A persuasive approach to antimicrobial stewardship in Christchurch hospitals produced a sustained decrease in intravenous clarithromycin dosing and expenditure via a switch to azithromycin orally

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ABSTRACT

AIMS: To assess a persuasive multimodel approach to decreasing unnecessary intravenous (IV) clarithromycin use for community-acquired pneumonia (CAP) in Canterbury District Health Board (CDHB) hospitals.

METHODS: In December 2013, CDHB guidelines for empiric treatment of CAP changed to prioritise oral azithromycin over IV clarithromycin. The multimodel approach we used to implement this change included obtaining stakeholder agreement, improved guidelines access, education and pharmacist support. The impact of the intervention was evaluated by comparing macrolide usage and expenditure for the four years pre- and post-intervention.

RESULTS: Mean annual clarithromycin IV use decreased by 72% from 6.4 to 1.8 defined daily doses (DDDs) per 1,000 occupied bed days (OBDs) post-intervention, while oral azithromycin increased by 833% (4.2 to 39.2 DDDs per 1,000 OBDs). Concurrently, oral clarithromycin use decreased by 91% (32.9 to 2.9 DDDs per 1,000 OBDs), and roxithromycin by 71% (17.0 to 5.0 DDDs per 1,000 OBDs). Mean annual total macrolide use decreased by 21% (68.2 to 53.9 DDDs per 1,000 OBDs), while expenditure decreased by 69% mainly through avoided IV administration.

CONCLUSIONS: A persuasive multimodel approach to support adoption of CAP guidelines produced a sustained decrease in IV clarithromycin use, which may have clinical benefits such as reduced occurrence of catheter-related complications.

Maximising the use of oral rather than intravenous (IV) antimicrobial agents is one of the safest and most cost-effective interventions available in antimicrobial stewardship (AMS), provided that an effective concentration reaches the site of infection with oral dosing. Advantages of the oral route include avoidance of IV line-related infections, increased patient mobility, reduced nursing time and earlier discharge from hospital.[1] Our unpublished internal audit (2011) of community-acquired pneumonia (CAP) management showed that many clinically stable patients unnecessarily received a macrolide via the IV route. Possible reasons for this include delays in clinical

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reassessment of patient progress, lack of clinical confidence in oral formulations, fear about patient complaints and medical team dynamics.[2,3] Local prescribers were particularly concerned that the oral regimen for CAP should be highly effective for treating Legionnaires' disease because of the high rates of *Legionella longbeachae* infection in the region.[4,5]

In 2013 our AMS committee recommended that the Canterbury District Health Board (CDHB) hospital guidelines for management of CAP include oral azithromycin (rather than oral roxithromycin or 'defaulting' to IV clarithromycin) when an agent active against *Legionella* spp., was indicated. The ability to prescribe azithromycin for inpatient management of CAP had been facilitated by the Pharmaceutical Management Agency ('PHARMAC') funding azithromycin in the community (five days' maximum per prescription for any indication) in December 2012 (improving accessibility and reducing cost), as well as in hospital. Clarithromycin IV was retained in the guideline for patients with severe disease and those unable to take medicines orally (Table 1). The committee gave the task of leading this change to a newly appointed AMS pharmacist. Key stakeholders including senior respiratory, general medicine and emergency medicine physicians agreed to the changes prior to release of the guidelines in December 2013. Here, we describe the collection of persuasive strategies used to facilitate adoption of the new CAP guidelines in our hospitals, together with an evaluation of the impact of this initiative on macrolide usage and expenditure.

Table 1: Empirical antimicrobial guideline for community-acquired pneumonia (CAP) in Canterbury District Health Board (CDHB) hospitals (2013), with key changes from the previous version identified.

