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FACULTY OF SCIENCES

Master of Statistics: Biostatistics

Masterproef

adaptive change-point mixed models to data on outpatient antibiotic use in Europe

Promotor :
Prof. dr. Niel HENS

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Master Thesis nominated to obtain the degree of Master of Statistics , specialization Biostatistics

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Abstract

Antibiotics are powerful medicines that fight bacterial infections. Used properly, antibiotics can save lives. There have been various attempts to educate the public about appropriate use of antibiotics through public campaign. Because the resistance to antibiotics is a major Europe and global public-health problem and antibiotic use is being increasingly recognized as the main selective pressure driving this resistance.

In this report, total outpatient antibiotic use (J01) and outpatient penicillin use (J01) data from 27 European countries during 1997 to 2009 were used for further analysis. These data were collected by the European Surveillance of Antimicrobial Consumption (ESAC) project. The antibiotic use data were expressed as the number of defined daily doses (DDD) per 1000 inhabitants per day (DID).

The main objective of the study is to develop an appropriate statistical model and to identify possible change points while accounting for country-specific global use as well as seasonal effect. In order to achieve the goal of the study adaptive change point mixed model is proposed.

Gibbs sampling is used for inference. Trace plot, Brooks-Gelmen-Rubin (BGR) diagnostic plot, and Geweke diagnostics plot used to assess the convergence of the model. Moreover, DIC were used as model selection tool.

In conclusion, addition to the trend over time and seasonal variation, two change points were found in total outpatient antibiotic use data and one random change point was found in penicillin use data. These change points were found in the period when there were public campaigns.

Keywords: antibiotic use, campaign, change point model, linear trend in time, seasonal variation, convergence.

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List of Abbreviations

ATC: Anatomical Therapeutic Chemical

BGR: Brooks-Gelmen-Rubin

DDD: Defined Daily Dose

DID: DDD per 1000 inhabitants per day

ECDC: European Centre for Disease Prevention and Control

EAAD: European Antibiotic Awareness Day

ESAC: European Surveillance of Antimicrobial Consumption

EU: European Union

MCMC: Markov Chain Monte Carlo

MH: Metropolis-Hastings

PID : Packages per 1000 inhabitant per day

PSRF: Potential scale reduction factor

WHO: World Health Organization

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1. Introduction

Antibiotics are powerful medicines that fight bacterial infections. Used properly, antibiotics can save lives. They either kill bacteria or keep them from reproducing (Midline Plus). The most common misuse and abuse of antibiotics are: physicians prescribing antibiotics for viral infections and not finishing the full dosage of the antibiotic (American Collage of Physician). The antibiotic misuse sometimes called antibiotic abuse or antibiotic overuse is a contributing factor to the creation of multidrug-resistance bacteria, informally called "super bugs": relatively harmless bacteria can develop resistance to multiple antibiotics and cause life-threatening infections (Harrison and Svec, 1998).

Resistance to antibiotics is a major Europe and global public-health problem and antibiotic use is being increasingly recognized as the main selective pressure driving this resistance. The increase in resistance rate of many pathogens to currently most available antibiotics has now been recognized as a universal health hazard and potentially life threatening problem. A large number of studies strongly suggested that this increase is directly related to the actual use of antibiotics (Goossens *et al*., 2005; Malhotra-Kumar *et al*., 2007; Costelloe *et al*., 2010). In high-income countries the majority of antibiotics for use in human beings are prescribed in the ambulatory-care setting for upper respiratory tract infections; a substantial proportion of these prescriptions are unnecessary (Gonzales *et al*., 2001).

There have been various attempts to educate the public about appropriate use of antibiotics. In November 2001, the European Union (EU) Health Ministers adopted a Council Recommendation on the prudent use of antimicrobial agents in human medicine (Council of the European Union) which stated that EU Member States should inform the general public of the importance of prudent use of antimicrobial agents by, in particular, raising awareness of the problem of antimicrobial resistance and encouraging realistic public expectations for the prescription of antimicrobial agents.

According to Huttner *et al.* (2010), during 2001-2006 there were national campaigns from simple low cost internet to expensive mass-media in many European countries at least once (for example in Belgium, France, Germany, Greece, Luxemburg, Norway, Portugal, Spain and United Kingdom). The goals of the campaigns were antibiotics awareness, prudent use of antibiotics and about not taking antibiotics for viral infections such as colds and flu.

In Belgium and France, national awareness campaigns to educate the public and primary care prescribers about appropriate outpatient antibiotic use have successfully resulted in a decrease in antibiotic prescriptions (Bauraind *et al*., 2004; Coenen *et al*., 2008; Goossens *et al*., 2008; Earnshaw *et al*., 2009). Additionally, in both countries, the savings from reductions in antibiotic expenses for the national insurance system as a result of the public campaign largely outweighed the cost of the public campaign itself (Goossens *et al*., 2006; Coenen *et al*., 2007). The success of these campaigns stimulated a European initiative coordinated by the European Centre for Disease Prevention and Control (ECDC), and named "European Antibiotic Awareness Day" (EAAD), to take place each year on 18 November since 2008. The focus of the first EAAD campaign was about not taking antibiotics for viral infections such as colds and flu (Earnshaw *et al*., 2009).

The field of drug utilization research has attracted increasing interest since its infancy in the 1960s. At a symposium in Oslo in 1969 entitled "The Consumption of Drugs", it was agreed that an internationally accepted classification system for drug consumption studies was needed. Then, Norwegian researchers developed a system known as the Anatomical Therapeutic Chemical (ATC) classification. In the ATC classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels. The drugs are divided into fourteen anatomical main groups (1^{st} level), with therapeutic subgroups (2^{nd} level). The 3^{rd} levels are pharmacological subgroups; the 4^{th} levels are the chemical subgroups and the 5^{th} level is the chemical substance (WHO Collaborating Center for Drug Statistics Methodology).

In order to measure drug use, it is important to have both a classification system and a unit of measurement. To deal with the objections against traditional units of measurement, a technical unit of measurement called the Defined Daily Dose (DDD) to be used in drug utilization studies was developed. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. A DDD will only be assigned for drugs that already have an ATC code. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations. The purpose of the ATC/DDD system is to serve as a tool for drug utilization research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels (WHO Collaborating Center for Drug Statistics Methodology).

Use data were expressed in DDD per 1000 inhabitants per day (DID) and packages per 1000 inhabitant per day (PID). In most of the participating countries, the denominator was based on the World Health Organization (WHO) mid-year population (WHO Regional Office for Europe).

The features of antibiotic use data has the non-linearity of the relationship between response (DID or PID) and time (quarterly collected), in longitudinal data context. Thus, they require a careful modeling strategy that compromises both best fit of the data and also delivering the seasonally interpretability of the parameters of interest. So that, in such situations, a non-linear mixed model was appropriate. Moreover, because of some campaign and some policies change, the overall trend would change after some point of time. Thus, the adaptive change point mixed model was proposed. The models are implemented in R using R2WinBUGS package.

The main objective of the study is to develop an appropriate statistical model and to identify possible change points while accounting for country-specific global use as well as seasonal effect.

In Section 2, the relevant background literature related to an antibiotic use and change point model are presented. In Section 3, the data sets are described. In Section 4, the statistical methodology will be elaborated, including adaptive change point model, prior specification, Gibbs sampling for Bayesian inference, convergence of Markov chain and model selection. In section 5, the result for total outpatient antibiotic use (J01) and outpatient penicillin use (J01C) are presented. And finally, discussions and conclusions are presented in Section 6.

2. Literature Review

In this section of literature review, literatures related to total outpatient antibiotic use, outpatient penicillin use and random change point models are discussed.

Goossens *et al*. (2005) investigated total outpatient antibiotic use in Europe that provided internationally comparable distribution or reimbursement data, between Jan 1, 1997, and Dec 31, 2002 using DID measurement. They showed that the use of antibiotics in primary care in Europe varied by a factor of 3.2 between 28 countries, with highest (32.2 DID) use in France and lowest (10.0 DID) use in the Netherlands. They also noted seasonal fluctuation with heightened winter peaks in countries with high yearly use in antibiotic. In addition, they showed higher rates of antibiotic resistance in high consuming countries, probably related to the higher consumption in Southern and Eastern Europe than in northern Europe.

Adriaenssens *et al*. (2011) described and analyzed the statistical trend of total outpatient antibiotic use in Europe from 1997 to 2009 using longitudinal data analysis. They showed that the total antibiotic use in 2009 varied by a factor 3.8 between 33 countries, with highest (38.6 DID) use in Greece and lowest (10.2 DID) use in Romania. In addition, they found significant increase in total outpatient antibiotic use, as well as significant seasonal variation, which decreased over time from 1997 to 2009.

Versporten *et al*. (2011) also described and analyzed the statistical trend of outpatient penicillin use in Europe from 1997 to 2009 using longitudinal data analysis. They showed that outpatient penicillin use in 2009 varied by a factor 3.8 between 33 countries, with highest (16.08 DID) use in France and lowest (4.23 DID) use in Russian Federation). They also found a significant increase in total outpatient antibiotic use, as well as significant seasonal variation. They also noted that penicillin represented the most widely used antibiotic subgroup.

Likewise, the longitudinal data analysis of the pharmacological subgroups, which are the therapeutic subgroup of J01, were done in different literatures. Such as J01M Quinolone (Adriaenssens *et al*., 2011), J01D Cephalosporin (Versporten *et al*., 2011), J01A Tetracycline, J01E Sulfonamides and J01X other antibacterials (Coenen *et al*., 2011), and J01A Tetracycline (Minalu *et al*., 2011). The results of those literatures showed either increase or decrease of the overall trend.

However, those results could cover the effect of campaign and the policy change. Thus, the change point model is appropriate. The general form of the change point problem is to determine the unknown locationτ, based on an ordered sequence of observation $x_1,\ x_2, \dots, x_n$ such that the two group observation $x_1,\ x_2, \dots, x_\tau,\ and\ x_{\tau+1}, \dots, x_n$ follow distinct models, the index of ordering frequently refers to time but in general, it can be associated with any variable (Armitage, P., and Colton, T. (editors), 1998). So that the purpose of the change point model is to detect breaks in an event window.

Random change point models have previously been used in several bioscience applications. These include studies of progression of HIV infection using CD4 T-Cell numbers (Lange *et al*., 1992; Kiuchi *et al*., 1995), development of prostate specific antigen (PSA) levels as a marker for prostate cancer (Slate and Turnbull, 2000) and cognitive function in old age (Hall *et al*., 2003). Moreover, adaptive change point mixed models has been applied to data on outpatient Tetracycline use in Europe which is under revision (Minalu *et al*., 2011).

Due to the nonlinearity of the response function in the random change point model, the likelihood does not have a closed-form expression, which complicates maximum likelihood estimation. Possible solutions to this problem include approximate likelihood methods and sampling-based inference methods (Dominicus *et al*., 2008).

Hall *et al*. (2003) compared the Bayesian approach with the profile likelihood approach for modeling cognitive function over time, and pointed out that the Bayesian method has an advantage over the profile likelihood method in that it does not require all subjects to have the same change-point.

Therefore, in this paper the adaptive Bayesian change point mixed model is proposed, where the change points are data-driven and can vary across countries.

3. The antibiotic Use Data

3.1. Total outpatient antibiotic Use Data (J01)

The Antibacterial for systemic use (ATC code J01) is the total outpatient antibiotic use, which is the therapeutic subgroup of the anatomical group J (Anti-infective for systemic use). Quarterly data on total outpatient antibiotic use were collected by the European Surveillance of Antimicrobial Consumption (ESAC) project for the period 1997–2009 from 27 European countries. Antibiotic use data is expressed as the number of defined daily doses (DDD - a standardized consumption measure) per 1000 inhabitants per day (DID). This data set consists of 1404 observation. However, some profiles start later in time and others show intermediate missing parts. In total 420 (30%) observations are missing. The country with the least number of observations is Cyprus (with four observations). Missing at random (MAR) is assumed, and the analysis was based on all available data.

Some countries were only able to provide total care (TC) data that is including both ambulatory and hospital care data, for example Cyprus and Lithuania. Greece provided TC data for 2004 – 08, Bulgaria and Iceland up to 2005 and Estonia for 2001. These data were, however, also included, because ambulatory care use data represent 90% of the total use (Goossens *et al*., 2005).

3.2. The outpatient Penicillin use data (J01C)

The beta-lactam antibacterial penicillin (J01C) is a pharmacological subgroup of the therapeutic group J01. The quarterly data was collected also by ESAC like total outpatient antibiotic use data with the similar general information.

4. Methodology

4.1. Exploratory data analysis

Explanatory data analysis plays an enormous role to get insight about the data set, and even used as vehicle for further statistical analysis. Country profile plot for antibiotic use in DID was used to see the pattern of the outpatient antibiotic use on a country specific level.

In section 4, methodology, the term "antibiotic use" is used as a collective name for both "total outpatient antibiotic use" and "outpatient penicillin use"

4.2. Adaptive change point models

Country profile plots for antibiotic use in DID (Figures 2 and 9) show the variability across repeated measurements from the same country as well as variability between countries. In addition to that, it shows a non-linear pattern of seasonal variation in each year. Thus, the nonlinear mixed model with sinusoidal component over time to account for seasonal variation is introduced. In addition to this, to address the effect of campaigns and policy changes, the nonlinear mixed model is extended by including the change point components. All models are fitted in a Bayesian paradigm.

4.2.1. Nonlinear mixed model

The following nonlinear mixed model is proposed to the antibiotic use in DID (Y_{ij}) for the country i $(i = 1, \dots, 27)$ at time points t_{ij} $(j = 1, \dots, 52)$. Time, $t_{ij} = 1$ correspond to the start of the study for the i^{th} country (first quarter of 1997).

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \Big((A_0 + a_{0i}) + (A_1 + a_{1i})t_{ij}\Big) sin\big(\omega t_{ij} + \delta\big) + \varepsilon_{ij} \qquad (1)$$

$$b_i \sim N(0, D)$$

$$\varepsilon_{ij} \sim N(0, \sigma^2)$$

where $\beta = (\beta_0,\ \beta_1,\ A_0,\ A_1,\ \delta)$ is a vector of fixed effects, β_0 is the global intercept, β_1 the global slope describing the marginal linear time trend, A_0 is the fixed amplitude of the seasonal variation, A_1 is the amplitude varying over time, ω (in radians) the angular frequency that is a known constant ($= 2\pi/P$ where *P(=4)* is the period or the length of each cycle for the sine curve which means the number of seasons in each year), δ is the phase shift which is unknown parameter, $b_i = (b_{0i},\ b_{1i},\ a_{0i},\ a_{1i})$ is the country-specific vector of random effects

where b_{0i} is the country-specific random intercept, b_{1i} is the country-specific random slope for time, a_{0i} is the country-specific random slope for amplitude and a_{1i} is the country specific damping effect on the seasonal variation. The matrix D is a general covariance matrix with elements $d_{ij} = d_{ji}$. ε_{ij} is the unexplained error term, usually assumed independent and normally distributed with mean zero and variance σ^2.

