FINAL DRAFT – for "Pharmacoepidemiology and Drug Safety"

FULL TITLE & SHORT TITLE

Measuring change in prescription drug utilization in Australia[†]

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† No conflict of interest was declared.

All costs were covered by the National Prescribing Service Ltd, an independent public company funded by the Australian Government.

KEY WORDS

claims database; longitudinal data; antibiotics; time series analyses; seasonality; regression methods; evaluation

SUMMARY

Purpose The National Prescribing Service Ltd (NPS) aims to improve prescribing and use of medicines consistent with evidence-based best practice. This study compares two statistical methods used to determine whether multiple educational interventions influenced antibiotic prescribing in Australia.

Methods Monthly data (July 1996 to June 2003) were obtained from a national administrative claims database. The outcome measures were the median number of antibiotic prescriptions per 1,000 consultations for each general practitioner (GP) each month, and the mean proportion (across GPs) of each subgroup of antibiotics (e.g. roxithromycin) out of the nine antibiotics having primary use for upper respiratory tract infection. Two methods were used to investigate shifts in prescribing: augmented regression, which included seasonality, autocorrelation and one intervention; and seasonally adjusted piecewise linear dynamic regression, which removed seasonality prior to modelling, included several interventions, a term for GP participation in NPS activities, and autocorrelated errors.

Results Both methods described a similar decrease in rates, with a non-significant increase after the first intervention in April 1999 - the inclusion of more interventions and the GP participation term made no difference. Using roxithromycin as an example of the analyses of proportions, both methods implied that after April 1999 the proportion significantly decreased. The statistical significance of this intervention disappears when all interventions and the GP term are included.

Conclusions The two analyses provide similar conclusions but raise questions about what is the best way to model drug utilization data, particularly regarding whether to include additional intervention terms when they are part of an extended roll-out of related interventions.

INTRODUCTION

The National Prescribing Service Ltd (NPS) aims to improve prescribing and use of medicines consistent with evidence-based best practice. This aim is achieved via a range of social marketing, quality improvement and educational programs which target particular therapeutic topics selected according to information needs identified by general practitioners (GPs) and other predetermined criteria.[1] A mix of interventional strategies has been shown to be most successful for improving physician prescribing.[2] Antibiotics are one drug group of concern in recent years both internationally and in Australia, including inappropriate and unnecessary prescribing contributing to an observed high community use.[3] Formal evaluation of NPS efforts to promote change in drug utilization is an essential component of the NPS programs. The NPS messages that most upper respiratory tract infection (URTI) antibiotics have no or limited role and to use first-line antibiotics preferentially for URTI if an antibiotic is necessary appear to have been successful, with a higher proportion of amoxycillin being prescribed, and declining proportions of cefaclor and roxithromycin being prescribed where an antibiotic was considered appropriate (NPS internal reports). The objective of this report is to compare two multiple regression methods used to determine whether the NPS multiple interventions (the NPS antibiotic program) influenced the volume and profile of antibiotic prescribing for URTI by GPs in Australia.

METHODS

Data

Monthly prescribing data for 84 months (July 1996 to June 2003) were obtained from a national administrative claims database (Pharmaceutical Benefits Scheme, or PBS) maintained by the Health Insurance Commission (HIC). Data were aggregated and de-identified by HIC at the provider level for each month prior to receipt by NPS. Providers are identified by the HIC by major specialty codes, and of particular interest for this study were GPs, that is, those described as “vocationally registered medical practitioner” and “other medical practitioners” (and not any other specialties). GPs were a major focus of NPS educational programs. Only drugs which incur a government benefit are included in the PBS database, and hence less expensive drugs are not well represented (being below the general patient co-payment threshold for most of the population), with coverage for concessional patients being the most complete (because of their much lower co-payment threshold). Moreover, drugs are provided for free, or at lower cost, to the patient if they are dispensed after the patient has incurred a set expenditure in the calendar year, called the “safety net” threshold.[4, 5] While these claims data represent approximately 55% of all primary care antibiotic prescriptions (based on 2000-2002 data for “general antiinfectives for systemic use” ATC group J)[5], it is thought that prescribing patterns are well captured by the available data, since there is no evidence that prescribing decisions for antibiotics for concessional patients would be very different from non-concessional patients. The general limitations of HIC data, including the fact that patient identity (and in particular indication for treatment) is not available, have been discussed elsewhere.[6-8] Original prescriptions (and not repeats), by date of prescribing, were the subject of analysis, since any impact by NPS should be reflected in the prescribing decision of the doctor. Because the NPS programs targeted individual GPs the prescribing data were summarised for analysis at the level of the GP (as medians and means across GPs within each month). Since treatment for URTI was the focus of the NPS antibiotics program, (nine) antibiotics used primarily to treat URTI in primary care were deemed to be relevant (amoxycillin, amoxycillin with clavulanic acid, cefaclor, cefuroxime, clarithromycin, doxycycline, erythromycin, phenoxymethylpenicillin, and roxithromycin). Numbers of consultations by GPs (used in rate calculations) were obtained from the Medical Benefits Scheme (MBS) database, also maintained by HIC. The number of consultations per month per GP was then linked to the PBS data by the anonymous scrambled provider numbers. In addition to the data being de-identified, all investigators were bound by confidentiality provisions of the HIC.