CAP severity	New guideline (published December 2013)	Key changes from previous version
Mild (CURB-65 0-1)	amoxicillin PO 500mg three times daily *or* azithromycin PO 500mg once daily[a]	azithromycin replaced roxithromycin
Moderate (CURB-65 2)	amoxicillin IV 1g every 8 hours *Add, if risk factors for Legionella spp.,* azithromycin PO 500mg once daily[a] *or* doxycycline PO 200mg once daily	oral azithromycin or doxycycline replaced IV clarithromycin
Severe (CURB-65 3-4)	amoxicillin+clavulanate IV 1.2g every 8 hours *and either* clarithromycin IV 500mg every 12 hours *or* azithromycin PO 500mg once daily	new recommendation to give only one or two clarithromycin IV doses before changing to oral azithromycin
Extremely severe[b] (CURB-65 5)	ceftriaxone IV 2g every 12 hours *and* gentamicin IV every 24 hours *and* clarithromycin IV 500mg every 12 hours	

CURB-65 pneumonia severity score, which predicts mortality based on assignment of points for **C**onfusion, **U**rea concentration, **R**espiratory rate, **B**lood pressure and age (65 years or older).[20]
IV, intravenous; PO, per os.
a. Acceptable alternative azithromycin regimen for mild to moderate CAP was 500mg initially then 250mg once each day for four days (both regimens comprised 1,500mg per course).
b. CDHB guidelines for immunocompetent patients with severe CAP treated in the intensive care unit differ and comprised ciprofloxacin IV plus amoxicillin+clavulanic IV.

Methods

Setting

CDHB provides government-funded healthcare services for a population of ~570,000 people in Canterbury, New Zealand.[6] The Christchurch Hospital campus, which is the largest CDHB facility at ~800 beds,[7] offers a full range of inpatient and outpatient services, and receives more than 95% of acute admissions for CDHB.

The CDHB hospital AMS committee has multidisciplinary (pharmacists, junior and senior doctors, nurses and laboratory scientists) membership from services that include Infectious Diseases, Pharmacy, Clinical Microbiology and Clinical Pharmacology. One of its core functions is to produce hospital guidelines for management of common infections. The committee primarily uses persuasive rather than restrictive approaches to influence antimicrobial prescribing. Persuasive measures include local consensus building processes and discussion with opinion leaders during guideline development as well as multimodal clinician education and verbal reminders from pharmacists.[8] There were some restrictive interventions in place prior to the intervention. These were selective laboratory reporting of susceptibilities to respiratory pathogens,[8] with some external antimicrobial restrictions applied by PHARMAC[9]. For example, levofloxacin is not publicly funded at all in New Zealand while moxifloxacin is only funded for specific subsets of patients with CAP such as those with multiresistant *Streptococcus pneumoniae*.

Multimodel approach to facilitate guidelines adoption

1. Guideline access: Access to CDHB antimicrobial guidelines was improved via a new easily searchable electronic format that replaced the existing Portable Document Format (PDF) and was accessible on mobile devices (tablets and phones) as well as computers.[10] Hardcopies (book and poster) of the guideline were also available in clinical areas.
2. Education: Verbal education sessions for medical, nursing and pharmacy staff were conducted by the AMS pharmacist. These comprised ~20 brief (10 minute) teaching sessions to staff in key clinical areas, such as the general medical wards and the emergency department. The presentations outlined the guideline changes as well as the relative advantages and disadvantages of IV clarithromycin versus oral azithromycin including consideration of IV catheter-related complications, drug interactions, dosing regimen and cost. An infectious diseases physician participated in the education sessions when the audience included senior medical doctors. Written information to support key messages comprised bulletins (single-sided A4 documents) disseminated electronically to clinical staff at baseline (December 2013) and at four months into the initiative (April 2014) highlighting the initial progress made, along with a poster placed in clinical areas.
3. Access to macrolides: Clarithromycin IV vials were removed from most wards except from locations such as the emergency department that need rapid access for acutely unwell patients. The intent was to have most requests for clarithromycin IV screened against the guidelines by the pharmacy department for appropriateness prior to supply. Prescriptions that appeared inconsistent with the guidelines would be discussed with the prescribing medical team, but clarithromycin IV could still be dispensed even if the intended use was not compliant with guidelines. Access to azithromycin 250mg tablets was assisted by adding it to clinical areas as a 'stock' item.
4. Ongoing support by healthcare providers: The specialist AMS pharmacist led this initiative, supported by infectious diseases physician champions who also worked in general medicine, likely assisting with changing practice. Additionally, pharmacy staff in clinical areas and the dispensary actively supported this initiative by engaging with prescribers when clarithromycin IV use appeared inconsistent with the guidelines, and by promoting an early switch to oral azithromycin.