4.2.2. Adaptive change point model

The general mixed model with country specific mean can be written as

$$Y_{ij} = \mu_i(t_{ij}) + \varepsilon_{ij}, \;\; i = 1, 2, \dots, N; \;\; j = 1, 2, \dots, n_i$$

$$\mu_i(t_{ij}) = \mu_i^T(t_{ij}) + \mu_i^S(t_{ij}) \quad (2)$$

where Y_{ij} is antibiotic use in DID for country i at time point t_{ij}, $\mu_i^T(t_{ij})$ is the trend component, $\mu_i^S(t_{ij})$ is the seasonal component and ε_{ij} is the measurement error. The country specific mean components $\mu_i^T(t_{ij})$ and $\mu_i^S(t_{ij})$ are modeled as:

$$\mu_i^T(t_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \mu_i^{CP}(t_{ij}) \quad (3.a)$$

$$\mu_i^S(t_{ij}) = \Big((A_0 + a_{0i}) + (A_1 + a_{1i})t_{ij}\Big) sin\big(\omega t_{ij} + \delta\big), \quad (3.b)$$

where $\mu_i^{CP}(t_{ij})$ in (3.a) is a change point component given by

$$\mu_i^{CP}(t_{ij}) = \sum_{k=1}^{K}(\beta_{(k+1)} + b_{(k+1)i})(t_{ij} - K_{ki})_+ \quad (4)$$

where K is the unknown number of change points; $(t_{ij} - K_{ki})_+ = max(t_{ij} - K_{ki},\ 0)$ is $t_{ij} - K_{ki}$ if t_{ij} is greater than or equal to K_{ki}, zero otherwise. $K_{ki} = C_k$ or $K_{ki} = C_{ki}$ or $K_{ki} = C_k + c_{ki}$ where $1 \le K_{ki} \le 52$; C_k denotes a global change point, C_{ki} is a country specific random change point and c_{ki} is a country specific random change point effect, it is normally distributed with mean zero and the variance $\sigma_{c_{ki}}^2$. If $\mu_i^{CP}(t_{ij}) = 0$, then there are no change points and the model reduces to model (1).

Substituting equation (3.a), (3.b) and (4) in equation (2) yields the model

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \sum_{k=1}^{K}(\beta_{(k+1)} + b_{(k+1)i})(t_{ij} - K_{ki})_+ + \Big((A_0 + a_{0i}) + (A_1 + a_{1i})t_{ij}\Big) sin\big(\omega t_{ij} + \delta\big) + \varepsilon_{ij} \quad (5)$$

where $\beta = (\beta_0,\ \beta_1,\ \beta_{(k+1)},\ C_k,\ A_0,\ A_1,\ \delta)$ is a vector of fixed effects, β_1 the global slope describing the marginal linear time trend before the first change point, $\beta_{(k+1)}$ is the difference in the linear time trend before and after the change point. $b_i = (b_{0i},\ b_{1i},\ b_{(k+1)i},\ c_{ki},\ a_{0i},\ a_{1i})$ is the q-dimensional vector of country specific random effects and is normally distributed with mean vector zero and covariance matrix D. b_{1i} is the country-specific random slope for time before the first change point and $b_{(k+1)i}$ is the country-specific random difference in the linear time trend before and after the change point. Random effects for global level of use, the trend effects, the amplitude of the seasonal effect, and the location of the change point are used to account for heterogeneity across the countries.

A graphical representation of the model with the meaning of fixed effect parameter is given in Heuristic figure (Figure 1).

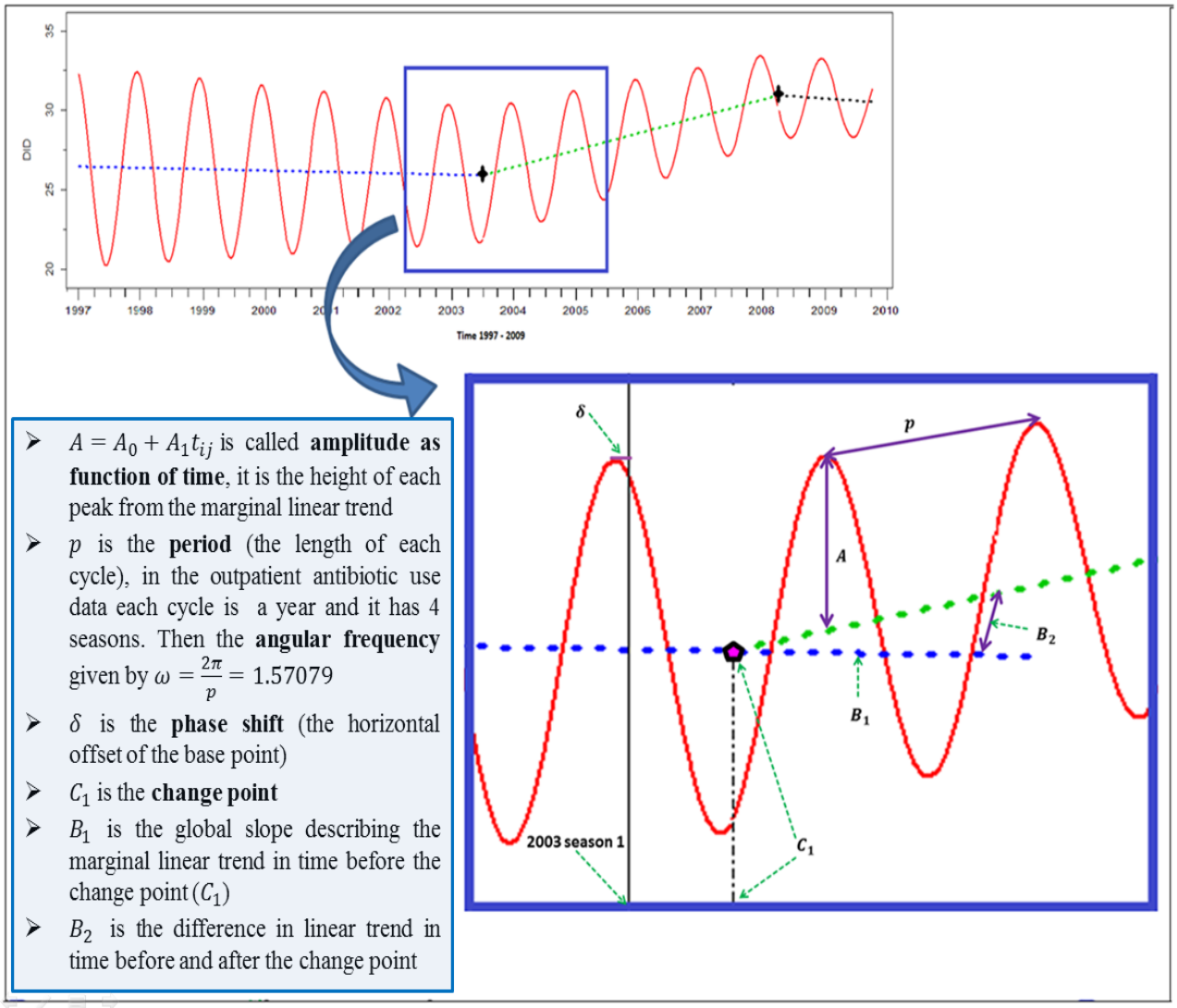


Figure1. *Antibiotic use data*. The heuristic figure for interpretation of model parameters

4.2.3. Prior Specification

The unique features that make the Bayesian paradigm attractive is, it allows for incorporation of prior knowledge in a statistical analysis. In contrast, its critics the necessity of specifying a prior makes the Bayesian approach unsuitable for research because of the introduction of subjectivity. The following non-informative prior distributions were used for the fixed effects. This prior is a function which is used in place of a subjective prior distribution when little or no prior information is available.

$\beta_0,\ \beta_1,\ \beta_{(k+1)},\ \ A_0,\ A_1,\ \delta \sim Normal(0,\ 1000)$, independent where $k = 1, \dots, K,$

The term "non-informative" is used to connote the lack of subjective beliefs used in formulating such a prior. Non-informative is better called weakly informative prior. Thus, loosely speaking the non-informative prior in the normal case is a normal distribution with a very large variance.

$C_k \sim uniform(a, b)$, independent where $1 \leq a < b \leq 52$

For random effects, a multivariate normal prior was used.

$b_i \sim MVN(0, D)$ where D is the variance covariance matrix for random effects.

$D \sim IW(\Psi, \nu)$ where Ψ inverse scaled pxp matrix and $\nu > p - 1$ degree of freedom.

Inverse Wishart distribution (IW) used as the conjugate prior for covariance matrix of a multivariate normal distribution. However, because of no convergence, some random effects used a normal prior separately.

$b_{1i} \sim Normal(0,\ \sigma^2_{b_1})$

$b_{(k+1)i} \sim Normal(0,\ \sigma^2_{b_{(k+1)}})$

$a_{1i} \sim Normal(0,\ \sigma^2_{a_1})$

Conjugate prior distributions are restrictive in their ability to represent the prior knowledge. Extending the flexibility in conjugate priors can be done by giving the parameters of the conjugate also a prior distribution. Thus, the hyperparameter in the prior distribution were chosen. An independent inverse gamma distribution with shape parameter $\alpha(= 0.001)$ and a scale parameter $\beta(= 1000)$ was used for the variance parameters.

$\sigma^2_{b_1}, \sigma^2_{b_{(k+1)}}, \sigma^2_{a_1}, \sigma^2_{\varepsilon} \sim IGamma(0.001,\ 1000)$, independently

where $V \sim IGamma(\alpha,\ \beta)$ that means $1/V$ has the gamma distribution, $1/V \sim IGamma(\alpha, \beta^{-1})$ with mean α/β and variance α/β^2.

4.2.4. Gibbs Sampling for Bayesian Inference

Analytical calculation of the posterior distribution and its summary measure is prohibitive because of the difficulty in determining the integration constant. Calculating the integral using numerical integration method is a practical alternative if only a few parameters are involved. Nevertheless, it becomes (nearly) impossible for problems that are encountered in real life application where the number of dimensions is often high.

An alternative to numerical integration is to take a Bayesian perspective and to perform Markov Chain Monte Carlo (MCMC) simulation to approximate the posterior distribution of the parameter. A Gibbs sampler (Geman Geman, 1984; Gelfand and Smith, 1990) to construct Markov chains was used. The Gibbs sampler (Gelman et a., 2004; Chib and Greenberg, 1995) is a special case of the Metropolis-Hastings (MH) algorithm where by the d sub steps of Gibbs sampling procedure can be seen as MH-algorithms with acceptance rate equal to 1.

Given a starting position $\boldsymbol{\theta^0} = (\theta_1^0, \theta_2^0, \dots, \theta_d^0)^T$, the multivariate version of the Gibbs sampler has the following iterative scheme. At iteration $(k+1)$

1. Sample θ_1^{k+1} from $p(\theta_1|\theta_2^k,\ \theta_3^k, \dots, \theta_{d-1}^k,\ \theta_d^k,\ \boldsymbol{y})$
2. Sample θ_2^{k+1} from $p(\theta_2|\theta_1^{k+1},\ \theta_3^k, \dots, \theta_{d-1}^k,\ \theta_d^k,\ \boldsymbol{y})$

   .

   .

   .

d. Sample θ_d^{k+1} from $p(\theta_d|\theta_1^{k+1},\ \theta_2^{k+1}, \dots, \theta_{d-1}^{k+1},\ \boldsymbol{y})$

The conditional distributions of $p(\theta_j|\theta_1^{k+1},\ \theta_2^{k+1}, \dots,\ \theta_{j-1}^{k+1},\ \theta_{j+1}^k, \dots, \theta_{d-1}^k,\ \theta_d^k,\ \boldsymbol{y})$ are called full conditional distributions, because θ_j is conditioned on all other parameters.

4.2.5. Convergence of a Markov chain

Convergence for Markov chain is an asymptotic property and implies that the distribution of θ^k, $p_k(\theta)$, becomes the target distribution of $p(\theta|\boldsymbol{y})$ for $k \to \infty$. This means that $d_k \equiv d\big(p_k(\theta), p(\theta|\boldsymbol{y})\big) < \varepsilon$ with $d(\cdot,\ \cdot)$ a distance measure between two distributions for k large

and for a given small value of ε. Thus, the convergence criteria assess the closeness of two distributions (Lesaffre and Lawson, 2012). In practice, checking convergence for Markov chain involves two aspects: stationarity of the chain and accuracy of the posterior summary measure. Among convergence of MCMC diagnostics, the following were used.

Trace plot

Trace plots of samples versus the simulation index can be very useful in assessing convergence. The trace plot shows whether the chain has not yet converged to its stationary distribution that is, if it needs a longer burn-in period. A trace can also show whether the chain is mixing well. A chain might have reached stationarity if the distribution of points is not changing as the chain progresses that is the plot appears as a horizontal strip and the individual moves are hardly discernible. The aspects of stationarity that are most recognizable from a trace plot are a relatively constant mean and variance.

Brooks-Gelmen-Rubin (BGR) diagnostic

The diagnostic is based on the multiple simulated MCMC chains by comparing the variance within the chain and the variance between the chains. Large deviation between two variances indicates nonconvergence. (Gelman and Rubin 1992; Brooks and Gelman 1998). Mathematically, if all chains have reached the target distribution, the posterior marginal variance estimate should be very close to the within chain variance. So the ratio is expected to be close to one. The square root of this ratio is referred to as the potential scale reduction factor (PSRF).

Geweke convergence diagnostics

Geweke (1992) suggests to formally testing the stationarity of a Markov chain by comparing the means of early and late part of the realized chain using a (frequentist) significant test. He suggests to take for early part the initial 10% of iterations and for the late part the last 50%, assuming that this creates enough distance to ensure the independence of the Markov chain.

4.2.6. Model selection

A natural way to compare models is to use a criterion based on the trade-off between the fit of the data to the model and the corresponding complexity of the model. Spiegelhalter *et al.* (2002) proposed a Bayesian model comparison criterion based on this principle:

Deviance Information Criterion, DIC = 'goodness of fit' + 'complexity'

Then, the fit measured via deviance

$$D(\theta) = -2logL(data|\theta)$$

And complexity measured by estimate of 'effective number of parameters":

$$p_D = E_{\theta|y}[D] - D\left(E_{\theta|y}[\theta]\right)$$

$$= \overline{D} - D(\bar{\theta})$$

That is posterior mean deviance minus deviance evaluated at the posterior of the parameters.

The DIC is then defined as analogously to AIC as

$$DIC = D(\bar{\theta}) + p_D$$

$$= \overline{D} + p_D$$

Models with smaller DIC are better supported by the data (Spiegelhalter *et al., 2002*).

5. Results

5.1. Result for Total Outpatient Systemic Antibiotic Use Data (J01)

The quarterly total outpatient antibiotic use data (Figure 2) shows the variability across repeated measurements from the same country (within-country variability) as well as variability between countries (between-country variability). In addition to that, it shows a non-linear pattern of seasonal variation in each year. Therefore, to study the country specific outpatient antibiotic consumption, a nonlinear mixed model that integrates the trend component and sinusoidal component is needed. Because of this reason, the series of papers on outpatient antibiotic use in Europe (1997-2009) were published using a nonlinear mixed model that consists of a trend and a seasonal component.

In addition to the trend over time and seasonal variation, it is important to assess any change of the trend at a specific time because of campaigns, policy changes or others. Minalu *et al.* (2011) extended that nonlinear mixed model by incorporating the change point component to identify the possible change points on outpatient tetracycline use data.