Interventions

The NPS antibiotic program employed a mix of "passive" and "active" interventions, which included messages about the limited indications for antibiotics in URTI (especially having no role in viral illness), as well as appropriate selection of specific antibiotics where antibiotics were indicated. The passive interventions were composed of mail outs to all GPs in Australia (around 20,000) of written materials, and prescribing feedback with clear education messages. The active interventions were those contacts where the GP (actively) participated in either one-to-one educational visiting programs (academic detailing), small group case study discussions (including problem-based learning), or participated in clinical audits or case studies.[1] Over 7,700 GPs "actively" participated in such activities during the study period (each GP having had on average, two contacts with the antibiotics program). The NPS also targeted the community during these years with several national campaigns encouraging symptomatic management of colds rather than the use of antibiotics.[9] The first national NPS program to reduce antibiotic prescribing for URTI in primary care commenced in April 1999. This meant that there were 33 months (of data points) prior to the first intervention, and 51 months in the following four years during which the NPS antibiotic program was repeated annually (at June 2000, April 2001, April 2002, and May 2003).

Providers

GPs with low numbers of consultations but unusually high numbers of scripts will have extremely high prescribing rates as a consequence. To prevent such atypical providers from further distorting already highly skewed prescribing data the most extreme cases were excluded, where an exclusion rule regarded as acceptable was to exclude GPs with less than 150 consultations per year (or less than 13 consultations per month for our monthly data). This resulted in the loss of less than 2% of the GPs who prescribed antibiotics. This rule was adopted from a far more conservative exclusion rule which has been used by several authors where they excluded all GPs with less than 1,500 Medicare services per year.[7, 10, 11] The latter version was not adopted because of concerns about a significant loss of prescribing data.

The providers who contribute monthly data form a dynamic cohort, with a small proportion of GPs dropping in and out each month while others are new GPs and others are retiring from practice. An average of around 20,000 GPs per month were included, while over the 7 years more than 29,600 GPs contributed data. In any month, over 75% of the GPs are from a stable group who have contributed data for all 84 months (a fixed cohort).

Outcome measures

The NPS antibiotic program was targeted primarily towards change in overall rate of antibiotic prescribing and relative prescribing rates of individual antibiotics commonly used for URTI. Of the nine antibiotics regarded as being commonly used in URTI, NPS key messages anticipated that some measurable change might be seen in five (amoxycillin, amoxycillin with clavulanic acid, cefaclor, phenoxymethylpenicillin, and roxithromycin), while the other four (cefuroxime, clarithromycin, erythromycin, and doxycycline) had low use or were new to the market, and little or no change in prescribing was expected. Changes over time were investigated for the proportion of each of the former five antibiotics (relative to all nine).

Two outcome measures were chosen to assess any possible impact of the NPS antibiotic program: (1) prescribing rates, expressed as the median number of antibiotic prescriptions per 1,000 consultations for each GP each month (for all GPs who had at least 13 consultations in that month); and (2) prescribing proportions, expressed as the mean proportion (across GPs) of each subgroup of antibiotics (e.g. roxithromycin) out of all nine antibiotics. Changes in proportions are expected to reflect changes in the GP's prescribing of the most appropriate antibiotic when it had been decided an antibiotic was indicated. Median rather than mean rates were chosen to reduce the influence of outliers (the data being highly skewed) although there was little difference between the two time series (of medians or means). The data expressed as proportions, do not have the same problem of skewness as the rate data, and here the mean was used. Both rates and proportions standardise the data and control for any changes in numbers of GPs over time.

