

Trends in penicillin dispensing during an acute rheumatic fever prevention programme

Julie Bennett, Anneka Anderson, June Atkinson, Emma Best, John Malcolm, Gary McAuliffe, Rachel Webb, Jeffrey Cannon

ABSTRACT

AIM: Acute rheumatic fever (ARF), a serious inflammatory condition, often leads to rheumatic heart disease (RHD). Between 2011 and 2016, Aotearoa New Zealand implemented a rheumatic fever prevention programme (RFPP) to reduce high rates of ARF through improved community access to timely diagnosis and early treatment of group A streptococcal (GAS) pharyngitis, which has been shown to prevent subsequent ARF. This study aimed to quantify the change in penicillin antibiotic dispensing rates among children aged 18 years or younger during the RFPP.

METHOD: This retrospective analysis utilised administrative data from the National Pharmaceutical Collection. Using a controlled, interrupted time series analysis, the effect of the RFPP on antibiotic dispensing rates was explored. Poisson regression models were used to assess the change in dispensing rates during the RFPP among control regions (those not in the RFPP) and regions participating in the RFPP. The primary measure was rate ratio (RR) for the difference between the observed versus counterfactual rates of penicillin dispensing.

RESULT: A total of 12,154,872 dispensing records between 2005 and 2018 were included. Amoxicillin was the most frequently dispensed penicillin (57.7%), followed by amoxicillin-clavulanate (23.4%). Amoxicillin dispensing increased by 4.3% in regions operating the RFPP compared to the increase in control regions ($p < 0.001$). The overall rate of penicillin dispensing decreased, driven by a rapid decline in amoxicillin-clavulanate dispensing.

CONCLUSION: During the RFPP an increase in amoxicillin dispensing was seen in regions participating in the programme and regions outside of the programme, indicating the programmatic approach led to improved adherence to recommended first-line antibiotics.

Acute rheumatic fever (ARF) is an inflammatory disease that can develop 2–4 weeks after group A streptococcal (GAS) infection and often progresses to permanent cardiac valve damage or rheumatic heart disease (RHD).^{1–3} Globally, ARF and RHD continue to cause considerable morbidity and mortality in low- and middle-income countries and among some disadvantaged populations living in high-income countries.⁴ RHD is responsible for around 300,000 deaths annually, predominantly in children and young adults.⁴

In Aotearoa New Zealand, the rates of ARF steadily increased during the 1990s.⁵ Between 2000 and 2018, the rate of initial ARF hospitalisations for Indigenous Māori children (5–14 years of age) was 36 per 100,000, and Pacific children had a rate of 80 per 100,000; this represents some of the highest ARF rates in the world.² By comparison, the rates for NZ European/Other ethnicities over the same time frame and age group was <2 per 100,000.²

ARF may be prevented by prompt treatment

of GAS pharyngitis with antibiotics.⁶ In Aotearoa New Zealand, the current guidelines for the treatment of GAS pharyngitis recommend that people at high risk of ARF (i.e., Māori and Pacific peoples aged 3–35 years, with emphasis on children and adolescents aged 4–19 years of age) who present to primary care or an emergency department with a sore throat are treated with a 10-day oral course of phenoxymethylpenicillin (penicillin V) two or three times daily, with amoxicillin once daily or with a single dose of intramuscular (IM) benzathine benzylpenicillin (BPG).⁷ Guidelines also outline treatment recommendations for children presenting to school-based sore throat clinics, including the recommendation to wait for confirmation of a GAS-positive throat culture before a 10-day course of antibiotics is dispensed. In addition, national guidelines recommended that children at high risk of ARF presenting to primary care with recurrent GAS pharyngitis be treated with either IM BPG or directly observed oral amoxicillin, with options including amoxicillin-clavulanate, clindamycin or adjunctive