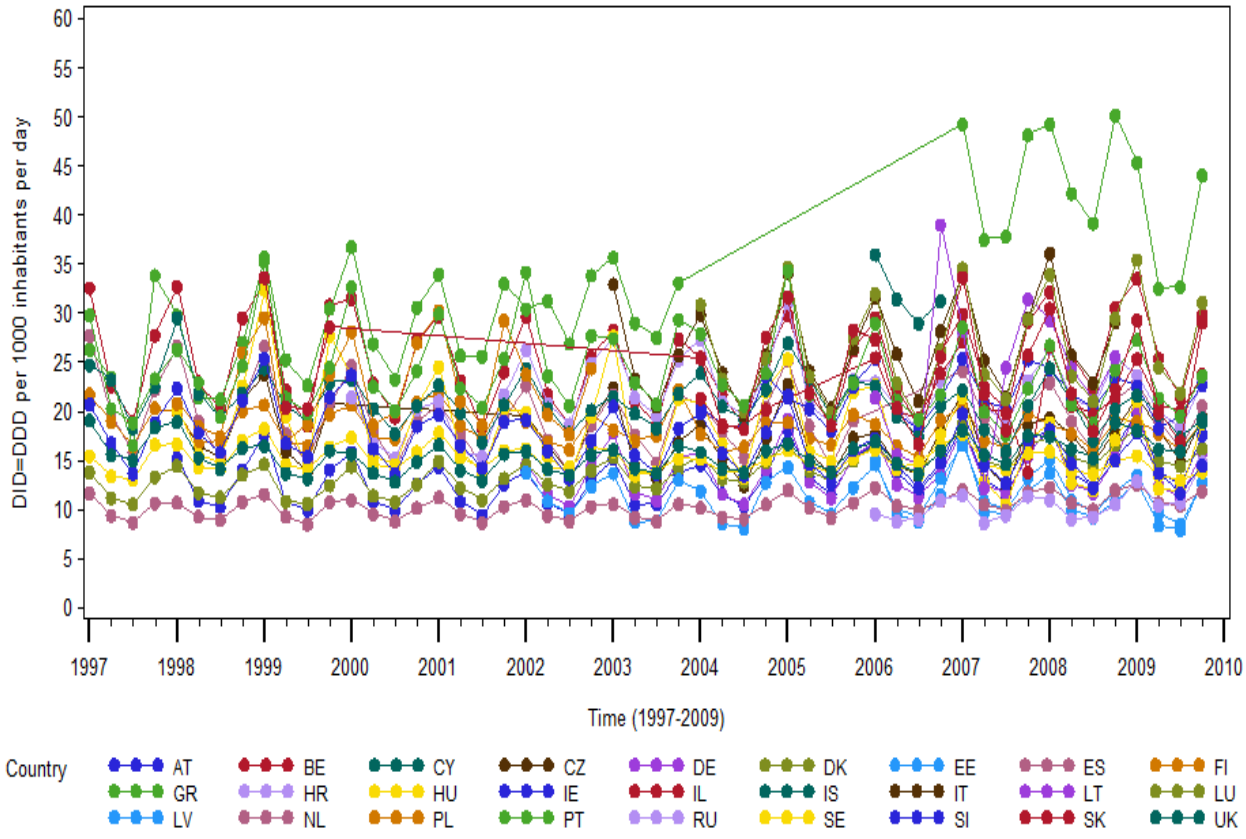


Figure 2. *Total outpatient antibiotic data J01*. Observed country-specific evolution for total outpatient antibiotic use in DID

Thus in this section, a change point model was fitted for total outpatient antibiotic use (J01). It was formulated from simple (model with no change point) to complex (model with two change point) adaptively using Bayesian approach. In the progression of model building: careful selection of starting values; inclusion and exclusion of random effects; and changing the variance and covariance matrix of the random effect was considered until the model convergence obtained. As well as choice of prior specification was considered.

Two independent chains of MCMC using Gibbs sampler were run, with different starting value. For each chain, 331,000 iterations were used, of which the first 11,000 iterations were discarded (burn in) and then the chain was thinned to every 40th sample, as there was autocorrelation for some parameters.

The following models were considered under the general change point model (equation 5, Section 4.2.2) with no random effect for country specific damping effect on seasonal variation (a_{1i}), because with the inclusion of this component no convergence was obtained. The model with the covariance matrix of random effects for all covariance equal to zero except between $b_{0i}\ and\ a_{0i}$ was considered as a parsimonious model, where b_{0i} is the country specific random intercept, and a_{0i} is the country specific random slope for amplitude.

Model 1: Non-linear mixed model without a change-point,

$$\mu_i^{CP}(t_{ij}) = 0$$

Model 2: Non-linear mixed model with one unknown common change-point (C_1),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - C_1)_+$$

Model 3: Non-linear mixed model with two unknown common change-points (C_1 and C_2),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - C_1)_+ + (\beta_3 + b_{3i})(t_{ij} - C_2)_+$$

Model 4: Non-linear mixed model with unknown random change points and one known common change-point (C_{ki} and $C_2 = 48$),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - C_{ki})_+ + (\beta_3 + b_{3i})(t_{ij} - 48)_+$$

Model 5: Non-linear mixed model with unknown random change points and one known common change-point (C_{ki} and $C_2 = 47$),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - C_{ki})_+ + (\beta_3 + b_{3i})(t_{ij} - 47)_+$$

Model 6: Non-linear mixed model with unknown random change points and one known common change-point (C_{ki} and $C_2 = 46$),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - C_{ki})_+ + (\beta_3 + b_{3i})(t_{ij} - 46)_+$$

Model 7: Non-linear mixed model with unknown random change points and one unknown common change-point (C_{ki} and C_2),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - C_{ki})_+ + (\beta_3 + b_{3i})(t_{ij} - C_2)_+$$

The results of Model 1 – 7 are shown in Table 3 (see Appendix I). The total outpatient antibiotic use data has been analyzed by Adriaenssens *et al*. (2011) using longitudinal data analysis to assess trend over time and seasonal variation. The result of this longitudinal data analysis was used as a starting value for Model 1, which is a model without change point. The result of Model 1 compared with the result of Adriaenssens *et al*. (2011) is nearly similar. However, this model got little support with highest DIC=3940.8.

Since the random of the change point is not yet known, Model 2 (with one unknown change point) was fitted by extending Model 1. Better DIC = 3856.8 was obtained and the estimate for the unknown common change point (C_1) was 26.56 (≈ between the 2nd and 3rd quarter of 2003). Note that a lower DIC is better. In addition, the Model 3 that included two unknown common change points was fitted, using uniform prior distribution over the total range of the time for the first unknown common change point and again uniform prior distribution over the above of the first change point to the end range of the time for the second unknown common change point. It provides a better DIC=3813.1 as compared to Model 2. The estimated unknown change points were 26.96 (≈ the 3rd quarter of 2003) and 45.95 (≈ the 2nd quarter of 2008).

A model that included three unknown common change points was tried; however, statistical convergence was not achieved. Furthermore, a model that included two common unknown change points with random change point effect was fitted; again, the model did not converge.

It is recognized from Huttner *et al*. (2010) that in many of Europe country there was a nation-wide campaign experience at least once between year 2000 to year 2006. Therefore, that it may have country wide effect. In November 2008 (≈ 4th quarter of 2008 = (time = 48)) there were European wide campaign, so that it could have European wide effect. Hence it elicited to build a model that have one country-specific random change points to account for the nation-wide campaigns and one common change point to account for a European wide campaign.

Because there was a European campaign at 4th quarter of 2008 (time = 48) and from Model 3 the second change point estimate was 2nd quarter of 2008 (time = 46), the Model 4 – 6 was fitted by fixing the second change point in between these periods (time = 46 to time = 48). From them the better DIC=3765.3 was exhibited on Model 6 (known change point, time = 46).

Furthermore, it was realized that in Model 4 – 6, the first change point happened before the 4th quarter of 2006 (time = 40). As a result, the final model (Model 7) was formulated to estimate the change points from the data by using uniform prior distribution between time = 1 to time = 40 for the first change point and uniform prior distribution between time = 40 to time = 52 for the second change point. The estimate of the first unknown random change point is listed in Table 4 (see Appendix I) and the second unknown common change point is 46.14 (≈ 2nd quarter of 2008). There was no substantial difference between DIC of Model 6 (3765.3) and Model 7 (3767.7) though Model 7 was more in parameter.

The convergence of the Markov chains for Model 7 was assessed as follow.

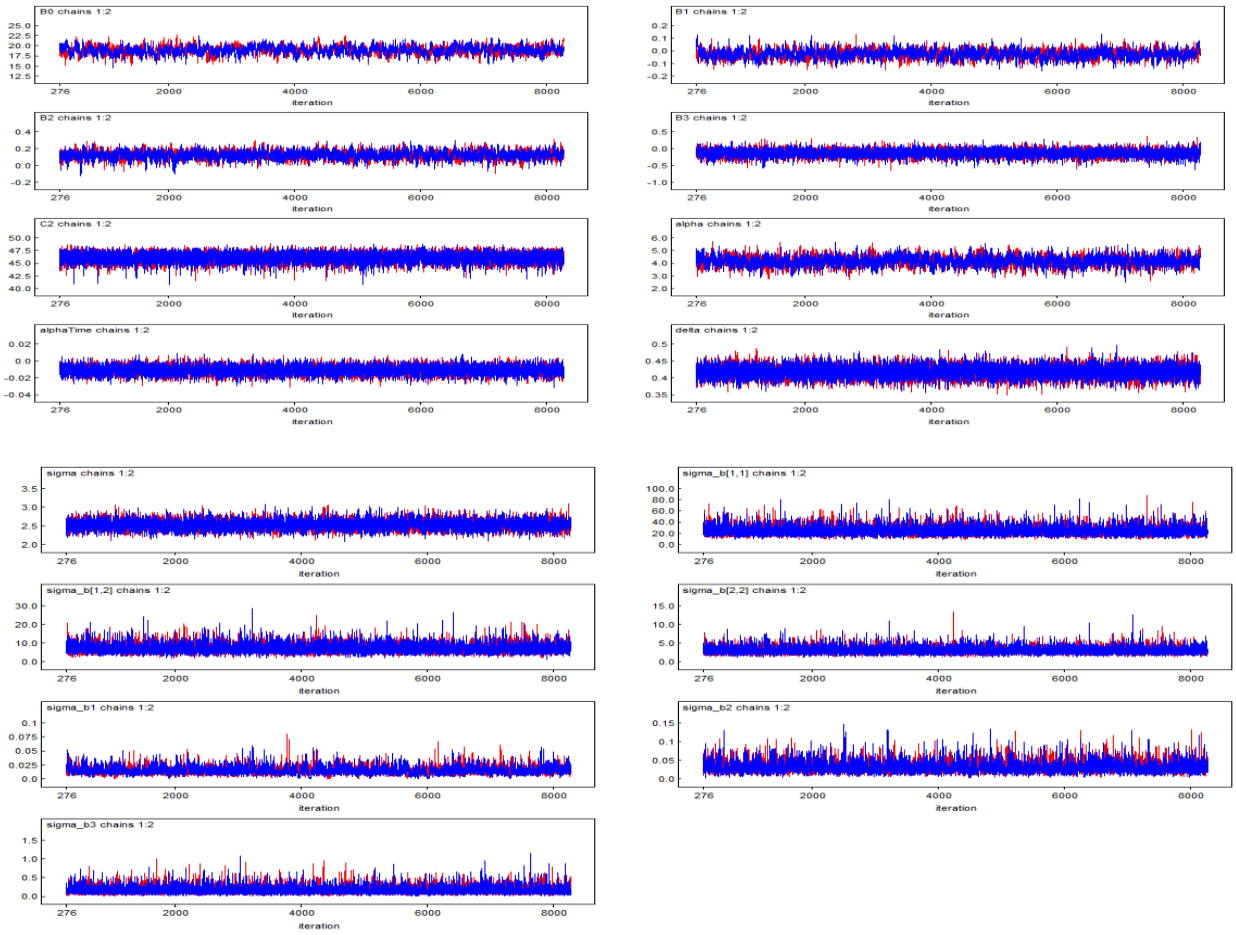


Figure 3. *Total outpatient antibiotic data use J01*. Trace plots for fixed effect parameters of Model 7

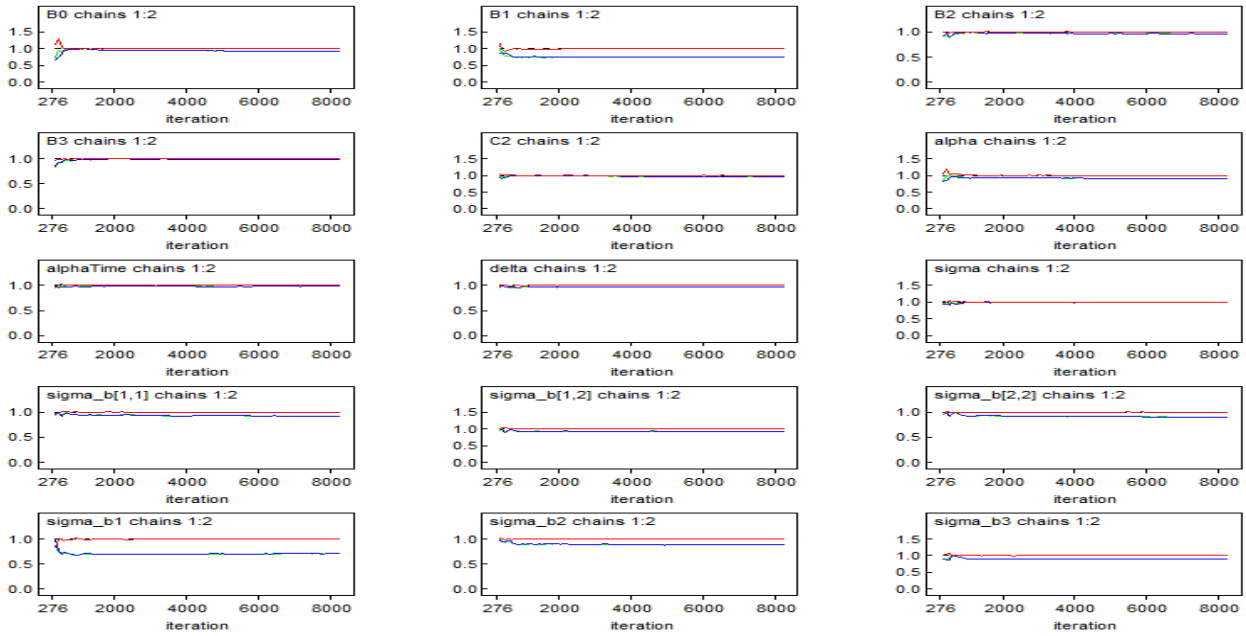


Figure 4. *Total outpatient antibiotic use data J01*. BGR diagnostic plots for fixed effect parameters of Model 7

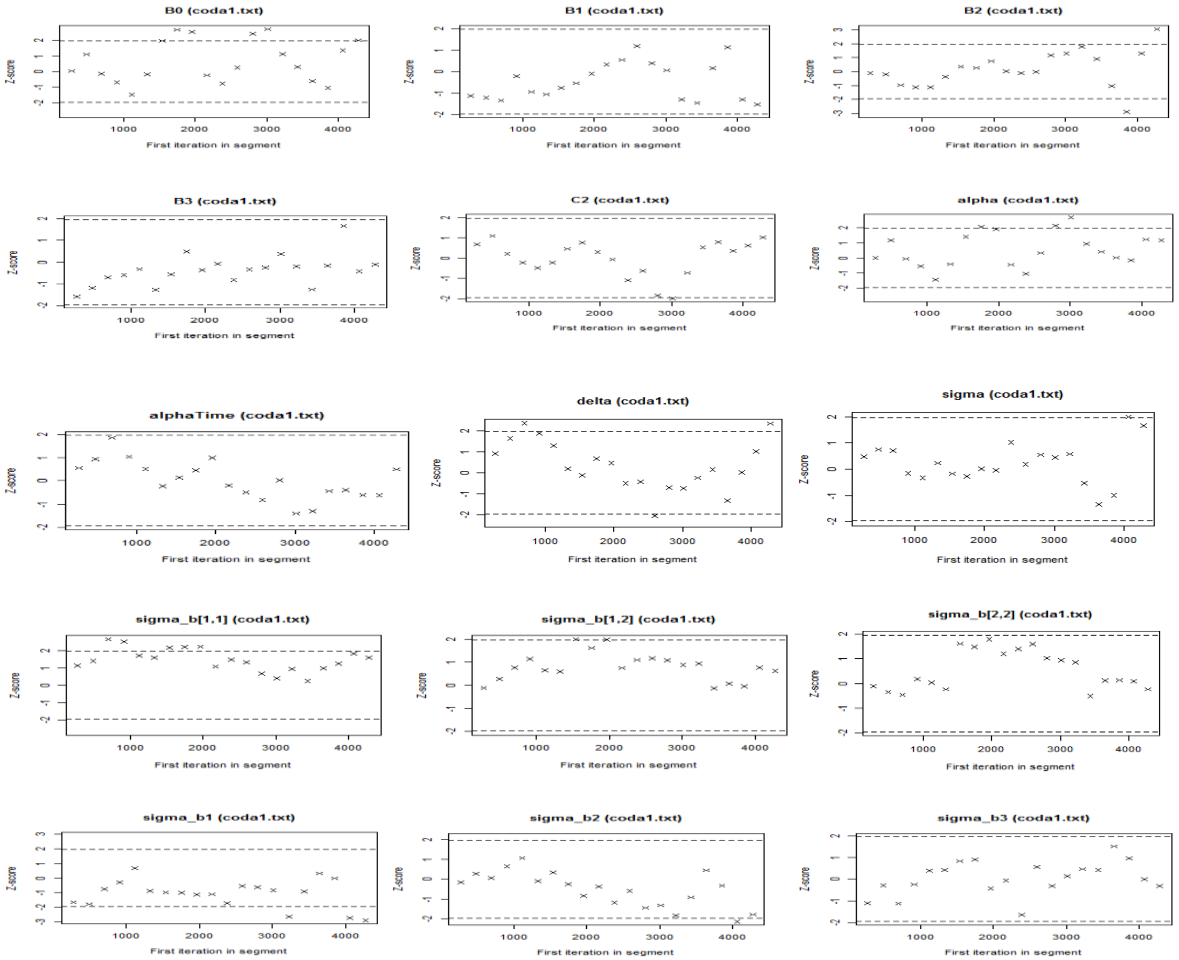


Figure 5. *Total outpatient antibiotic use data J01*. The Geweke diagnostic plots for fixed effect parameters of Model 7

The suitable diagnostics to evaluate the mixing and the convergence of the sampler are used. Trace plots (Figure 3) show the horizontal and the individual moves are hardly discernible, it tells the stationarity of Markov chain.