Statistical analysis

The monthly prescription time series data used in this study demonstrate clear seasonal patterns due to both seasonal variation in prescribing (winter peaks for antibiotics) as well as seasonal variation induced by PBS deadlines for the safety net threshold (which can generate more scripts at the end of the calendar year as many patients take advantage of reduced patient contribution to costs).[4, 6, 12, 13] Two regression models were used to investigate possible shifts in prescribing behaviour. Each of the models was a piecewise linear dynamic regression (PLDR) model[14] and included autoregressive error terms and a piecewise linear underlying trend with change points at times of intervention.

The first approach adopted used augmented regression[12] or "harmonic PLDR" (using SAS©, v8.2[15]), which included seasonality (as first and higher order harmonic terms as required), autocorrelated error terms, and one (passive) intervention point[16] (Badcock CA. The impact of the NPS educational program on antibiotic prescribing. Report for NPS, 2004. Unpublished). The second approach adopted was a seasonally adjusted PLDR (using R for Windows, v2.0.1[17]) which had seasonality removed prior to modelling (using a seasonal decomposition procedure known as STL[18]), had several (passive) intervention points, a term for cumulative GP participation in NPS activities (active intervention), and an autocorrelated error term which reflected any other changes in trend (Hyndman RJ, Akram Md. Analysis of NPS antibiotic interventions. Report for NPS, 2004. Unpublished). This latter modelling approach assumed constant seasonality, while the former augmented regression approach allows relatively easy adjustment for irregularities in seasonality by the addition of more terms into the models. For example, there was an unusually high level of antibiotic prescribing in Australia in the winter of 1997 (which may have been a response to an outbreak of influenza B in that year[19]) which the augmented regression models could deal with relatively simply (by inclusion of interaction terms). Both methods have certain appealing features: the augmented regression approach provides the ability to determine the level of (seasonal) modelling one wants to use; while the STL method provides a visual display of the data split into its seasonal and underlying trend components, thus potentially facilitating better understanding of the data. Both approaches assume that the trends would remain the same if there was no intervention effect, and that if there was an effect, a simple change in trend would occur. The modelling of only the first intervention in some models (and not the subsequent “annual” interventions) is consistent with a sustained longevity of educational intervention effects as has been observed for example by May *et al.*[20] The term for active GP participation was a continuous variable which was the cumulative count of GPs over time who participated at least once in any of the four core NPS activities (educational visiting or academic detailing, clinical audits, case studies, and small group case study discussions).

RESULTS

Both regression methods described a similar decrease in median prescription rates over the 84 months (Figure 1.), with a non-significant increase after the first intervention in April 1999 (p=0.10 or 0.30 for the augmented regression and seasonally adjusted PLDR models respectively), while the inclusion of more (passive) interventions and the GP term (active intervention) made no difference to this conclusion (p=0.68 or 0.40) (Table1.). It is not meaningful to compare the coefficients of the two different approaches directly because they occur in the context of different models with other additional different terms. Figure 1. also clearly demonstrates the highly seasonal nature of the data which needs to be catered for in any statistical models fitted to these data.

The difference between pre- and post-intervention for the median prescription rate was not statistically significant (p=0.1 for both methods) indicating that there was no obvious association between the rollout of the NPS antibiotic program and the overall decrease in prescribing of the nine selected antibiotics for URTI.

INSERT FIGURE 1 ABOUT HERE

INSERT TABLE 1 ABOUT HERE

Using the proportion of roxithromycin (out of the nine antibiotics for URTI) as an example of the analyses of proportions (Figure 2.), both regression methods showed that after April 1999 (and consistent with NPS messages) the proportion significantly decreased (p<0.0001) (Table 2.). The significance of this first intervention "disappears" in the regression model which includes all (passive) interventions and the GP term (active intervention) (p=0.63). Again, it is not meaningful to compare the coefficients of the two different approaches. Furthermore, the models for the other four antibiotic proportions tested were also consistent with each other. The proportions tested were for amoxycillin (a significant increase, p= 0.000 or p<0.0001 for the augmented regression and seasonally adjusted PLDR models respectively), amoxycillin with clavulanic acid (no significant change, p=0.99 or 0.40 for the augmented regression and seasonally adjusted PLDR models respectively), cefaclor (a significant decrease, p<0.003 or p<0.0002 for the augmented regression and seasonally adjusted PLDR models respectively), and phenoxymethylpenicillin (no significant change, p=0.28 or 0.30 for the augmented regression and seasonally adjusted PLDR models respectively). Figure 2., like Figure 1. clearly demonstrates the highly seasonal nature of the data which needs to be catered for in any statistical models fitted to these data.