Macrolide usage and expenditure

Data on adult inpatient macrolide usage and expenditure at the four main CDHB hospitals—Christchurch, Christchurch Women's, Burwood and the Princess Margaret—were extracted from hospital pharmacy dispensing software (ePharmacy, v1.7, DXC Technology, VA, US) into Microsoft Excel™. The time periods evaluated were the four years before (2010–2013) and after (2014–2017) the guideline change. Data for adult inpatients were included. Paediatric and psychiatric inpatients, and all outpatient areas were excluded. All dosage formulations (IV, and solids and liquids for oral administration) of macrolides used at CDHB hospitals were included (Table 2). Usage was expressed as defined daily doses (DDDs) per 1,000 occupied bed days (OBDs) for the individual macrolides, and for all macrolides combined.[11]

Table 2: Mean annual macrolide usage and expenditure for adult inpatients in Canterbury District Health Board (CDHB) hospitals for the four years before (2010–2013) and after (2014–2017) the changes in empiric antimicrobial guidelines for community-acquired pneumonia (CAP). Oral formulations (tablets and suspension) for each macrolide are combined, as relevant.

Formulations in use at CDHB hospitals		**DDDs per 1,000 OBDs (mean usage per year)**			**Expenditure (unadjusted mean cost in $NZ per year)**		
Form	**Strength (cost per unit*)**	**2010–2013**	**2014–2017**	**% Change**	**2010–2013**	**2014–2017**	**% Change**
Azithromycin							
Tab Susp	250mg ($0.30–$0.35) 500mg ($0.53–$3.12)[a] 200mg/5mL ($6.60–$12.50)[b]	4.2	39.2	↑ 833%	$1,035	$4,133	↑ 300%
Clarithromycin							
Vial	500mg ($12.04–$30.00)[c]	6.4	1.8	↓ 72%	$106,734	$23,967	↓ 78%
Tablet Susp	250mg ($0.28–$0.58)[d] 500mg ($0.74–$1.75)[e] 125mg/5mL ($23.12) 250mg/5mL ($23.12)	32.9	2.9	↓ 91%	$12,018	$710	↓ 94%
Erythromycin**							
Vial	1g ($10.99–$16.00)[f]	2.5	2.5	↔	$8,243	$10,559	↑ 28%
Tablet Susp	250mg ($0.23) 400mg ($0.18) 500mg ($0.47) 200mg/5mL ($4.57–$5.18) 400mg/5mL ($6.04–$6.99)	5.1	2.6	↓ 49%	$1,438	$748	↓ 48%
Roxithromycin							
Tablet	150mg ($0.15–$0.19) 300mg ($0.29–$0.35)	17.0	5.0	↓ 71%	$1,706	$409	↓ 76%
Total		**68.2**	**53.9**	**↓ 21%**	**$131,175**	**$40,526**	**↓ 69%**

DDD, defined daily doses; OBDs, occupied bed days; Susp, suspension; $NZ, New Zealand dollars.
*Prices were CDHB hospital pharmacy acquisition costs (unpublished) per unit [tablet, vial or bottle (liquid)] until March 2013 when Pharmaceutical Management Agency (PHARMAC) subsidy prices were used.[9] Dates for a price change greater than 20% were as follows: a: decrease from $3.12 to $0.63 February 2013, and to $0.53 July 2015; b: increase from $6.60 to $12.50 per 15mL August 2015; c: decrease from $30.00 to $20.40 July 2015, and to $12.04 December 2017; d: decrease from $0.58 to $0.28 June 2014; e: decrease from $1.75 to $0.82 February 2012, and to $0.74 July 2014; f: increase from $10.99 to $16.00 March 2013.
**Erythromycin salts were lactobionate (IV), stearate (250mg, 500mg) and ethylsuccinate (400mg, 200mg/5mL, 400mg/5mL).