rifampicin, reserved for high-risk recurrent cases.⁷

In response to Aotearoa New Zealand's high and inequitable rates of ARF, from 2011 the government implemented the rheumatic fever prevention programme (RFPP) in 11 out of 20 regions or district health boards (DHBs) that experienced the highest rates of ARF.⁵ This multi-faceted intervention aimed to reduce ARF incidence by improving access to timely diagnosis and antibiotics for GAS pharyngitis.⁸ The RFPP included school-based sore throat services,^{9,10} community "rapid response" clinics for sore throats (from 2014), and mass media health promotion campaigns (2014 and 2015). By 2014, 244 schools were participating, involving an estimated 53,376 children aged 5–12 years.¹¹ The success of the programme on reducing ARF was variable and those areas that had high-risk populations geographically concentrated were found to be more effective.¹¹ A 2014 evaluation of antimicrobial use in one region's school-based clinics reported that 91% of prescriptions were for GAS pharyngitis and 9% for skin infections. School-based programmes treated skin infections opportunistically, rather than as an intervention to prevent ARF. For skin infections, topical management is recommended for simple impetigo, with oral flucloxacillin tablets or cephalexin suspension for multi-lesional impetigo and other infective skin conditions. As part of the RFPP almost all children (98%) with GAS pharyngitis were treated with first-line antibiotics and the majority of skin infections (35%) were prescribed topical fusidic acid or cephalexin (37%).¹⁰

The impact of the RFPP on antibiotic consumption in Aotearoa New Zealand has not previously been assessed, particularly whether this altered treatment of GAS pharyngitis outside the at-risk population, or whether the programmatic approach led to improved adherence to recommended first-line antibiotics. Accordingly, the aims of this study are to explore trends in penicillin dispensing between 2005 and 2018 in the context of the RFPP.

Method

Data

In Aotearoa New Zealand, antibiotics for systemic use are only available with a prescription and/or under standing orders. From 2014, there has been no prescription charge for children under the age of 14 years. Each medicine dispensed is recorded in the National Pharmaceutical Collection (using

the Anatomical Therapeutic Chemical system) along with the age of the person receiving the prescription and the funding DHB. Pharmaceutical data from 2005 to 2018 were obtained from the Ministry of Health, who manage the Pharmaceutical Collection. Included in the analysis were selected beta-lactam antibiotics from the penicillin class, commonly recommended in Aotearoa New Zealand, for the treatment of GAS pharyngitis (amoxicillin, BPG, penicillin V, flucloxacillin, and amoxicillin-clavulanate). While our dataset accounted for 97% of antibiotics dispensed (2012–2016), it did not include supply orders (practitioner and bulk). Statistics NZ estimate resident population (ERP) and projections (children 0–18 years) based off census data were used as denominator data for the period 2005–2018.

Study design and analysis

This study utilised a controlled, interrupted time series (CITS) analysis, as described elsewhere,¹² and Poisson regression models. The models comprised a dependant variable for the rate of penicillin dispensing and independent variables for calendar year, and an indicator for RFPP implementation (see Appendix for model formulae). Because the RFPP was implemented at varying coverage levels among participating regions (DHBs) during approximately 2012 to 2016, the RFPP indicator was time invariant and represented the average effect of the RFPP on dispensing rates throughout the RFPP period.

The models were used to predict the counterfactual penicillin dispensing rates had the RFPP not been implemented. The counterfactual rates were predicted based on the rates of dispensing outside of the RFPP period (i.e., 2005–2011 and 2017–2018). The primary measure was the rate ratio (RR) for the change in observed versus counterfactual rates of dispensing among residents of regions participating in the RFPP compared to the change in rates among residents of regions not participating in the RFPP (controls). The change in dispensing rates among regions not participating in the RFPP were used to control for temporal trends and spill-over effects (from mass media campaigns) on dispensing rates, which was quantified through an interaction term in the models. Data were analysed using R, version 4.1.0.

Ethical approval

Ethical approval for the study was obtained from the University of Otago, New Zealand (Minimal Risk Health Research reference HD19/033).

Results

All penicillins

Included in the analysis were all amoxicillin, BPG, penicillin V, flucloxacillin and amoxicillin-clavulanate records dispensed to individuals aged 18 years or under (n=12,154,872) between 2005 and 2018 (Table 1). The most frequently dispensed agent during this period was amoxicillin, which made up 57.7% of dispensed penicillin. Amoxicillin-clavulanate made up 23.4% and flucloxacillin made up 13.2%.

Overall, there was a reduction in penicillin dispensing during the years that the RFPP was in operation (2012–2016) (Figure 1). The baseline dispensing rates were higher in regions participating in the RFPP compared to controls (regions not in the RFPP; RR 1.46, $p<0.001$). The RFPP had no effect on dispensing rates among controls ($p=0.204$), but it did increase dispensing rates in regions with the RFPP (RR 1.031, $p<0.001$). See Appendix Figure 1 for observed incidence rates for penicillin dispensing stratified by DHB.