The difference between the yearly percentage changes pre- and post-intervention for the mean proportion of original roxithromycin prescriptions (out of the nine antibiotics for URTI) was statistically significant (p<0.0001 in both models) indicating that there was an association between the rollout of the NPS educational programs and a decrease in the prescribing of roxithromycin (as a proportion of the nine antibiotics for URTI).

INSERT FIGURE 2 ABOUT HERE

INSERT TABLE 2 ABOUT HERE

DISCUSSION

The time series data available for analysis had 84 data points (months), 33 prior to first intervention and 51 after. A rule of thumb is to have at least 60 data points both before and after intervention for proper analysis of a stationary series using traditional time series methods such as autoregressive integrated moving average (ARIMA) methods, although modest changes in utilization levels can often be detected after as few as 7-12 months.[2] Soumerai *et al.*[21] recommend two or more years of follow-up data to ensure capture of the stability of changes in utilization. Pérez *et al.*[22] determined that for their interrupted (and essentially stationary) time series analyses of antibiotic use they would need at least 20 data points pre- and post-intervention, while Wagner *et al.*[23] suggest that as few as 12 data points pre- and post- are sufficient (although this number is not based on estimates of power, and they also suggest that at least 24 monthly data points are required for accounting for seasonally correlated errors). Antibiotics data as reported in the present study are highly seasonal (i.e. not stationary), presenting added complexity for any time series analysis, where the research design needs to be able to determine whether any intervention causes change beyond the underlying trends.[13] The seasonality is due both to more antibiotics being prescribed in the winter months, as well as usage induced by the safety net, while major changes in co-payment can also have significant impact upon the pattern of drug utilization (although there were no major changes during the study period).[4, 6, 12, 13] ARIMA models were previously considered for these antibiotics data but had a major disadvantage of "losing" 12 months data at the beginning of the series for estimation purposes.[16] Both modelling approaches reported in this paper allowed inclusion of all 84 measurement points, each approach dealing with seasonality in a slightly different way.

Although such regression analyses (and ARIMA time series methodologies) provide formal tools for understanding changes in time series data, the real usefulness of any conclusion depends on whether all extraneous factors have been properly accounted for, since there is no certainty that significant changes are due to the NPS antibiotic program. This pre-post study design lacks a comparison (or control) series (none is available for these national data) and as such may be prone to producing biased or misleading results in terms of concluding whether or not the NPS antibiotic program was effective.[21] However, the focus of the paper is on comparing the two regression methodologies, in the hope that any conclusions would be supported by similar findings from the different methodologies (ignoring the lack of any comparison series) as well as providing some understanding of the limitations and best method for evaluation of multifaceted repeated interventions. The major difference between the approaches is in how they each deal with the underlying cycle of seasonality. A case study of events which led to changes in the use of the antibiotic flucloxacillin in Australia illustrates the potential complexity of the role of unknown extraneous factors, and how a "simple" time series analysis (without any comparison series) may well lead to erroneous conclusions because certain factors and their inter-relatedness were not taken into account.[24] In the present study for example, the models have not considered the incidence of URTI in Australia during the same time period.[25]

The modelling of one intervention point (rather than several) is consistent with an assumption of a cumulative effect of multiple interventions (which prevent regression back to the previous state)[20], and having just one intervention point in the models did suggest an intervention effect. The inclusion of subsequent interventions in the models changed the significance of the initial intervention toward the null because each test as a consequence uses fewer points of data from the time series. Consideration of several interventions in this way can erroneously suggest that nothing has happened in terms of statistical significance (by naïve inspection of their individual coefficients) when there is in fact an overall change in prescribing (which requires these several interventions to be tested as a group). Also, the lack of sufficient time series data points makes it difficult to properly understand how each intervention might build on the previous one(s). Furthermore, these so-called multiple interventions are not actually a set of true discrete interventions, but reflect major peaks in activity in the NPS antibiotic program, which was spread out over time with different divisions of general practice commencing program activities at different times and with different types of activity overlapping.