Expenditure was determined in New Zealand dollars ($NZ) using the pharmacy purchasing price per unit until 1 March 2013, after which PHARMAC subsidy prices were used.[9] Costs of consumables for IV administration were set as $NZ8.49 per dose for a giving set (Alaris secondary set, CareFusion, Switzerland), plus two sodium chloride 0.9% infusion bags for the dose (250mL) and for the post-dose flush (100mL). Other direct costs such as those of water for injection, syringes and needles for reconstitution, and indirect costs such as nursing time were not included.

Results

Macrolide usage and expenditure

Mean annual macrolide usage for the four years before and after commencement of this initiative are shown in Figure 1 and Table 2. Overall mean annual macrolide use, as DDDs per 1,000 OBDs, decreased by 21% post-initiative due to reductions in use of clarithromycin IV (by 72%), along with decreases in use of oral clarithromycin (by 91%), erythromycin (by 49%) and roxithromycin (by 71%). These reductions were offset by a substantial increase in use of azithromycin (by 833%). The mean number of IV clarithromycin doses used (not standardised against OBDs) annually was 3,601 pre-initiative and 985 post-initiative. This equated to approximately 2,617 avoided IV clarithromycin doses each year. There was no change in the mean annual usage of erythromycin IV, which is the other IV macrolide in use at CDHB hospitals.

Mean annual expenditure for the four years pre- and post-initiative are shown in Figure 2 and Table 2. Overall, mean expenditure on macrolides decreased by 69% ($NZ90,649) from $NZ131,175 per annum before the initiative to $NZ40,526 per annum after the initiative. Most of this resulted from savings attached to avoided use of clarithromycin IV and orally ($NZ82,767 and $NZ11,308 saved annually, respectively), and was offset by a small increase in costs associated with azithromycin orally ($NZ3,098). The annual savings ($NZ82,767) from avoided use of clarithromycin IV were greater ($NZ104,000) if giving sets and infusion bags are also considered (data not shown).

Figure 1: Macrolide usage per quarter in adult inpatients at four CDHB hospitals (2010–2017). Data presented as individual (combined oral formulations, and IV vials) and total macrolides, as defined daily doses (DDDs) per 1,000 occupied bed days (OBDs). Erythromycin not shown.