To assess convergence, the BGR diagnostic plots are shown in the Figure 4. It shows convergence under stationarity as red line (ratio of the length of total chain interval to average length of the within-chain interval) is equal to one for all parameters. As well as the estimated potential scale reduction factor (PSRF) was approximate to 1.0 for all parameters.

In addition to that, the Geweke formal diagnostics shows the stationarity of the Markov chain because the majority of Z-values were inside the interval (Figure 5).

Therefore, there is no problem in the convergence of the Markov chain. Moreover, it shows a better DIC.

Ultimately, Model 7 is the best for Total Outpatient Antibiotic Use Data (J01) to assess the possible change points.

$$E(Y_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + (\beta_2 + b_{2i})\left(t_{ij} - C_{1i}\right)_+ + (\beta_3 + b_{3i})\left(t_{ij} - C_2\right)_+ + \left((A_0 + a_{0i}) + A_1 t_{ij}\right) sin\left(\omega t_{ij} + \delta\right)$$

$$where\ \ 1 < C_{1i} \leq C_2 < 52$$

In this model, the fixed effects ($\beta_0,\ \beta_1, \beta_2, \beta_3, A_0,\ A_1,\ \delta$) accounted for the European wide while the random effects ($b_{0i},\ b_{1i}, b_{2i}, b_{3i},\ a_{0i}$) accounted for a country specific total outpatient antibiotic use. In the case of change points, C_{1i} gives the country specific change point while C_2 gives the common change point in Europe wide. Since two change points are found, the model will implement under three time subspace, which are 1 to C_{1i}, C_{1i} to C_2, and C_2 to 52. Then

$$E(Y_{ij}) = \begin{cases} (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \left((A_0 + a_{0i}) + A_1 t_{ij}\right) sin\left(\omega t_{ij} + \delta\right) & \ldots \quad if\ 1 \leq t_{ij} < C_{1i} \\ \left((\beta_0 + b_{0i}) - (\beta_2 + b_{2i})C_{1i}\right) + \left((\beta_1 + b_{1i}) + (\beta_2 + b_{2i})\right)t_{ij} + \left((A_0 + a_{0i}) + A_1 t_{ij}\right) sin\left(\omega t_{ij} + \delta\right) & \ldots \quad if\ C_{1i} \leq t_{ij} < C_2 \\ \left((\beta_0 + b_{0i}) - (\beta_2 + b_{2i})C_{1i} - (\beta_3 + b_{3i})C_2\right) + \left((\beta_1 + b_{1i}) + (\beta_2 + b_{2i}) + (\beta_3 + b_{3i})\right)t_{ij} + \left((A_0 + a_{0i}) + A_1 t_{ij}\right) sin\left(\omega t_{ij} + \delta\right) & \ldots \quad if\ C_2 \leq t_{ij} \leq 52 \end{cases}$$

The posterior estimate for mean, standard error and credible interval of the parameters for fixed effect and the parameter for variance-covariance components are presented in Table 1.

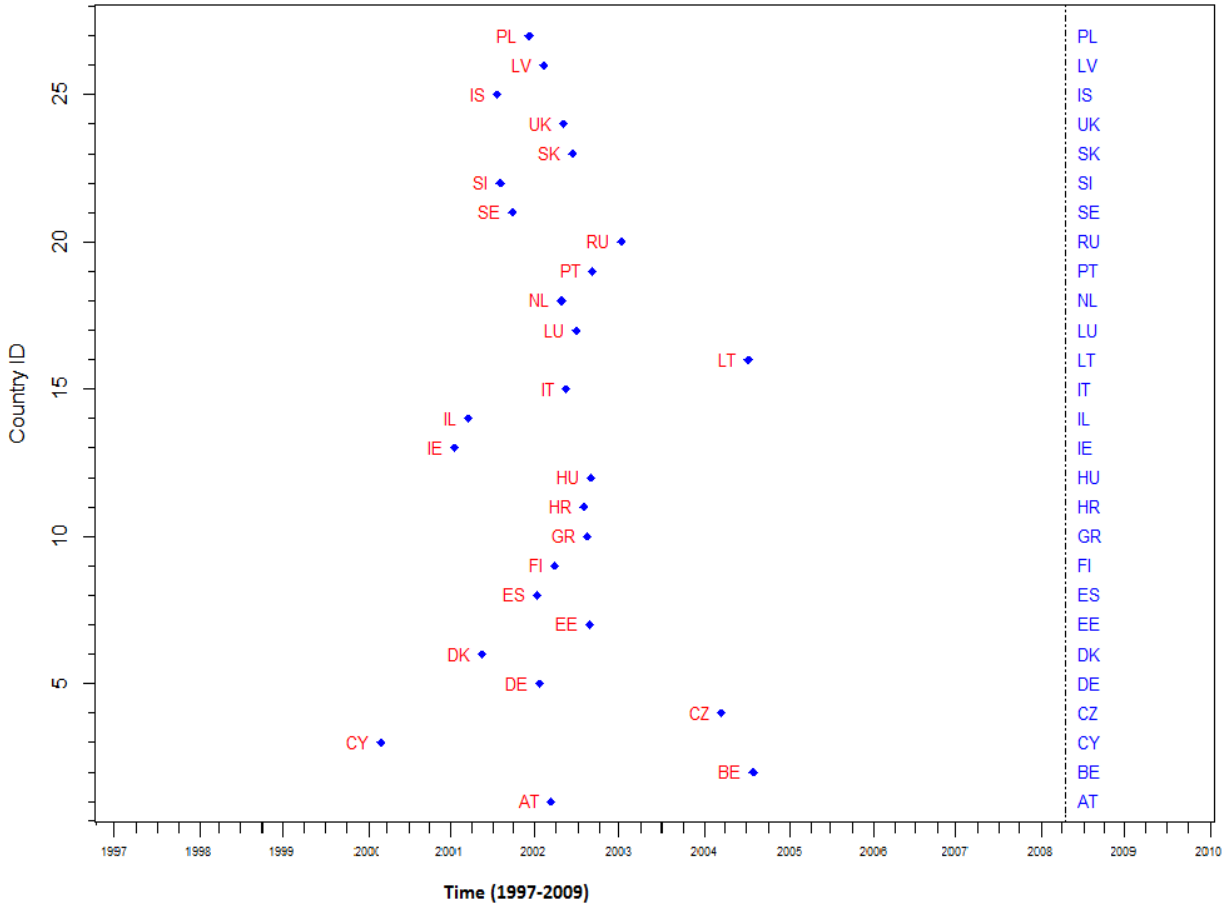
Table 1. *Total outpatient antibiotic use data J01*. Parameter estimate: posterior mean, standard error, and 95% credible interval for the parameters of fixed effects and the parameter of variance-covariance components.

Effects	**parameters**	**Mean**	**S.e**	**2.5%, 97.5%**
	β_0	18.8947	1.044	16.820, 20.910
	β_1	-0.0259	0.035	-0.095, 0.045
	β_2	0.1214	0.049	0.022, 0.215
	β_3	-0.1323	0.105	-0.349, 0.073
	***C_{1i}**	-	-	-
	C_2	**46.1385**	**0.951**	**44.130, 47.830**
	A_0	4.1687	0.385	3.424, 4.935
	A_1	-0.0107	0.005	-0.021, -0.0004
	δ	0.4181	0.130	0.382, 0.454
$Var(b_{0i})$	d_{11}	24.4105	7.987	13.020, 43.880
$Var(b_{1i})$	d_{22}	0.0148	0.007	0.005, 0.032
$Var(b_{2i})$	d_{33}	0.0312	0.014	0.011, 0.068
$Var(b_{3i})$	d_{44}	0.1655	0.101	0.038, 0.423
$Var(a_{0i})$	d_{55}	3.0624	0.948	1.708, 5.399
$Cov(b_{0i}, a_{0i})$	d_{15}	7.1047	2.432	3.606, 13.010
$Var(\varepsilon_{ij})$	σ^2	2.5256	0.130	2.282, 2.793

***C_{1i}** -The random change point of J01 are presented in Table 4 (*appendix I*)

Table 1 shows the posterior parameter estimates (standard error) and 95% credible interval. The fixed effect β_1 indicates that there was decreasing in global trend of total antibiotic use in DID before the first change point. β_2 indicates positive global difference in the linear trend before and after the first country specific random change point. β_3 indicates the negative global difference in linear trend before and after the second common change point (2nd quarter of 2008). A_0 indicates overall seasonal variation and also A_1 shows overall seasonal variation trend over time. In addition to that it's found that there is positive correlation between random intercept and random slope for amplitude. It indicates a country which has high total outpatient antibiotic use at 1st quarter of 1997 could have high seasonal variation in antibiotic use.

The graphical presentation of the change points is shown on Figure 6. It shows a clear picture of the estimate of country specific random change points and the common change point. The first country specific random change points obtained in between year 2000 to year 2004. The second common change point was 2nd quarter of 2008.



Country abbreviations

AT: Austria BE: Belgium CY: Cyprus CZ: Czech Republic DE: Germany

DK: Denmark EE: Estonia ES: Spain FI: Finland GR: Greece

HR: Croatia HU: Hungary IE: Ireland IL: Israel IS: Iceland

IT: Italy LT: Lithuania LU: Luxembourg LV: Latvia NL: Netherlands

PL: Poland PT: Portugal RU: Russian Federation SE: Sweden SI: Slovenia

SK: Slovakia UK: United Kingdom

Figure 6. *Total outpatient antibiotic use data J01.* Scatter plot of estimate of country specific random change point and the common change point obtained from Model 7.

The estimated linear trend, the estimated change point model from Model 7 and the observed average DID for Europe, are shown in Figure 7. The predicted mean is based on the predicted outcomes from the posterior distribution of the country-specific random effects. The Figure show how well the model fit the data. The total outpatient antibiotic use in Belgium and the observed average DID in Europe were compared (Figure 16, see Appendix III). It shows the total antibiotic use in Belgium is higher. In contrast, the decreasing linear trend in time higher in Belgium before the first change point. In addition the first change point is obtained earlier in observed average DID in Europe. After the second change point the linear trend in time is a bit higher in Belgium as compared to the observed average DID in Europe.

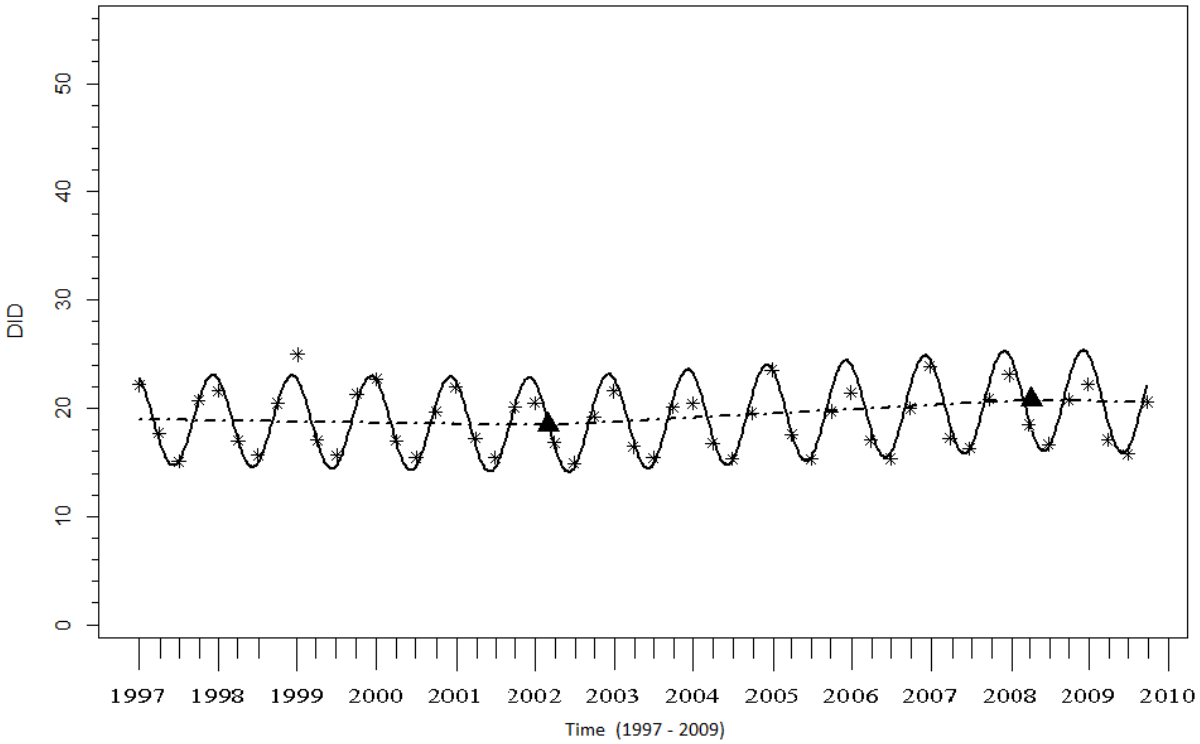


Figure 7. *Total outpatient antibiotic use data J01.* The observed average DID (stars), the predicted mean profile (solid line), and the predicted linear trend (dashed line) and the change points (dense triangle) obtaining from fitting Model 7.