One potential criticism of the augmented regression models which contain explicit terms to deal with seasonality is that they have been over-parameterised and this may decrease the sensitivity of such models. However, given that both modelling approaches lead to the same conclusion, it is not clear whether this concern is problematic. Furthermore, such augmented regression models do have the advantage of allowing relatively easy modelling of perturbations to the regular seasonality such as that possibly due to the 1997 influenza B outbreak[19] while the number of parameters in the model is also explicit.

Another criticism of both models is that they assume an underlying linear trend and a simple shift in prescribing after intervention (i.e. change in trend). Also, neither model has allowed for any lag in change of prescribing, which may take several months to occur, and is further complicated by different rates of program uptake by different divisions of general practice. More realistic models might allow for the intervention effect to decay over time. Preliminary analyses with other HIC drug utilization data have in fact supported the notion that such decay models may provide a better and more informative description of such data. Difficulties include knowing what is an appropriate amount of decay to use in a model, as is how to separate decay from seasonal variation. If there is just one intervention with sufficient data points post intervention (at least 12 months), the data may be used to estimate the decay term, but if there are several interventions relatively close together, this approach is not possible, and it is necessary to estimate the decay terms based on other research into prescribing behaviour and learning theory (Hyndman RJ. Statistical models for intervention analysis of therapeutic prescription practice. Report for NPS, 2004. Unpublished). However, there is a lack of informative literature in this area on which to base such estimates. For example, while a few studies have shown educational intervention effects (including ongoing education) on drug utilization to persist for up to five years[20, 26, 27], they do not explicitly consider the half-lives or persistence (in quantitative terms) of these effects. One study which assessed the effect of educational reminder messages over one year (on primary care radiology referrals - and not drug utilization) did explicitly consider whether decay occurred during the year of the study and found no evidence for any decay.[28]

A strength of this study is that the data were considered at the level of the provider (in terms of medians and means over individual provider data each month) rather than monthly aggregate data, since intervention was at the provider level. In some situations it is thought that analyses of monthly aggregate data may be prone to bias.[21] Analysis at provider level takes into account any changes in the GP workforce and any changes in patient presentations, and enables control of individual provider-level covariates.[29] However, a proper analysis of data at the provider level would require looking at change at the level of each GP and then to summarise this, using random effects models. This alternate approach was considered but not pursued because of complications (non-convergence) arising due to the complexity of the models (Badcock CA. The impact of the NPS educational program on antibiotic prescribing. Report for NPS, 2004. Unpublished).

The use of median rates rather than mean rates can be problematic, because median values can be zero (over some or many months) for drugs with low prescription rates. In this case, means or trimmed means provide a more reliable statistic for modelling – where trimming the largest 5% of values may be appropriate. The use of median proportions induces horizontal segments in the time series if the time series crosses fractional values such as 1/2, 1/3, 1/4 etc. because data clusters at these values if the data for that month is around that range. However, proportion data do not have the wide variability which rate data have, and so the use of mean proportions provides an appropriate description of the data.

In addition to these possibly problematic mathematical properties of the outcome variables there is also the question of whether they provide the most appropriate measures to capture any impact of the NPS antibiotic program. Rates and proportions were chosen because they standardise the data and control for any changes in numbers of GPs over time. However, the use of proportions as a valid outcome measure may have yet other problems not addressed directly by this work. First, the approach presumes that low prescribers and high prescribers behave the same (eg. 1 script in 5 prescribed is deemed the same as 10 in 50, while the latter prescriber is much more active). And second, changes in proportions can reflect changing denominators as well as changing numerators and this may invalidate any simple interpretation. Nevertheless, Robertson *et al.*[7] concluded that ratios (which reflect choice of agent within a drug class) may be more valid prescribing measures than rates, particularly when data capture is incomplete (as happens with HIC data because of the co-payment system), since ratios are less affected by changes in data capture over time, than are prescribing rates (which reflect volume of prescribing as estimated by the HIC data).

The fact that active GP involvement in NPS programs was not detected as a significant contributing factor in the regression models does not necessarily imply that active participation is not important. It is quite possible that our method of accounting for (cumulative) GP participation was not the most appropriate way of doing this. The models assume that passive intervention and active intervention are independent terms when in fact they would be highly correlated. Also, the possible issue regarding proportions, where the prescribing for all providers (having different degrees of activity) is nevertheless given the same weight in the analyses, may contribute to no effect of GP involvement being detected.