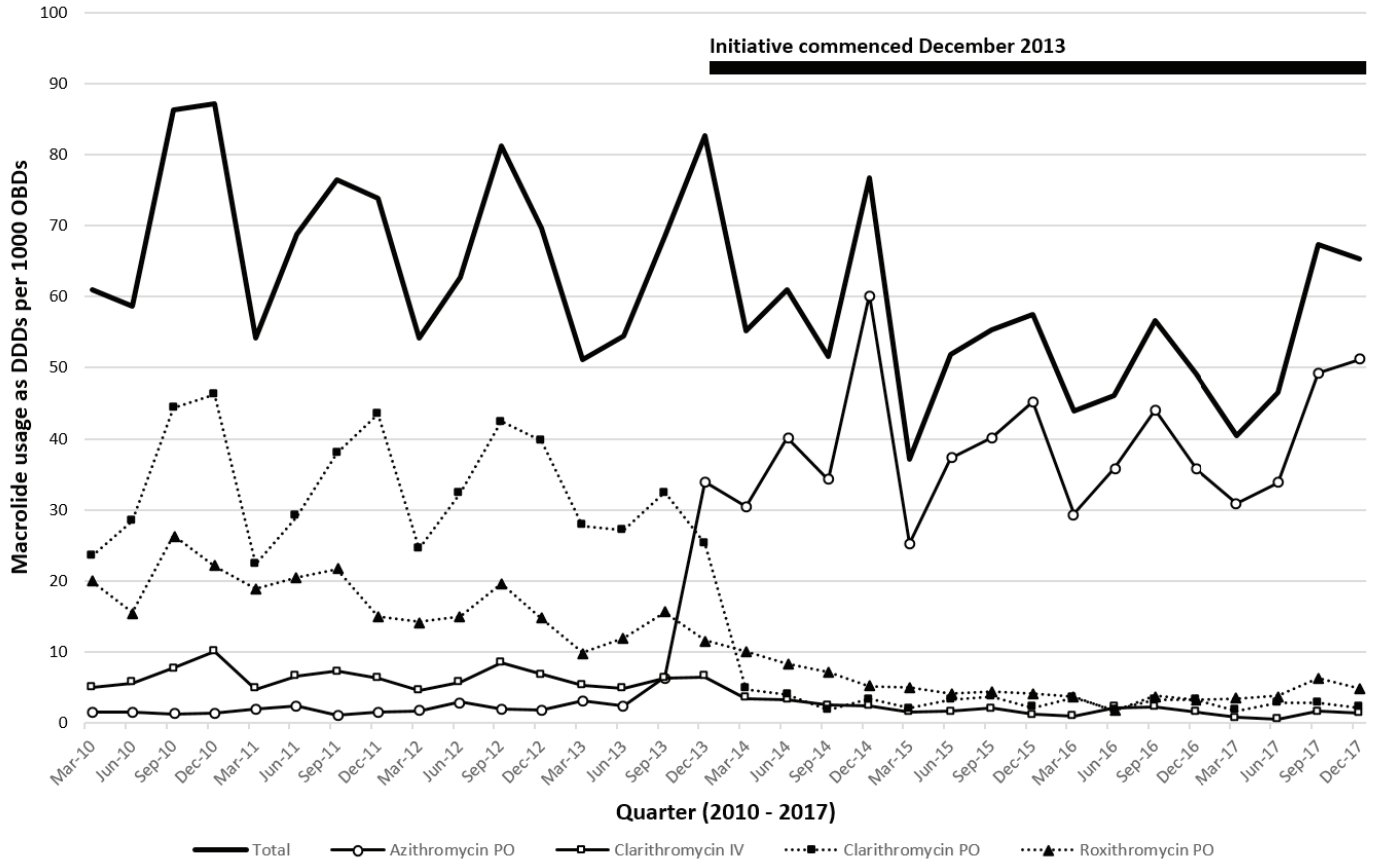