Penicillins by group

The rates of dispensing of BPG, penicillin V and flucloxacillin over time are shown in Figures 2c and 2d. A downward trend in dispensing rates of amoxicillin-clavulanate was observed over time, particularly among regions that were implementing the RFPP (Figure 2b). In contrast, dispensing rates of amoxicillin increased predominately among regions operating RFPP (Figure 2a).

Amoxicillin

Figure 3 shows a model for 2005–2016 amoxicillin dispensing rates. There was a significant increase in amoxicillin dispensing during the period the RFPP was operated in, which occurred in regions both participating and not participating in the RFPP. Among regions not participating in the RFPP, the dispensing rate increased by 4.3% during the RFPP (2012–2016) relative to the counterfactual rate (RR 1.043, $p<0.001$). In comparison, among those regions participating in the RFPP the rate increased an additional 4.3% (RR 1.043, $p<0.001$), such that the difference in rates during the RFPP were 8.9% higher relative to the counterfactual rate among controls.

Amoxicillin-clavulanate

Rates of amoxicillin-clavulanate dispensing have declined since 2005 (Figure 4). However, there was an increase in amoxicillin-clavulanate dispensing rates during the RFPP. During that period, rates of amoxicillin-clavulanate dispensing increased by 1.9% in regions not in the RFPP (RR 1.019, $p<0.001$) and an additional 3.9% in regions operating the RFPP relative to the increase in non-RFPP regions (RR 1.039, $p<0.001$).

Discussion

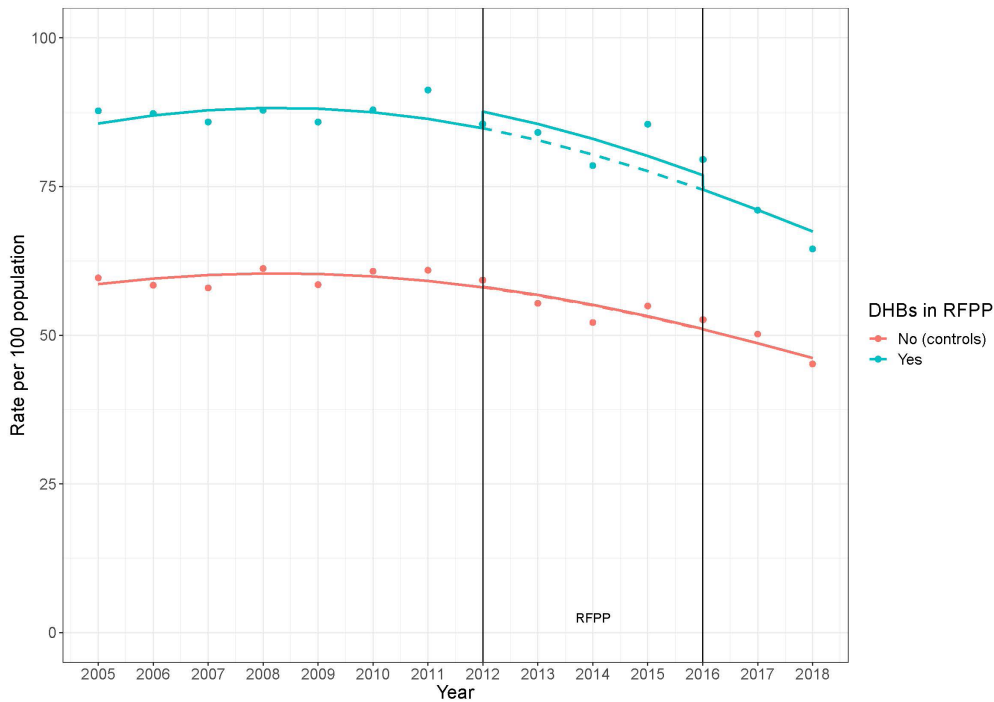
Our findings show there was a non-sustained increase in amoxicillin dispensing during the RFPP that was greatest in RFPP regions, but also occurred in non-RFPP regions. This occurred on the back of declining overall rates of penicillin

Table 1: Summary of national penicillin dispensing frequency between 2005 and 2018.