The two regression analyses of monthly time series drug utilization data reported in this paper provide similar general conclusions but raise questions about what is the most appropriate way to model drug utilization data, particularly regarding whether or how to include additional intervention terms when they are part of an extended roll-out of related interventions (the NPS antibiotic program), as well as what is the most meaningful outcome variable to consider.

ACKNOWLEDGEMENTS

We thank the Health Insurance Commission for provision of data. We also thank Dr Lisa Pont and Dr Stephen Kerr formerly of NPS, and Md Akram of Monash University, who contributed to parts of this work, and Emma Slaytor for comments on the manuscript. Helpful discussions on various aspects of this work were also had with Neil Donnelly, Dr Timothy Dobbins, Dr Elizabeth Roughead, Dr Jane Robertson, and Dr Tim Driscoll.

KEY POINTS *(up to 5 bulleted messages)*

- Australia has a unique national administrative claims database derived from pharmacy claims which describes patterns of drug utilization for subsidised prescription medicines.
- Pharmacoepidemiology research which uses regression methods to analyse time series data can provide useful quantitative interpretation of possible changes in prescribing behaviour resulting from interventions.
- Specification of several intervention points in regression models may be misleading by inferring apparent non-significance for each intervention, when in fact there is an overall effect.
- Over-simplified (time series) analyses (especially those lacking a comparison or control group) may lead to misleading conclusions because the full complexity of the prescribing environment has not been adequately taken into account.
- A proper understanding of what the outcome measures actually measure is critical, since changes over time may occur due to unanticipated (or not well understood) properties of such variables, and not the interventions or factors of immediate interest.

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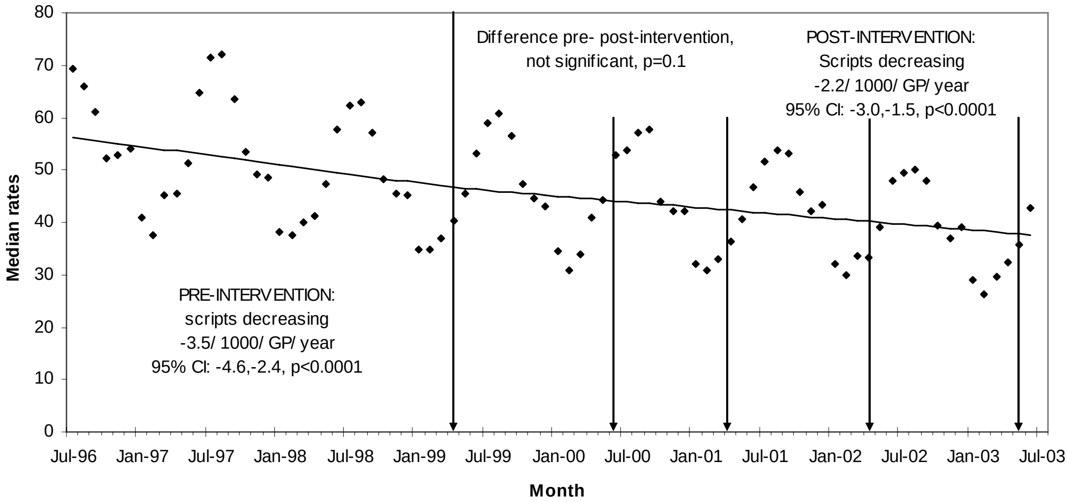
figure pasted from MS Office Excel 2003 as an "Enhanced Metafile")

Figure 1. Median rates: number of original scripts (for nine antibiotics for URTI) /1000 consultations /GP /month*



* Fitted trends based on single intervention at April 1999. All five "passive" interventions are displayed - at April 1999, June 2000, April 2001, April 2002, and May 2003.

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Table 1. Coefficients from models of antibiotic median rates*