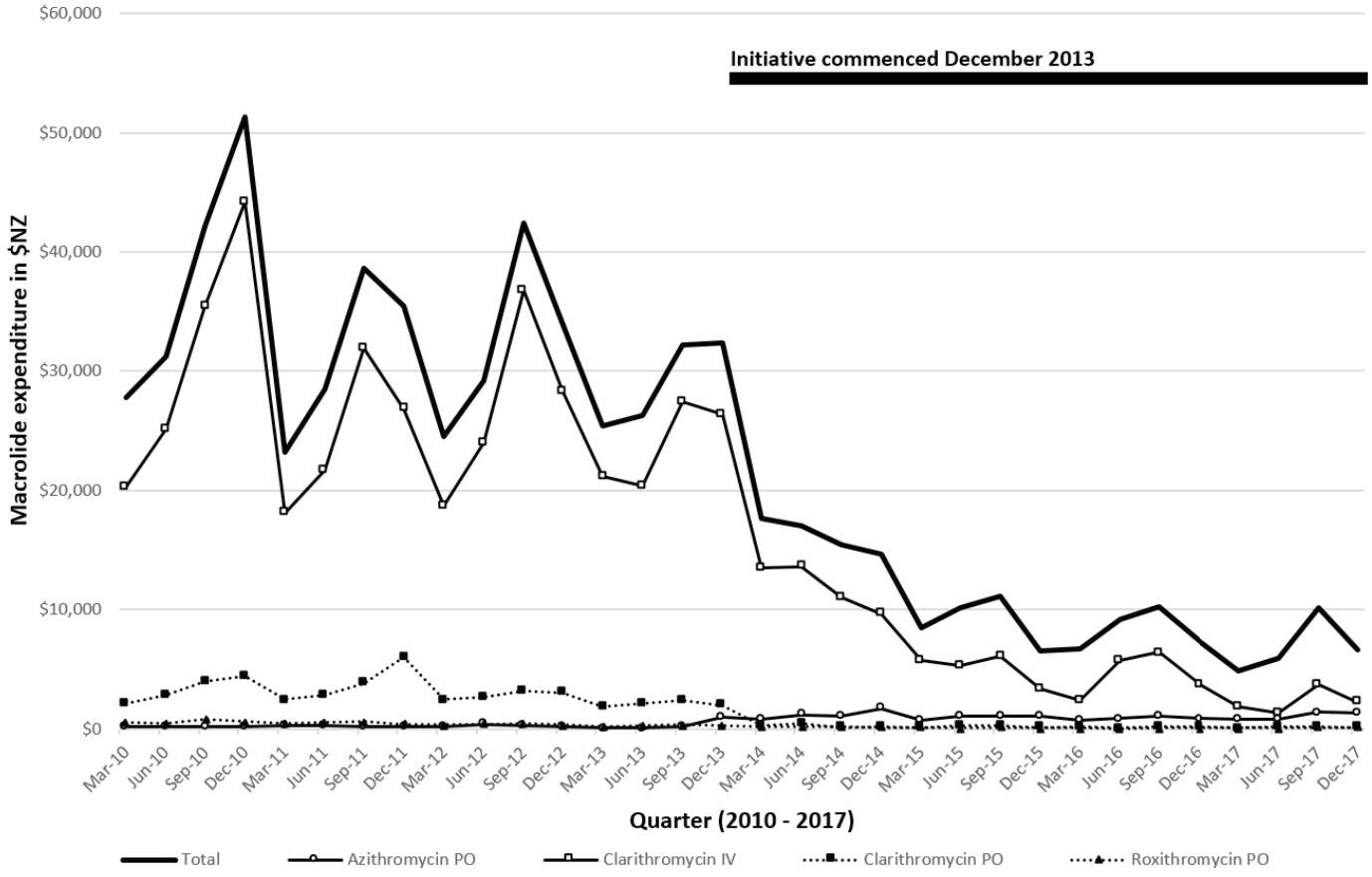