Moreover, to see how well the Model 7 fits the data in country specific, it has explored for some of the selected courtiers using the parameter estimate in Table 1 for fixed effect and in Table 4 (Appendix I) for country specific random effect. The observed country specific profiles and the predicted country specific profiles from model for three selected countries (Belgium, Spain and the Netherlands) are shown in Figure 8. As can been seen from the Figure 8, the predicted country specific profiles follow closely the observed country specific DID values

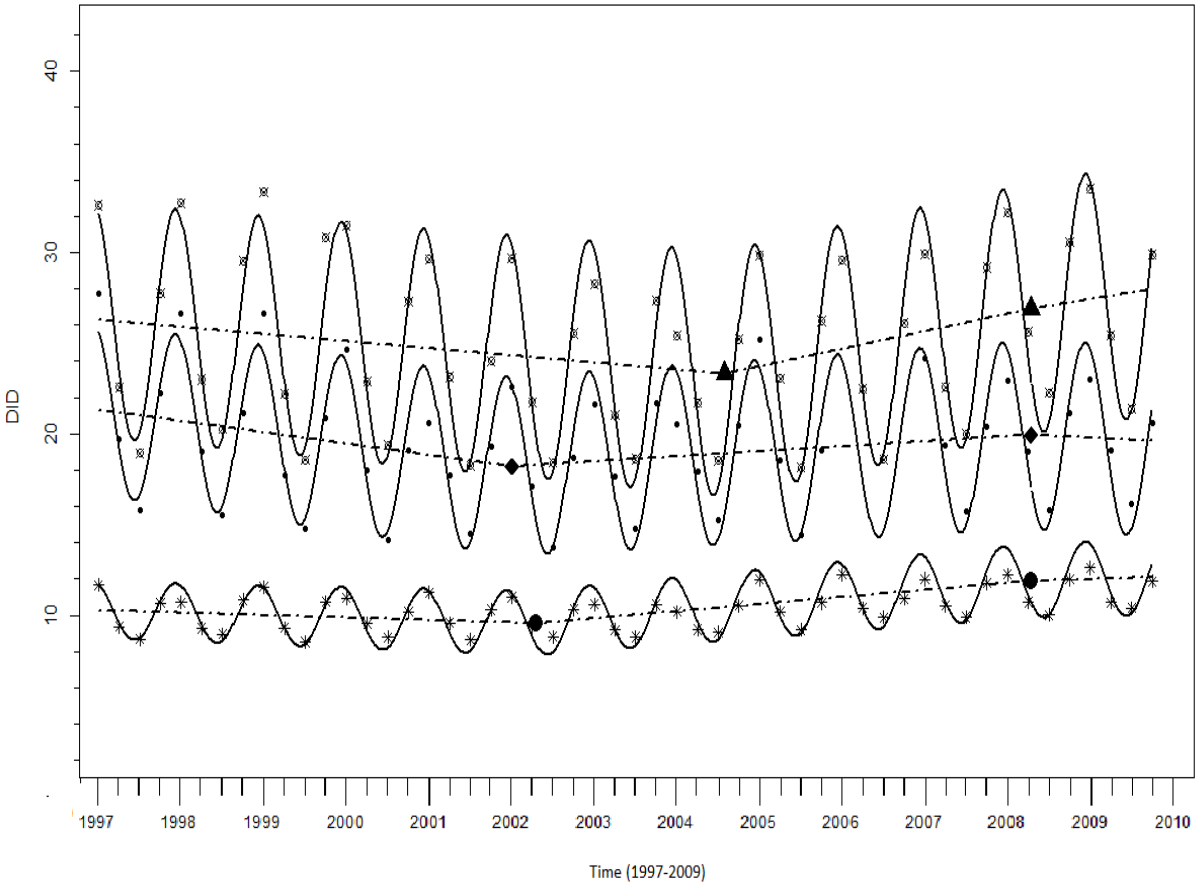


Figure 8 *Total outpatient Antibiotic use data*: The observed country-specific DID (stars, dot), the predicted country-specific profiles (solid lines) , the country-specific predicted linear trends (dashed lines) and the change points (dense pictures) obtained from fitting Model 7 for three selected countries (Belgium, Spain and Netherlands from top to bottom)

5.2. Result for Penicillin Use Data (J01C)

The quarterly outpatient penicillin use data J01C (Figure 9) shows a nearly similar pattern compared to total antibiotic use data (J01). This means it shows the within country variability and the between country variability and also the seasonal variability.

To assess the possible change points the similar mechanism is used. So that two independent chains of MCMC using Gibbs sampler were run. 410,000 iteration, 11,000 burn in and 40 number of thin was used. The model with the covariance matrix of random effects for all covariance equal to zero except between $b_{0i}\ and\ a_{0i}$ was considered as a parsimonious model, where b_{0i} is the country specific random intercept, and a_{0i} is the country specific random slope for amplitude.

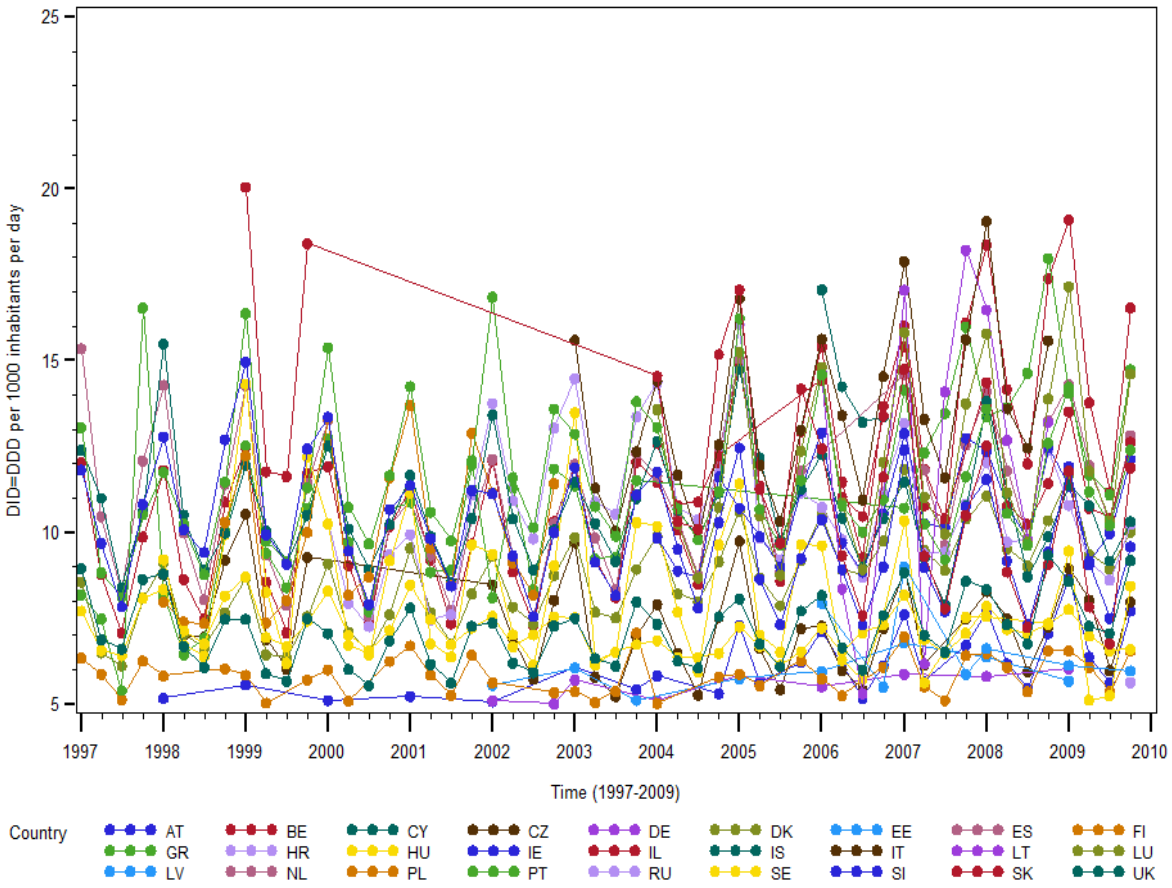


Figure 9. *Outpatient penicillin use data J01C*. Observed country-specific evolution for outpatient penicillin use in DID

The following models were considered under the general change point model (equation 5, Section 4.2.2) in order to get the best model that fit the data with possible change points.

Model 1*: Non-linear mixed model without a change-point,

$$\mu_i^{CP}(t_{ij}) = 0$$

Model 2*: Non-linear mixed model with one unknown common change-point (C_1),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - C_1)_+$$

Model 3*: Non-linear mixed model with unknown random change points

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - C_{ki})_+$$

The results of Model 1* – 3* are shown in Table 5 (see Appendix II). The Model 1* was fitted without including the change point component. Versporten *et al*. (2011) analyzed the outpatient penicillin use data using the longitudinal data analysis to assess the trend over time and the seasonal variation. Hence, the result of the longitudinal analysis was use again as

initial value for model one. As expected the result of Model 1* and Versporten *et al*. (2011) for outpatient penicillin use were close to similar though it was supported by highest DIC = 2830.3.

Since a change point is possible in outpatient penicillin use, the Model 1* is extended by including one unknown common change point component in the model (Model 2*). Convergence of the model was obtained. The result shows a better DIC=2699.2 and the estimated unknown common change point was 25.82 (≈ 2nd quarter of 2003). It is closed to the first unknown common change point of total antibiotic use data (J01) in Model 2 (between the 2nd and 3rd quarter of 2003). Thus it is an indication that penicillin is accounted for the first change point in total antibiotic use (J01).

Though Model 2* was extended by including two unknown change points, the convergence didn't obtained. On the other hand the model 1* was extended by including the unknown random change point component. And the better fit was obtained with DIC = 2635.7. Because the model that included two change point model failed to converge, Model 3* choose as best model.

The convergence of the Markov chains for Model 3* was assessed as follow.

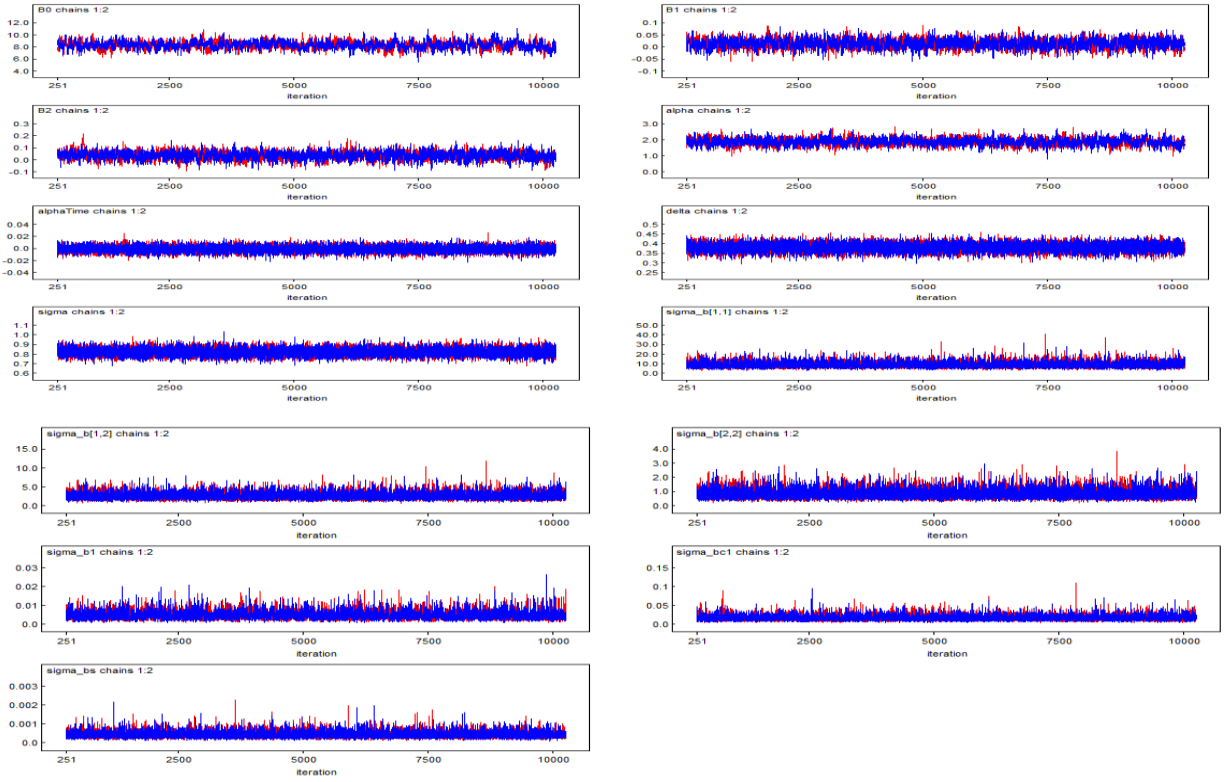


Figure 10. *Outpatient penicillin use data J01C.*. Trace plots for fixed effect parameters of Model 3*

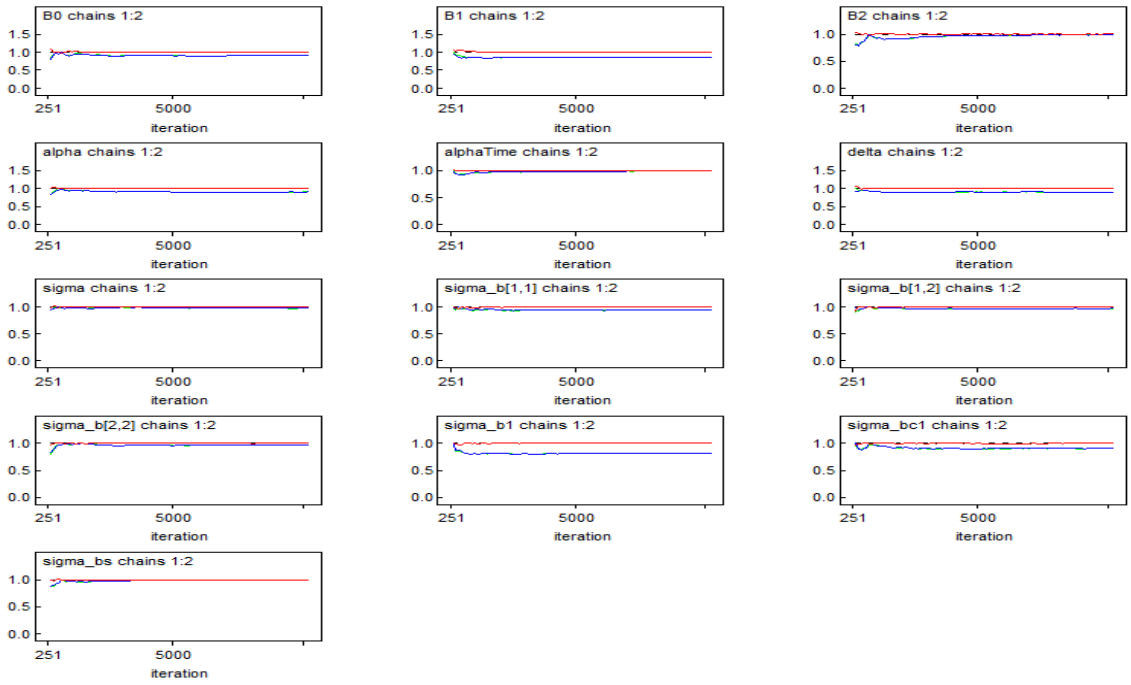


Figure 11. *Outpatient penicillin use data J01C*. BGR diagnostic plots for fixed effect parameters of Model 3*