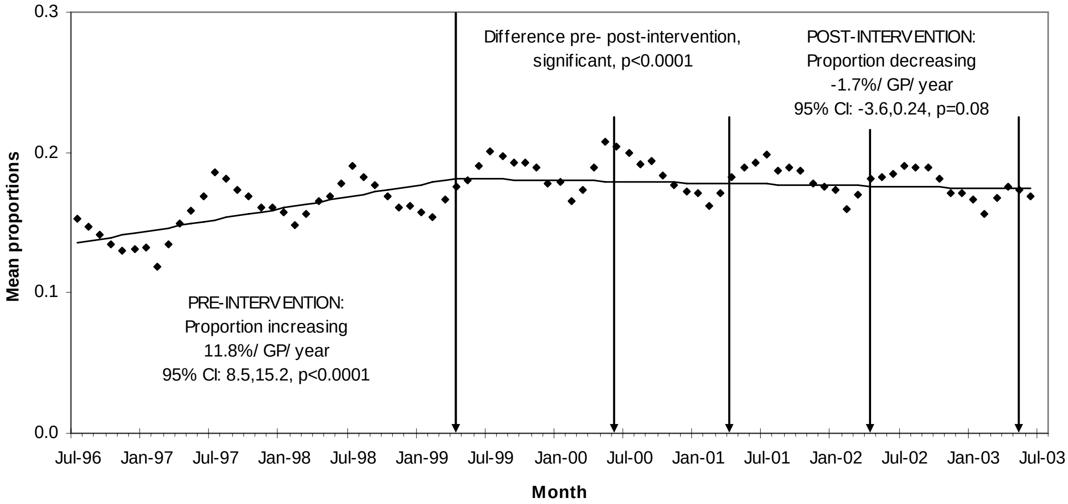
Regression Parameter	Model 1	Model 2a	Model 2b	Model 2c
Intercept	56.50	55.56	55.59	55.68
p-value	*0.000*	*0.000*	*0.000*	*0.000*
Initial trend	-0.29	-0.25	-0.25	-0.26
p-value	*0.000*	*0.000*	*0.000*	*0.000*
Interven 1	0.11	0.07	0.08	0.22
p-value	*0.100*	*0.295*	*0.680*	*0.400*
Interven 2	-	-	-	-0.07
p-value	-	-	-	*0.812*
Interven 3	-	-	-	0.10
p-value	-	-	-	*0.767*
Interven 4	-	-	-	-0.24
p-value	-	-	-	*0.429*
GPs	-	-	-0.038	-0.58
p-value	-	-	*0.974*	*0.657*

* For nine antibiotics for URTI. Terms of major interest only are presented. Terms dealing with seasonality, autocorrelation and residuals are not presented to simplify presentation.
Model 1 is from augmented approach.
Model 1 has one intervention (Interven 1). Seasonality, autocorrelation and error were dealt with by other (harmonic) terms not presented here.
Models 2a,b,c are from seasonally adjusted PLDR approach.
Model 2a has one intervention. Seasonality was removed prior to modelling using STL method, and terms for autocorrelation and error are not presented here.
Model 2b has one intervention and GP contribution.
Model 2c has four interventions (spaced about a year apart) and GP participation (the fifth intervention is excluded because we had only one month of data after that time).

(figure formatted to journal requirement of two column width of 155mm -

figure pasted from MS Office Excel 2003 as an "Enhanced Metafile")

Figure 2. Mean proportion of original scripts of roxithromycin (over nine antibiotics for URTI) /GP / month*



* Fitted trends based on single intervention at April 1999. All five "passive" interventions are displayed - at April 1999, June 2000, April 2001, April 2002, and May 2003.

(table formatted to journal requirement of one column width of 75mm)

Table 2. Coefficients from models of roxithromycin mean proportions*

Regression Parameter	Model 1	Model 2a	Model 2b	Model 2c
Intercept	13.53	13.41	13.41	13.63
p-value	*0.000*	*0.000*	*0.000*	*0.000*
Initial trend	0.93	0.15	0.15	0.13
p-value	*0.000*	*0.000*	*0.000*	*0.000*
Interven 1	-1.09	-0.18	-0.18	-0.04
p-value	*0.000*	*0.000*	*0.001*	*0.634*
Interven 2	-	-	-	-0.19
p-value	-	-	-	*0.060*
Interven 3	-	-	-	0.14
p-value	-	-	-	*0.224*
Interven 4	-	-	-	-0.16
p-value	-	-	-	*0.111*
GPs	-	-	-0.001	-0.09
p-value	-	-	*0.997*	*0.766*

* Over nine antibiotics for URTI. Terms of major interest only are presented. Terms dealing with seasonality, autocorrelation and residuals are not presented to simplify presentation.
Model 1 is from augmented approach.
Model 1 has one intervention (Interven 1). Seasonality, autocorrelation and error were dealt with by other (harmonic) terms not presented here.
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Model 2a has one intervention. Seasonality was removed prior to modelling using STL method, and terms for autocorrelation and error are not presented here.
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