Aotearoa New Zealand		
Name	Total dispensing N=34,152,401 (%)	Dispensing among children (≤ 18 years) N=12,154,872 (%)
Amoxicillin	15,108,527 (44.2)	7,016,771 (57.7)
Benzathine benzylpenicillin (BPG)*	38,157 (0.1)	695,417 (5.7)
Phenoxymethylpenicillin (penicillin V)*	1,583,782 (4.6)	
Flucloxacillin	6,246,620 (18.3)	1,602,276 (13.2)
Amoxicillin-clavulanate	11,136,556 (32.6)	2,840,408 (23.4)

* Due to small numbers, data for BPG and penicillin V were only available as combined data for children ≤ 18 years.

Figure 1: Timeline of all penicillin dispensing for children (<18 years-old) before (2005–2011), during (2012–2016) and after the rheumatic fever prevention programme (2017–2018), by district health boards participating in the programme and district health boards that were not participating.



*Dotted line indicates the expected (counterfactual) rate.

Figure 2: Summary of penicillin dispensing rates among children <18 years by penicillin class period (before [2005–2011], during [2012–2016] and after [2017–2018] the rheumatic fever prevention programme) and DHBs participating in the programme and those that were not participating (controls).

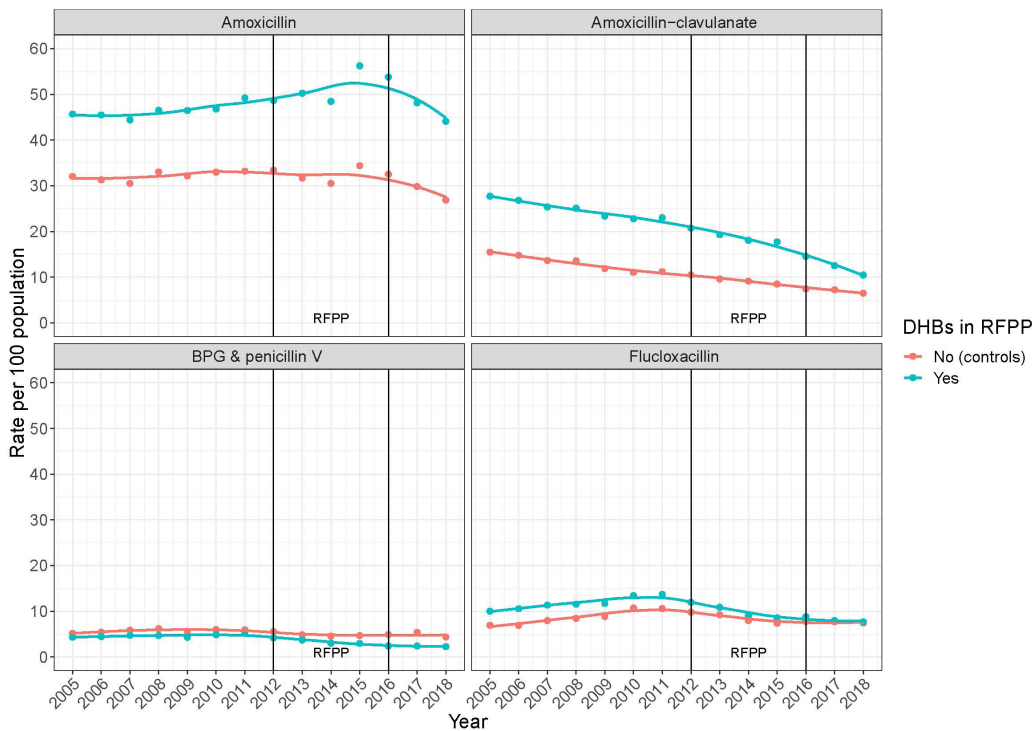
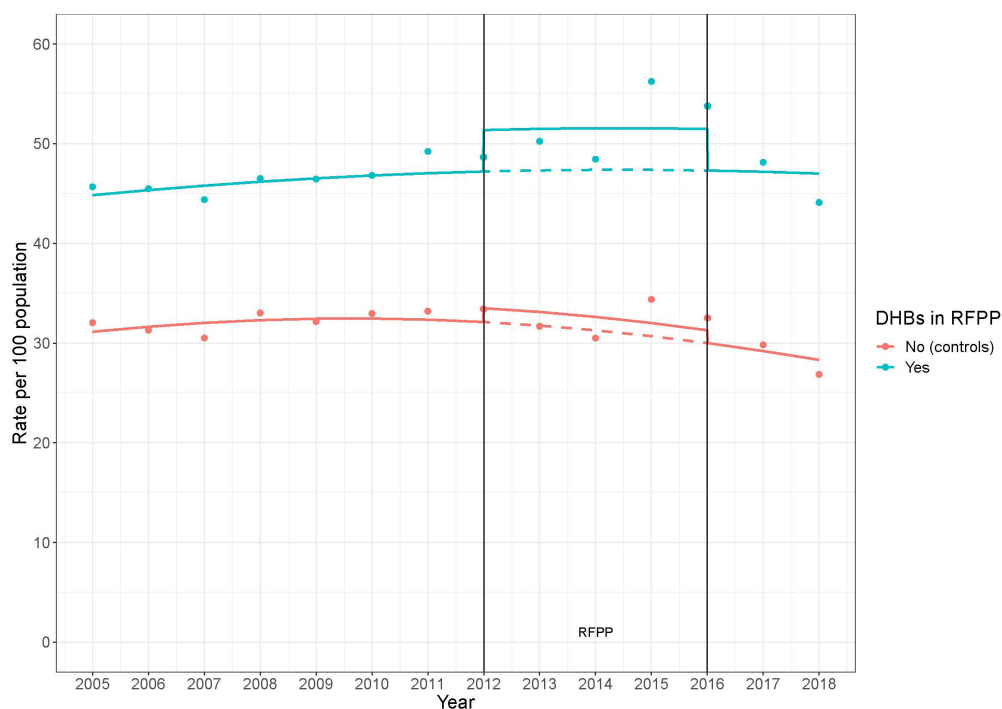
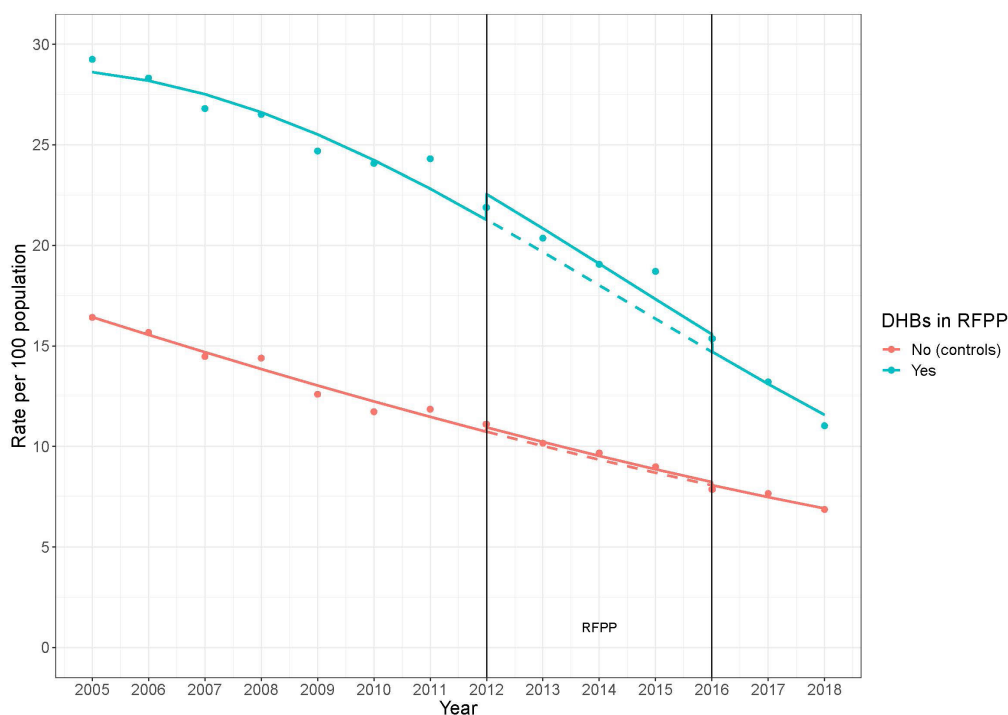


Figure 3: Timeline of amoxicillin dispensing rates among children ≤18 years before (2005–2011), during (2012–2016) and after (2017–2018) the rheumatic fever prevention programme by DHBs participating in the programme and those that were not participating.



*Dotted line indicates the expected (counterfactual) rate.