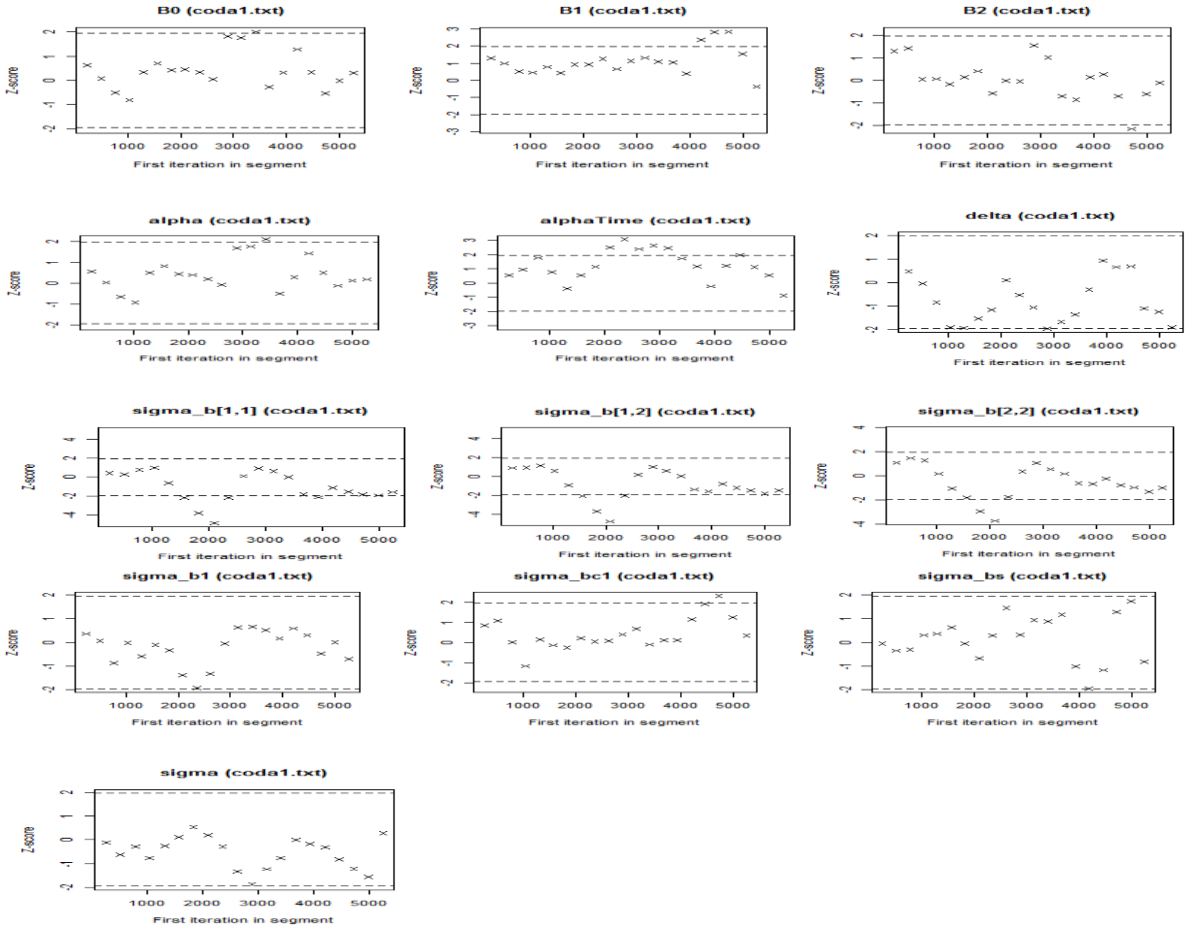


Figure 12. *Outpatient penicillin use data J01C*. The Geweke diagnostic plots for fixed effect parameters of Model 3*

The convergence of the Markov chain was assessed using trace plot, Geweke diagnostic plots, BGR interval based and PSRF. Thus, the trace plots (Figure 10) shows thick pen test and since chain are highly mixed, it's hardly discernible. Thus, staitionarity is achieved. The BGR plots (Figure 11) show the ratio (red line) is equal to 1 for all parameters. In addition from the result, the PSRF value for each parameter was near to 1.0. And the last the Geweke plot (Figure 12) is clear that most of Z value are inside the interval. So, from these diagnostics results, its notice that the model obtained the convergence.

Therefore, the Model 3* considered as best model because it is converged with lower DIC.

$$E(Y_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + (\beta_2 + b_{2i})(t_{ij} - C_{ki})_+ + \Big((A_0 + a_{0i}) + (A_1 + a_{1i})t_{ij}\Big) sin(\omega t_{ij} + \delta)$$

With similar fashion in this model also, the fixed effects ($\beta_0,\ \beta_1, \beta_2, \beta_3, A_0,\ A_1,\ \delta$) accounted for the European wide while the random effects ($b_{0i},\ b_{1i}, b_{2i}, b_{3i},\ a_{0i}, a_{1i}$) accounted for a country specific outpatient penicillin use. In the outpatient penicillin use data only one change point was found and which is a country specific random change point. The model could implemented under two time subspace which are 1 to C_{1i}, C_{1i} to 52. Then,

$$E(Y_{ij}) = \begin{cases} (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \Big((A_0 + a_{0i}) + (A_1 + a_{1i})t_{ij}\Big) sin(\omega t_{ij} + \delta) \ldots if\ \ 1 \le t_{ij} < C_{ki} \\ \Big((\beta_0 + b_{0i}) - (\beta_2 + b_{2i})C_{ki}\Big) + ((\beta_1 + b_{1i}) + (\beta_2 + b_{2i}))t_{ij} \\ \qquad + \Big((A_0 + a_{0i}) + (A_1 + a_{1i})t_{ij}\Big) sin(\omega t_{ij} + \delta) \qquad \ldots if\ \ C_{ki} \le t_{ij} \le 52 \end{cases}$$

The posterior estimate for mean, standard error and 95% credible interval of the parameters for fixed effect and the parameter for variance-covariance components are presented in Table-2. The fixed effect β_1, indicates that there was increasing in global trend of outpatient penicillin use in DID before the change point. β_2 also indicates the positive difference in linear trend after and before the change point. So that the trend of outpatient penicillin use before and after the change point is increasing. So that the increasing linear trend in time is higher after the change point.

Table 2. *Outpatient penicillin use data J01C*. Parameter estimate: posterior mean, standard error, and 95% credible interval for the parameters of fixed effects and the parameter of variance-covariance components.

Effects	**parameters**	**Mean**	**s.e**	**2.5%, 97.5%**
	β_0	8.3176	0.627	7.107, 9.592
	β_1	0.0144	0.018	-0.022, 0.049
	β_2	0.0350	0.033	-0.031, 0.101
	*C_{1i}	-	-	-
	A_0	1.8596	0.212	1.442, 2.291
	A_1	-0.0009	0.005	-0.011, 0.009
	δ	0.3797	0.022	0.337, 0.422
$Var(b_{0i})$	d_{11}	8.8341	2.942	4.638, 16.030
$Var(b_{1i})$	d_{22}	0.0047	0.002	0.0018, 0.0100
$Var(b_{2i})$	d_{33}	0.0169	0.007	0.0074, 0.0345
$Var(a_{0i})$	d_{44}	0.8423	0.319	0.394, 1.640
$Var(a_{1i})$	d_{55}	0.0004	0.0002	0.0002, 0.0008
$Cov(b_{0i}, a_{0i})$	d_{14}	2.6066	0.896	1.338, 4.809
$Var(\varepsilon_{ij})$	σ^2	0.8193	0.039	0.745, 0.901

*C_{1i} -The random change point of J01C were presented in table 6(*appendix II*)

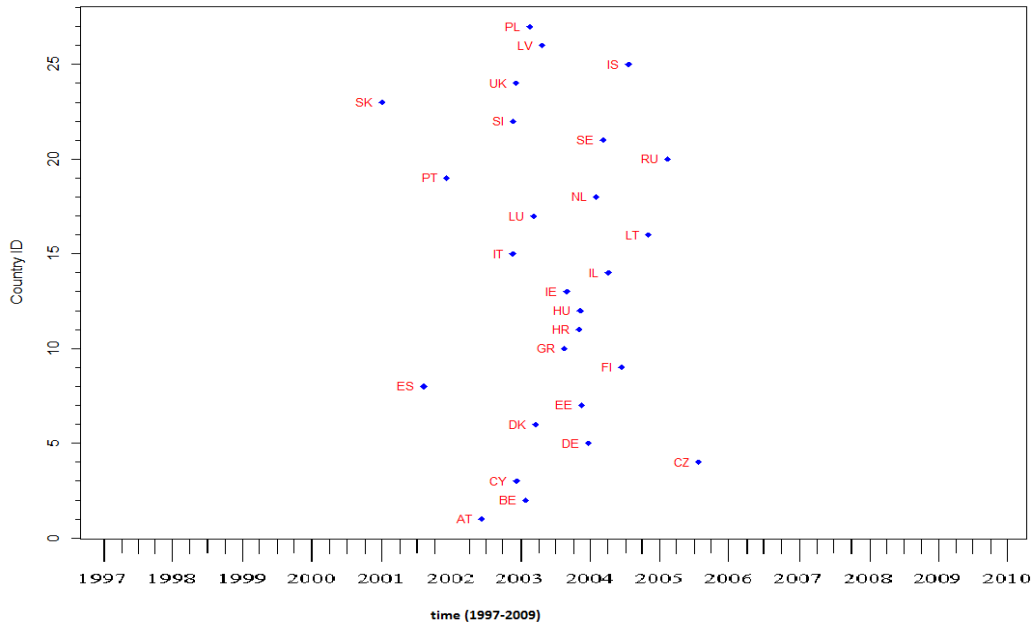


Figure 13. *Outpatient penicillin use data J01C.* Scatter plot of estimate of country specific random change point and the common change point obtained from Model 3*.

The graphical presentation of the change points with the corresponding country shown on Figure 13. It shows a clear picture on the estimate of country specific random change point. In addition, it seems most of country had change points in antibiotic in between year 2003 and year 2004.

The estimated linear trend, the estimated change point model from Model 3* and the observed average DID for Europe, are shown in Figure 14. The predicted mean is based on the predicted outcomes from the posterior distribution of the country-specific random effects. The Figure show how well the model fit the data. The outpatient penicillin use in Belgium and the observed average DID in Europe were compared (Figure 17, see Appendix III). It shows the outpatient penicillin use in Belgium is higher, specifically after the first change point. Moreover, the increasing linear trend in time moderately higher in Belgium after the first change point.

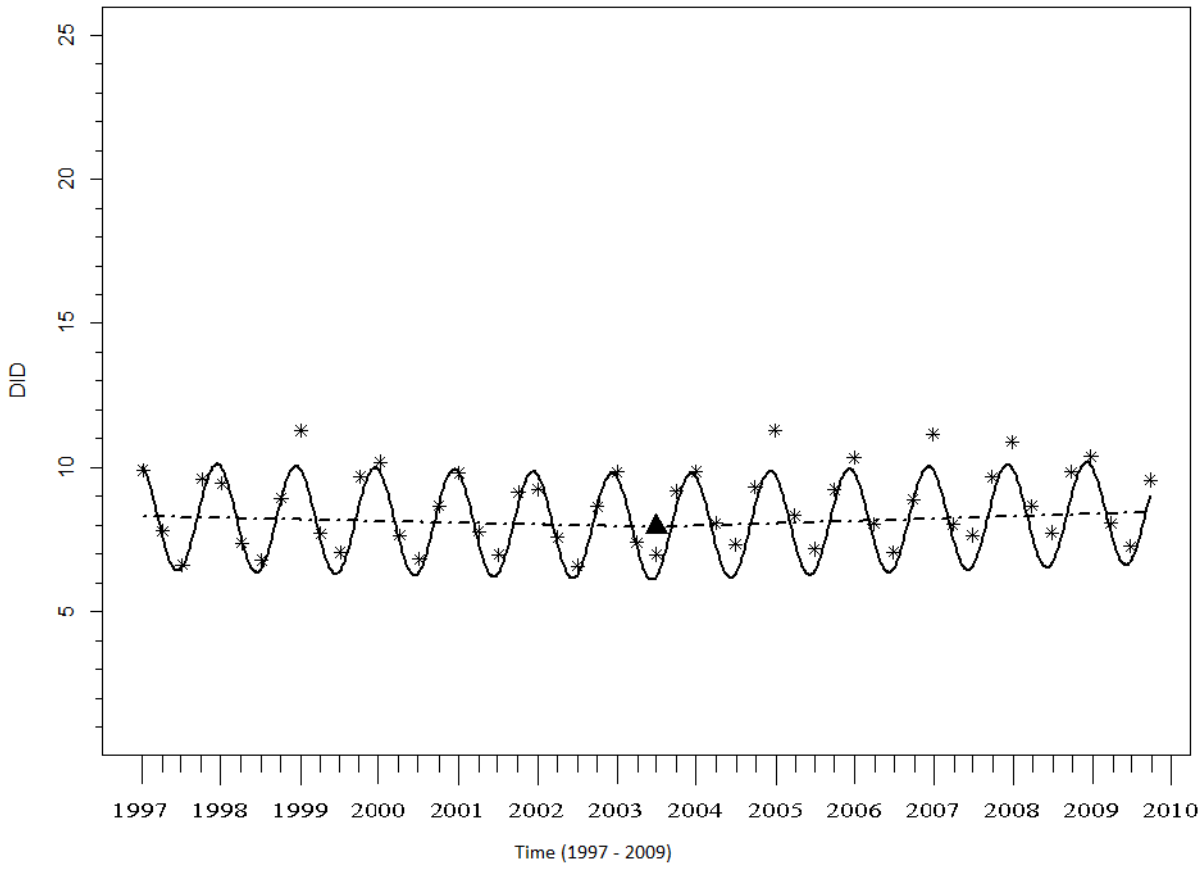


Figure 14. *Outpatient penicillin use data J01*. The observed average DID (stars), the predicted mean profile (solid line), and the predicted linear trend (dashed line) and the change point (dense triangle) obtaining from fitting Model 3*.

Moreover, in order to see how well the Model 4 fits the data in country specific, it was explored for some of the selected courtiers using the parameter estimate in Table 2 for fixed effect and in Table 6 (Appendix II) for country specific random effect. The observed country specific profiles and the predicted country specific profile from model for two selected countries (Belgium, United Kingdom) are shown in Figure 15. As can been seen from the Figure 15, the predicted country specific profiles follow closely the observed country specific DID values. So it may give a support how well the model fitted the data.

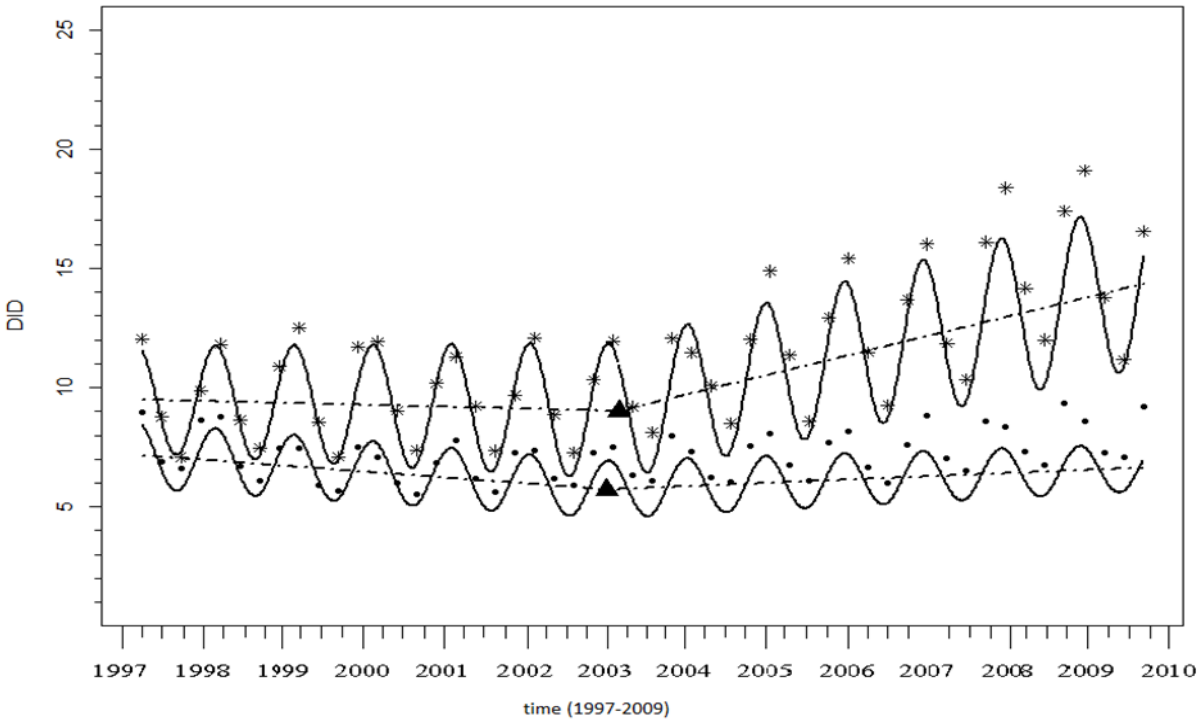


Figure 15. *Outpatient penicillin use data J01C*. The observed country-specific DID (stars, dot), the predicted country-specific profiles (solid lines) , the country-specific predicted linear trends (dashed lines) and the change points (dense triangle) obtained from fitting Model 3* for three selected countries (Belgium and United Kingdom from top to bottom)

Note: In order to see the effect of missing data, the very beginning models (Model 1 and Model 1*) which didn't include the change point component were compared with and without Cyprus(a country which has only 4 observation) data (Table 7 and 8, see Appendix IV). In both case, total outpatient antibiotic use and outpatient penicillin use resulted in better DIC when the data exclude Cyprus.. It may be an indication for the influence of missing data.

