effective first-line therapies should be sought and can conceivably be achieved with regimens tailored to predicted resistance patterns. Further study to examine eradication rates in the local population utilising alternative first-line therapies like sequential, concomitant or bismuth-based quadruple therapy should be undertaken.

**Note 1:** During the writing of this paper, the findings from our study were presented to the NZ government drug authority (PHARMAC) to suggest improving the availability of bismuth and tetracycline for first-line *H.pylori* eradication. As a result, bismuth and tetracycline have been approved as Section 29 drugs (special hospital approval) requiring pre-approval from PHARMAC at a subsidised price.

**Competing interests:** None identified.

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Reference:


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