Figure 4: Timeline of amoxicillin-clavulanate dispensing rates among children ≤18 years before (2005–2011), during (2012–2016) and after (2017–2018) the rheumatic fever prevention programme by DHBs participating in the programme and those that were not participating.



*Dotted line indicates the expected (counterfactual) rate.

dispensing, driven predominately by reduced use of amoxicillin-clavulanate. In Aotearoa New Zealand, total community antibiotic dispensing declined between 2015–2018.¹³ The increase in amoxicillin use is expected, given it was the recommended first-line antibiotic for the RFPP, which intensified detecting and treating GAS pharyngitis.

Tracking the impact of population-wide interventions on antibiotic use and antibiotic resistance is important^{14,15} as increased use of antibiotics has the potential to facilitate resistance not only in the bacteria they are targeting but also in bystander pathogens.¹⁶ Increasing amoxicillin minimum inhibitory concentrations (MICs) have been noted in several studies.^{17,18} A recent clinical report detected a novel GAS mutation in the penicillin binding protein (pbp2x) of isolates collected from two patients with extensive and repeat histories of prior penicillin use, with resultant elevated MICs to ampicillin, amoxicillin and cefotaxime.¹⁹ An additional study was undertaken to determine if the findings of the clinical report were isolated cases or reflective of a broader prevalence of mutations.²⁰ This study found that across a global database of GAS isolates, pbp mutations occurred infrequently with only four of the 9,667 strains containing mutations near transpeptidase active sites of pbp2x or pbp1a.²⁰ While there is no evidence of pbp mutations becoming fixed in the GAS population, further surveillance of local GAS isolates is warranted.

This study provides valuable information on patterns of antibiotic prescribing over an extended timeline, including the period when the RFPP was in operation. However, there are some limitations. While our dataset accounted for 97% of antibiotics dispensed (2012–2016), it did not include supply orders (practitioner and bulk). The

3% of unaccounted antibiotics may have underestimated the rates of amoxicillin dispensing, particularly as the sore throat component of the RFPP uses supply orders to access antibiotics. However, if the marginal amoxicillin rates are not an underestimate, it may indicate that children most at risk of developing ARF were not treated with recommended antibiotics,²¹ with ethnic disparities previously reported.^{13,22} This in part may explain why, despite best efforts, ARF incidence reductions were less than expected (28% from 4.0 per 100,000 to 2.9 per 100,000).¹¹ In addition, we used dispensing rates post- and pre-RFPP intervention to estimate the counterfactual rate of dispensing, which may have led to conservative counterfactual trends—potentially reducing the effect of the RFPP. We would expect that any increase in dispensing during the RFPP would likely linger post-RFPP. Finally, as the RFPP focussed primarily on treating GAS pharyngitis, the study did not include the assessment of trends in dispensing of cephalexin, which is a preferable treatment for skin infections. Given the mounting evidence that GAS skin infections also precede ARF,^{23–25} this may account for disparities in the success of the RFPP, as only some areas treated skin infections.

Conclusions

In summary, during the RFPP an increase in amoxicillin dispensing was seen in regions participating in the programme and to a lesser extent, regions outside of the programme, indicating the programmatic approach overall led to improved adherence to recommended first-line antibiotics. Treating children at risk of ARF presenting with GAS pharyngitis is critical, but potential overuse of amoxicillin should be assessed.

COMPETING INTERESTS

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Appendix

Model formulae

For total penicillin dispensing rates:

$$\text{Log}\left(\frac{Y_t}{P_t}\right) = \beta_0 + \beta_1 T + \beta_2 T^2 + \beta_3 D + \beta_4 I_t + \beta_5 DI_t$$

For amoxicillin and amoxicillin-clavulanate dispensing rates, such that the trend in dispensing rates differs depending on RFPP group:

$$\text{Log}\left(\frac{Y_t}{P_t}\right) = \beta_0 + \beta_1 T + \beta_2 T^2 + \beta_3 D + \beta_4 I_t + \beta_5 DI_t + \beta_6 DT + \beta_7 DT^2$$

Where:

T = time (calendar year)

D = a dummy variable indicating the DHBs participating in the RFPP (coded 1) or not participating (coded 0)

I_t = a dummy variable indicating the RFPP intervention period coded 1, else 0

P_t = population size at time t

Y_t = penicillin dispensing at time t

Appendix Figure 1: Observed incidence rates for penicillin dispensing (all classes) between 2005–2018, stratified by DHB.