6. Conclusion and Discussion

Though these data were analyzed by Adriaenssens et al. (2011) and Versporten et al. (2011), it was required to see the effects of public campaign on antibiotic or policy changes on it. This was the core motivation of this study. To do that adaptive change point mixed models were used in order to explore the possible change points.

Thus, two change points were found in total outpatient antibiotic use data. Additionally, one random change point was found in penicillin use data. These change points were found in the period when there were public campaigns.

Positive correlation coefficient in between random intercept and random slope in time was found in both total outpatient antibiotic use and outpatient penicillin use. So that a country which has high antibiotic use (J01, J01C) at 1st quarter of 1997 could have high seasonal variation in antibiotic use (J01, J01C).

Since penicillin is the most widely used antibiotic subgroup, it is expected to account on change points of total outpatient antibiotic use. So it appear to have had significant account on the first change point. The second change point of total antibiotic use will be accounted by the remain subgroup of antibiotic use.

In case of total outpatient antibiotic date: for the second common change point it could have mixed interpretation of seasonal effect and campaign effect. Through the period of 1997 to 2009 the 2nd and the 3rd quarter of the year exhibit lower use of antibiotics so they could pull the linear time trend down ward, in another way the 1st and the 4th quarter of the year exhibit higher use of antibiotics, and could pull the linear time trend upward. There was a European wide campaign in the 4th quarter of 2008. Decreasing antibiotic use then might have resulted in decreasing upward pull of linear time trend. So the change point of linear time trend may appear before the 4th quarter of 2008..

The total outpatient antibiotic use in Belgium is higher as compared to the observed average DID in Europe. In contrast, the decreasing linear trend in time higher in Belgium before the first change point. In addition the first change point is obtained earlier in observed average DID in Europe. After the second change point the linear trend in time is a bit higher in Belgium as compared to the observed average DID in Europe.

The outpatient penicillin use in Belgium is also higher as compared to the observed average DID in Europe, specifically after the first change point. Moreover, the increasing linear trend in time higher in Belgium after the first change point.

The adaptive change point model could be extended with more change points. However, for the penicillin use data, the convergence was not reached when including two change points.

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Appendix

Appendix I: Models for Total outpatient antibiotic use data

Table 3. *Total outpatient Antibiotic data*. Parameter estimate: posterior mean (and standard error), and Model comparison: DIC values

Effects	**parameters**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**
	β_0	18.0647(1.044)	18.9167(1.039)	18.9827(1.048)	18.8219(1.047)	18.8373(1.036)	18.9097(1.046)	18.8947(1.044)
	β_1	0.0447(0.023)	-0.0060(0.028)	-0.0094(0.028)	-0.0136(0.034)	-0.0192(0.034)	-0.0198(0.034)	-0.0259(0.035)
	β_2	-	0.0858(0.034)	0.1087(0.039)	0.1121(0.051)	0.1257(0.052)	0.1301(0.052)	0.1214(0.049)
	β_3	-	-	-0.1369(0.334)	-0.1469(0.145)	-0.1658(0.119)	-0.1483(0.101)	-0.1323(0.105)
	C1	-	**26.5634(1.913)**	**26.9678(1.766)**	$\boldsymbol{C_{1i}^*}$	$\boldsymbol{C_{1i}^*}$	$\boldsymbol{C_{1i}^*}$	$\boldsymbol{C_{1i}^*}$
	C2	-	-	**45.9568(0.953)**	**48***	**47***	**46***	**46.1385(0.951)**
	A_0	4.1799(0.390)	4.1666(0.389)	4.1878(0.386)	4.1819(0.384)	4.1607(0.381)	4.1845(0.383)	4.1687(0.385)
	A_1	-0.0110(0.005)	-0.0103(0.005)	-0.0109(0.005)	-0.0110(0.055)	-0.0104(0.005)	-0.0106(0.005)	-0.0107(0.005)
	δ	0.4139(0.019)	0.4130(0.018)	0.4176(0.0182)	0.4165(0.0184)	0.4180(0.018)	0.4191(0.018)	0.4181(0.130)
$Var(b_{0i})$	d_{11}	27.3681(8.767)	25.7841(8.401)	25.4338(8.325)	24.6926(8.166)	24.7127(8.107)	24.5340(8.078)	24.4105(7.987)
$Var(\ b_{1i})$	d_{22}	0.0125(0.004)	0.0149(0.005)	0.0151(0.005)	0.0144(0.006)	0.0142(0.006)	0.0147(0.006)	0.0148(0.007)
$Var(\ b_{2i})$	d_{33}	-	0.0200(0.008)	0.0257(0.011)	0.0315(0.015)	0.0311(0.015)	0.0331(0.017)	0.0312(0.014)
$Var(\ b_{3i})$	d_{44}	-	-	0.1631(0.096)	0.2947(0.155)	0.2049(0.105)	0.1491(0.075)	0.1655(0.101)
$Var(a_{0i})$	d_{55}	3.0955(0.979)	3.0651(0.948)	3.0626(0.946)	3.0714(0.955)	3.0656(0.956)	3.0647(0.947)	3.0624(0.948)
$Cov(b_{0i}, a_{0i})$	d_{15}	7.0138(2.531)	7.2507(2.490)	7.1893(2.473)	7.1034(2.470)	7.1293(2.4521)	7.1003(2.443)	7.1047(2.432)
$Var(\varepsilon_{ij})$	σ^2	2.9808(0.140)	2.6957(0.130)	2.5293(0.124)	2.5516(0.131)	2.5349(0.1297)	2.5218(0.128)	2.5256(0.130)
DIC		**3940.8**	**3856.8**	**3813.1**	**3783.4**	**3770.7**	**3765.3**	**3767.7**

C_{1i}^* - random change point , to account National-wide campaigns. 46*(2nd quarter of 2008), 47*(3rd quarter of 2008),48*(4th quarter of 2008) known common change point to account the Europe-wide campaign

Table 4. *Total outpatient Antibiotic data.* Parameter estimates: posterior mean (and standard error) for the country specific and random effect obtained from Model 7.

Country	$^{*}C_{1i}$	b_{0i}	b_{1i}	b_{2i}	b_{3i}	a_{0i}
AT	21.691 (5.012)	-5.478 (1.304)	-0.051 (0.066)	0.097 (0.081)	0.089 (0.225)	-0.836 (0.456)
BE	31.303 (3.531)	7.390 (1.173)	-0.072 (0.047)	0.218 (0.094)	0.076 (0.251)	2.248 (0.448)
CY	13.633 (9.991)	2.807 (3.324)	0.121 (0.109)	0.115 (0.152)	-0.004 (0.406)	0.289 (0.941)
CZ	29.779 (9.341)	-0.045 (1.239)	-0.054 (0.055)	0.036 (0.106)	0.239 (0.259)	-0.079 (0.469)
DE	21.143 (9.316)	-4.260 (1.987)	-0.056 (0.088)	0.030 (0.100)	0.047 (0.229)	-0.372 (0.506)
DK	18.404 (9.357)	-6.574 (1.184)	0.024 (0.072)	0.016 (0.082)	-0.061 (0.224)	-1.994 (0.449)
EE	23.543 (8.851)	-5.556 (2.050)	-0.075 (0.081)	0.038 (0.100)	-0.137 (0.229)	-1.065 (0.495)
ES	21.024 (4.517)	2.491 (1.204)	-0.130 (0.061)	0.104 (0.077)	0.007 (0.227)	0.528 (0.455)
FI	21.868 (12.523)	0.143 (1.157)	-0.010 (0.063)	-0.083 (0.092)	0.119 (0.229)	-1.706 (0.452)
GR	23.415 (5.034)	5.638 (1.203)	0.285 (0.068)	0.208 (0.085)	-1.178 (0.371)	2.082 (0.474)
HR	23.262 (9.984)	-1.342 (1.994)	0.159 (0.122)	-0.218 (0.171)	-0.164 (0.250)	0.163 (0.473)
HU	23.595 (12.160)	1.829 (1.237)	-0.051 (0.068)	-0.200 (0.104)	0.264 (0.252)	1.539 (0.454)
IE	17.119 (10.561)	-1.605 (2.153)	0.050 (0.093)	0.012 (0.110)	-0.297 (0.240)	-0.999 (0.539)
IL	17.763 (11.008)	-0.842 (2.167)	0.039 (0.091)	-0.025 (0.114)	0.104 (0.234)	-0.795 (0.561)
IT	22.396 (11.190)	5.291 (2.131)	0.029 (0.083)	0.041 (0.102)	-0.093 (0.379)	2.234 (0.538)
LT	31.074 (6.269)	1.693 (2.807)	0.005 (0.0790	0.282 (0.148)	-0.185 (0.395)	1.724 (0.672)
LU	22.908 (11.150)	6.109 (2.277)	-0.002 (0.082)	0.032 (0.105)	0.177 (0.244)	2.933 (0.546)
NL	22.200 (10.518)	-8.683 (1.167)	-0.008 (0.063)	-0.010 (0.083)	0.071 (0.232)	-2.624 (0.450)
PT	23.640 (5.348)	4.913 (1.186)	0.085 (0.056)	-0.307 (0.081)	0.294 (0.237)	1.382 (0.453)
RU	25.041 (10.543)	-7.149 (2.643)	-0.066 (0.082)	0.030 (0.128)	0.432 (0.276)	-2.266 (0.611)
SE	19.867 (12.223)	-3.562 (1.153)	0.019 (0.067)	-0.114 (0.090)	-0.108 (0.225)	-2.265 (0.452)
SI	19.290 (12.341)	0.077 (1.176)	-0.032 (0.074)	-0.139 (0.103)	-0.009 (0.224)	-0.284 (0.448)
SK	22.717 (10.120)	7.286 (1.465)	-0.067 (0.073)	-0.030 (0.104)	0.116 (0.244)	2.814 (0.515)
UK	22.291 (7.571)	-2.573 (1.215)	-0.069 (0.068)	0.072 (0.080)	0.206 (0.234)	-1.967 (0.449)
IS	19.140 (10.158)	3.441 (1.205)	-0.053 (0.067)	-0.063 (0.092)	-0.088 (0.224)	-0.824 (0.454)
LV	21.353 (11.193)	-2.906 (2.501)	-0.090 (0.085)	-0.087 (0.124)	0.076 (0.245)	-0.670 (0.601)
PL	20.654 (11.897)	2.276 (1.298)	0.094 (0.086)	-0.039 (0.175)	0.002 (0.404)	1.030 (0.550)

Appendix II: Models for Outpatient penicillin use data

Table 5. *Outpatient penicillin use data J01C*. Parameter estimate: posterior mean (and standard error), and Model comparison: DIC values

Effects	**parameters**	**Model 1***	**Model 2***	**Model 3***
	β_0	8.1027(0.654)	8.3220(0.627)	8.3176(0.627)
	β_1	0.0287(0.139)	0.0131(0.016)	0.0144(0.018)
	β_2	-	0.0324(0.025)	0.0350(0.033)
	C1	-	25.8179(1.404)	C1*
	A_0	1.8937(0.222)	1.9587(0.258)	1.8596(0.212)
	A_1	-0.0021(0.005)	-0.0035(0.005)	-0.0009(0.005)
	δ	0.3845(0.023)	0.3830(0.022)	0.3797(0.022)
$Var(b_{0i})$	d_{11}	10.4820(3.324)	9.8328(3.278)	8.8341(2.942)
$Var(\ b_{1i})$	d_{22}	0.0047(0.0016)	0.0050(0.002)	0.0047(0.002)
$Var(\ b_{2i})$	d_{33}	-	0.0124(0.005)	0.0169(0.007)
$Var(a_{0i})$	d_{44}	0.9089(0.338)	1.4182(0.4676)	0.8423(0.319)
$Var(a_{1i})$	d_{55}	0.0004(0.0002)	0.0004(0.0002)	0.0004(0.0002)
$Cov(b_{0i}, a_{0i})$	d_{14}	2.6685(0.948)	2.2592(0.998)	2.6066(0.8964)
$Var(\varepsilon_{ij})$	σ^2	0.9582(0.045)	0.8205(0.040)	0.8193(0.039)
DIC		2830.3	2699.2	2635.7

Table 6. *Outpatient penicillin use data J01C.* Parameter estimates: posterior mean (and standard error) for the country specific and random effect obtained from Model 3*.

Country	$^*C_{1i}$		b_{0i}		b_{1i}		b_{2i}		a_{0i}		a_{1i}	
AT	22.694	(11.735)	-4.062	(0.793)	-0.007	(0.044)	0.044	(0.061)	-1.179	(0.302)	0.013	(0.009)
BE	25.229	(2.532)	1.191	(0.699)	-0.005	(0.029)	0.184	(0.044)	0.358	(0.269)	0.026	(0.009)
CY	24.714	(15.144)	2.142	(1.978)	0.053	(0.057)	0.021	(0.116)	0.591	(0.606)	-0.012	(0.017)
CZ	35.177	(9.999)	-0.092	(0.744)	-0.054	(0.029)	0.063	(0.074)	-0.019	(0.286)	-0.005	(0.009)
DE	28.847	(15.573)	-3.472	(1.021)	-0.033	(0.044)	-0.014	(0.078)	-1.001	(0.369)	0.010	(0.010)
DK	25.807	(16.695)	-1.232	(0.694)	0.026	(0.040)	-0.010	(0.077)	-0.413	(0.268)	-0.004	(0.008)
EE	28.443	(15.011)	-3.408	(1.067)	-0.034	(0.047)	-0.010	(0.080)	-0.950	(0.374)	0.011	(0.011)
ES	19.381	(2.764)	3.099	(0.716)	-0.093	(0.035)	0.129	(0.047)	0.969	(0.279)	-0.012	(0.009)
FI	30.744	(14.639)	-2.795	(0.688)	-0.017	(0.031)	0.010	(0.072)	-0.974	(0.284)	-0.005	(0.009)
GR	27.446	(10.867)	0.294	(0.700)	0.060	(0.033)	0.037	(0.069)	0.085	(0.269)	-0.022	(0.009)
HR	28.306	(1.831)	-0.965	(0.967)	0.140	(0.038)	-0.263	(0.055)	-0.144	(0.331)	0.005	(0.010)
HU	28.372	(12.547)	0.873	(0.744)	-0.038	(0.035)	-0.082	(0.075)	0.473	(0.294)	0.006	(0.009)
IE	27.604	(15.956)	-0.324	(1.229)	0.037	(0.050)	-0.023	(0.087)	-0.137	(0.408)	-0.004	(0.011)
IL	29.984	(13.719)	2.252	(1.426)	0.023	(0.049)	-0.071	(0.090)	0.589	(0.462)	-0.016	(0.012)
IT	24.489	(12.747)	1.762	(1.355)	0.038	(0.054)	0.070	(0.075)	0.564	(0.432)	0.015	(0.012)
LT	32.283	(6.768)	1.645	(1.840)	-0.010	(0.050)	0.203	(0.092)	0.640	(0.580)	0.032	(0.015)
LU	25.688	(13.635)	1.114	(1.353)	0.018	(0.053)	0.049	(0.072)	0.397	(0.440)	0.023	(0.012)
NL	29.280	(15.734)	-4.511	(0.693)	-0.015	(0.032)	-0.001	(0.073)	-1.358	(0.293)	-0.001	(0.009)
PT	20.667	(7.389)	2.185	(0.715)	0.063	(0.036)	-0.125	(0.054)	0.728	(0.276)	-0.005	(0.009)
RU	33.382	(10.798)	-5.061	(1.793)	-0.041	(0.051)	0.098	(0.084)	-1.487	(0.563)	0.007	(0.013)
SE	29.685	(16.255)	-1.026	(0.692)	-0.017	(0.035)	-0.026	(0.077)	-0.535	(0.289)	-0.021	(0.009)
SI	24.514	(17.247)	2.377	(0.713)	-0.017	(0.051)	-0.052	(0.086)	0.611	(0.281)	-0.009	(0.009)
SK	16.987	(9.917)	7.386	(0.972)	-0.045	(0.064)	-0.169	(0.082)	2.234	(0.406)	-0.022	(0.011)
UK	24.683	(9.685)	-1.105	(0.718)	-0.046	(0.037)	0.059	(0.052)	-0.460	(0.277)	-0.007	(0.009)
IS	31.154	(15.091)	2.251	(0.685)	-0.007	(0.031)	-0.062	(0.076)	0.488	(0.285)	-0.018	(0.009)
LV	26.178	(15.518)	-0.435	(1.548)	-0.049	(0.052)	-0.068	(0.087)	-0.103	(0.490)	0.001	(0.012)
PL	25.467	(15.529)	0.049	(0.768)	0.074	(0.052)	-0.001	(0.123)	0.077	(0.289)	0.015	(0.016)