Figure 2: Macrolide expenditure per quarter in adult inpatients at four CDHB hospitals (2010–2017). Data presented as individual (combined oral formulations, and IV vials) and total macrolides, in New Zealand dollars. Erythromycin not shown.



Discussion

This initiative demonstrates that a collection of persuasive measures can produce immediate and sustained changes in antimicrobial prescribing practice with substantial cost savings. In this case, a multipronged campaign focusing on oral azithromycin as the preferred macrolide for CAP resulted in a ~70% decrease in use of both clarithromycin IV and roxithromycin PO. With the mass shifts away from use of other macrolides at CDHB use of azithromycin increased by ~800% because of the low starting point. The large decrease (~90%) in use of oral clarithromycin was likely because it had been used as the logical follow-on to clarithromycin IV.

This initiative had strong support from medical staff who were confident in the efficacy of azithromycin in Legionnaires' disease.[12] Routine polymerase chain reaction testing of lower respiratory specimens for *Legionella* spp., commenced in 2010, which was prior to our initiative.[5]

While not directly involved in the macrolide initiative, our guideline changes for CURB-2 pneumonia also included doxycycline as an alternative to oral azithromycin when cover against *Legionella* spp., was required. Doxycycline usage (reported briefly for completeness) increased from around 16–17 per 1,000 OBDs pre-initiative to around 20–23 DDDs per 1,000 OBDs post-intiative. However, we recently changed our CAP guidelines to cease recommending doxycycline for *Legionella* spp., as local research suggested it may be ineffective.[13]

The readily quantifiable benefits of our initiative were mainly through avoided IV doses (~2,600 annually). The direct cost savings (drug plus some consumables) of ~$NZ90,000 point to the ability of AMS programmes to generate financial savings, potentially covering any investment in resourcing.[14] The clinical benefits of appropriate avoided IV antimicrobial administration include reduced complications from IV access, shorter hospital length

of stay and a lower need for outpatient parenteral antimicrobial therapy.[1] A further benefit of the shift away from clarithromycin (IV and PO) is that azithromycin does not inhibit drug metabolism by cytochrome P450 3A appreciably, and thus carries a much lower potential for adverse drug interactions.[15] We have not made any estimate of the administration, health or cost benefits of this initiative, other than those related directly to drug expenditure. However, it is probable that these extend beyond those presented here.

We cannot determine the relevant weightings of the various components of our multimodel initiative (specialist AMS pharmacist, physician champions, stakeholder support, multifaceted and repeated education strategies, and ongoing pharmacy involvement) in terms of their contribution to its overall success. However, it was largely a 'front-loaded' approach that was completed within six months. One factor that we believe was integral to its success was obtaining the support of senior clinicians from relevant specialties prior to implementation, and ensuring that there were multiple opportunities (verbal education sessions plus memos, bulletins, posters) for senior clinicians not involved in the initial guideline development to become aware of the changes. This recognises the role of 'prescribing etiquette' (related to medical hierarchy) in antimicrobial prescribing behaviours within clinical teams, and the ability of healthcare leaders to influence the success of a quality improvement initiative.[3] The improved efficacy of azithromycin compared with other macrolides has been affirmed since then which may contribute to the sustained acceptance of the regimen.[16]

The limitations of this work relate primarily to the rather blunt mechanism for assessing macrolide usage and patient outcomes. First, our data on macrolide usage were extracted from CDHB hospital pharmacy dispensing software, which is a composite of dispensings to individual patients and to clinical areas. The assumption that dispensings to clinical areas (eg, wards) match patient usage is often applied in hospital settings,[17] but is clearly several steps away from administrations to patients. Second, we assumed that CAP was the dominant indication for macrolide use in hospitalised patients at CDHB. This seems likely from the bulk shifts in macrolide usage associated with our initiative, but some other infective (eg, atypical mycobacterial infections) and non-infective (eg, prokinetic and anti-inflammatory effects) indications will also be in play. Third, an external restrictive element for access to clarithromycin IV was applied on 1 July 2013, with PHARMAC restricting clarithromycin IV to second-line treatment of CAP until 1 June 2015.[18] While these restrictions added a useful 'argument' to drive a change in prescribing, the shift in macrolide prescribing coincided with our initiative rather than with initiation of the restrictions. Finally, this and other persuasive initiatives at CDHB[19] may have been successful, in part, because of a long history of prioritising a collegial approach over removing the prescriber's autonomy with enforced antimicrobial restrictions. On this basis, it should be noted that while restrictive interventions may produce a swifter change in antimicrobial prescribing, both persuasive and restrictive approaches produce a comparable effect at 12 months.[8]

In conclusion, we demonstrated that a multipronged initiative designed to improve adoption of antimicrobial guidelines can produce a substantial and sustained change in prescribing. In particular, we did not use formal behaviour change techniques such as audit and feedback to individual teams or prescribers. Rather, the aim was to create an enabling environment with which to change clinical practice.

Competing interests:
Dr Werno reports that she is a Member of the Anti-Infective subcommittee, Pharmacology and Therapeutics Advisory Committee (PTAC), PHARMAC (www.pharmac.health.nz).

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