Appendix III: Comparison between Belgium and observed average DID in Europe

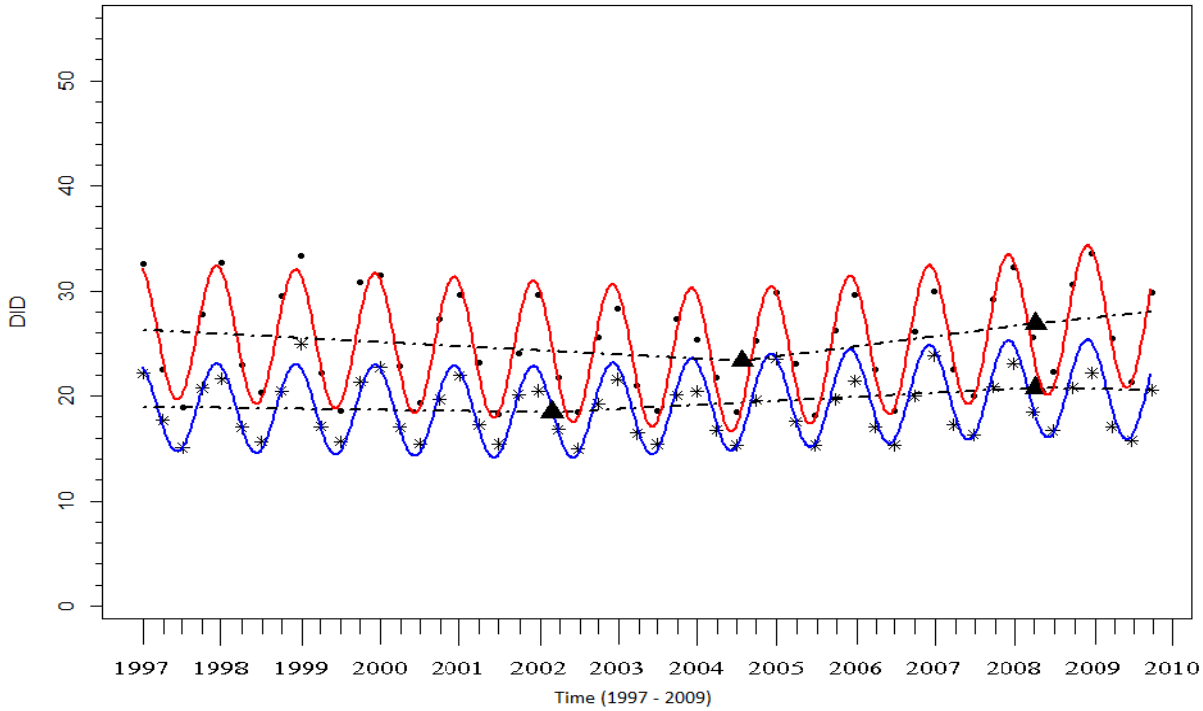

Figure 16. *Total outpatient antibiotic use data J01*. Comparison of the predicted mean profile (solid line), and the predicted linear trend (dashed line) and the change point (dense triangle) between Belgium and observed average DID in Europe

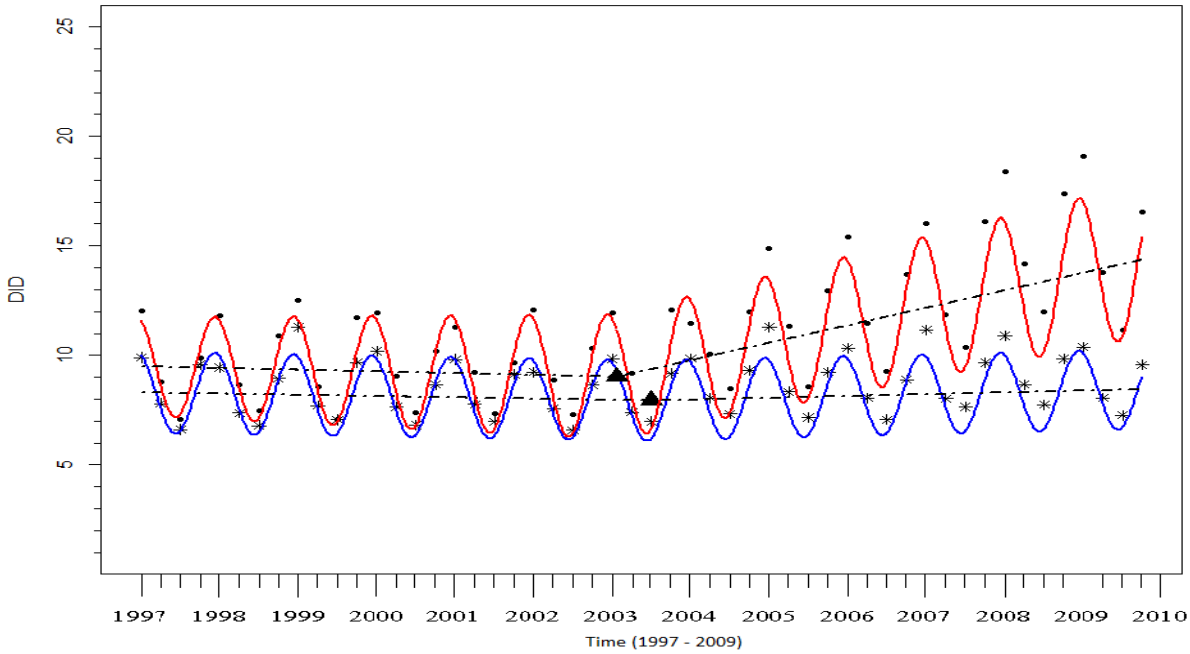

Figure 17. *Outpatient penicillin use data J01C.* Comparison of the predicted mean profile (solid line), and the predicted linear trend (dashed line) and the change point (dense triangle) between Belgium and observed average DID in Europe

Appendix IV: Comparison of antibiotic use model without change point by including and excluding the data from Cyprus

Table 7. *Total outpatient antibiotic use data J01.* Comparison of Model 1 between including and excluding the Cyprus data.

Effects	**parameters**	**Model 1 with Cyprus**	**Model 1 without Cyprus**
	β_0	18.0647(1.044)	17.8849(1.0781)
	β_1	0.0447(0.023)	0.0339(0.0223)
	A_0	4.1799(0.390)	4.1588(0.4103)
	A_1	-0.0110(0.005)	-0.0107(0.0058)
	δ	0.4139(0.019)	0.4159(0.0197)
$Var(b_{0i})$	d_{11}	27.3681(8.767)	26.6392(8.4866)
$Var(\ b_{1i})$	d_{22}	0.0125(0.004)	0.0113(0.0037)
$Var(a_{0i})$	d_{33}	3.0955(0.979)	3.1943(1.0134)
$Cov(b_{0i}, a_{0i}$	d_{13}	7.0138(2.531)	7.1730(2.5449)
$Var(\varepsilon_{ij})$	σ^2	2.9808(0.140)	2.9772(0.1404)
DIC		**3940.8**	**3922.4**

Table 8. *Outpatient penicillin use data J01C.* Comparison of Model 1 between including and excluding the Cyprus data.

Effects	**parameters**	**Model 1* with Cyprus**	**Model 1* without Cyprus**
	β_0	8.1027(0.654)	8.0477(0.6424)
	β_1	0.0287(0.139)	0.0259(0.0135)
	A_0	1.8937(0.222)	1.8487(0.2107)
	A_1	-0.0021(0.005)	-0.0011(0.0050)
	δ	0.3845(0.023)	0.3876(0.0236)
$Var(b_{0i})$	d_{11}	10.4820(3.324)	10.1976(3.2719)
$Var(\ b_{1i})$	d_{22}	0.0047(0.0016)	0.0043(0.0015)
$Var(a_{0i})$	d_{33}	0.9089(0.338)	0.8135(0.3164)
$Var(a_{1i})$	d_{44}	0.0004(0.0002)	0.0003(0.0002)
$Cov(b_{0i}, a_{0i})$	d_{13}	2.6685(0.948)	2.7203(0.9451)
$Var(\varepsilon_{ij})$	σ^2	0.9582(0.045)	0.9597(0.0459)
DIC		**2830.3**	**2815.1**

Appendix V: R and WinBUGS codes

```
##############################################################################
############# Model  7 for Total outpatient antibiotic use data#################
##############################################################################

####### for WinBUGS#######

model{

#####  Basic model ######
for (i in 1:N){
            Y[i] ~ dnorm(mu[i],tau)
            mu[i]<- (B0 + b[ID[i],4]) +
                        (B1 + b[ID[i],1])*T[i] +
                        (B2 + b[ID[i],2])*(T[i]-C1[ID[i],1])*(step(T[i]-C1[ID[i],1])) +
                        (B3 + b[ID[i],3])*(T[i]-C2)*(step(T[i]-C2)) +
                        (alpha + b[ID[i],5] + alphaTime*T[i])*sin(omega*T[i] + delta)
    }

#### Priors for fixed effects #####
B0   ~   dnorm(0,0.0001)
B1   ~   dnorm(0,0.0001)
B2   ~    dnorm(0,0.0001)
B3   ~    dnorm(0,0.0001)
alpha~   dnorm(0,0.0001)
alphaTime~ dnorm(0,0.0001)
delta ~   dnorm(0,0.0001)
 C2  ~   dunif(40,52)

####  Priors for random effects ####
for (j in 1:M){
            b[j,1] ~     dnorm(0,b1.tau)
            b[j,2] ~     dnorm(0,b2.tau)
            b[j,3]~      dnorm(0,b3.tau)
            b[j,4:5] ~  dmnorm(mean[],b.tau[1:2, 1:2])
            C1[j,1] ~   dunif(1, 40)
        }

##### prior for random change point ####
for (j in 1:M){
            C1[j,1]~ dunif(1, 40)
        }


#### Hyper priors ####
tau   ~     dgamma(0.001, 0.001)
b1.tau ~  dgamma(0.001, 0.001)
b2.tau ~  dgamma(0.001, 0.001)
b3.tau ~  dgamma(0.001, 0.001)
 b.tau[1:2, 1:2]~ dwish(R[1:2,1:2],2)

sigma <-      1/tau
sigma_b1<- 1/b1.tau
sigma_b2<- 1/b2.tau
sigma_b3<- 1/b3.tau
 sigma_b[1:2,1:2] <-inverse(b.tau[1:2, 1:2])
}
```

```
########## For R############

####The remove the contents of the workspace####
rm(list=ls(all=TRUE))

####R2WinBUGS package #####
library(R2WinBUGS)

####Set the directory ####
setwd("C:\\Users\\tadele\\Desktop\\thesis\\Results\\results for total antibiotic use J01")
BugsPath = "C:/Users/tadele/Desktop/deskttop/WinBUGS14"

#### Import the original data ####
dat = read.table("data1.txt",header=TRUE)
names(dat)
dat<-dat[order(dat[,3],dat[,1]), ]
attach(dat)

#### Create the data for the WinBUGS model ####
country=as.data.frame(unique(dat[,2]))
Y=dat$DID
T=dat$time
ID=dat$country_ID
M=length(unique(dat$country_ID))
N=length(T)

data<-list(N=N,M=M,Y=Y,ID=ID,T=T,omega=1.570796, mean = c(0,0),
        R = structure(.Data = c(0.01, 0,
                                0, 0.01), .Dim = c(2,2)))

#### Give initial values ####
inits1=list(B0=18.9827, B1=-0.0094, B2=0.1082, B3=-0.1369,  C2=47, alpha=4.1878, alphaTime=-0.0109,
delta=0.4176,
        tau=(1/2.5293), b1.tau=(1/0.0151), b2.tau=(1/0.0257), b3.tau=(1/0.1631),
        b.tau = structure(.Data = c((1/25.4338), (1/7.1893),
                          (1/7.1893), (1/3.0626)), .Dim = c(2, 2)),
        b=structure(.Data=c(rep(0,each=5,times=M)),.Dim=c(M,5)),
        C1=structure(.Data=c(rep(29,each=1,times=M)),.Dim=c(M,1)))
inits2=list(B0=20.0007, B1=-0.0054, B2=0.1097, B3=-0.1352, C2=48, alpha=4.1851, alphaTime=-0.0115,
delta=0.4165,
        tau=(1/2.5303), b1.tau=(1/0.0155), b2.tau=(1/0.0255), b3.tau=(1/0.1636),
        b.tau = structure(.Data = c((1/25.2838), (1/7.2193),
                          (1/7.2193), (1/3.1826)), .Dim = c(2, 2)),
        b=structure(.Data=c(rep(0,each=5,times=M)),.Dim=c(M,5)),
        C1=structure(.Data=c(rep(27,each=1,times=M)),.Dim=c(M,1)))
inits=list(inits1,inits2)


####Give the parameters you want to monitor####
parameters=c("B0","B1","B2","B3","C1","C2","alpha","alphaTime","delta","sigma","sigma_b1","sigma_b2",
             "sigma_b3", "sigma_b", "b")

####Give the model (.txt file) ####
modelex="Model 5C-c-C1.txt"

####MCMC parameters ####
nchainex=length(inits)
niterex=331000
nburninex=11000
nthinex=40
```

```
#### Call the bugs function ####
sims1<-bugs(data, inits, parameters, modelex, nchainex, niterex, nburninex, nthinex, digits=4,
                bugs.directory=BugsPath, debug=T)

#### display the output####
print(sims1,digits=4)

#############################################################################################
############## Model 3* Outpatient penicillin use data ######################################
#############################################################################################

######## for WinBUGS#######

model{

#### Basic model ####
for (i in 1:N){
          Y[i] ~ dnorm(mu[i],tau)
          mu[i]<- (B0 + b[ID[i],2]) +
                    (B1 + b[ID[i],1])*T[i] +
                    (B2 + b[ID[i],5])*(T[i]-C1[ID[i],1])*step(T[i]-C1[ID[i],1]) +
                     (alpha + b[ID[i],3] + (alphaTime + b[ID[i],4])*T[i])*sin(omega*T[i] + delta)
               }

#### Priors for fixed effects ####
B0  ~    dnorm(0,0.0001)
B1  ~    dnorm(0,0.0001)
B2  ~    dnorm(0,0.0001)
alpha ~ dnorm(0,0.0001)
alphaTime~dnorm(0,0.0001)
delta ~  dnorm(0,0.0001)


  ####  Priors for random effects ####
for (j in 1:M){
          b[j,1] ~    dnorm(0,b1.tau)
          b[j,4] ~    dnorm(0,bs.tau)
          b[j,5] ~    dnorm(0,bc1.tau)
         b[j,2:3] ~  dmnorm(mean[],b.tau[1:2, 1:2])
                      }

##### prior for random change point ####
for (j in 1:M){
           C1[j,1]~ dunif(1,52)
                    }


#### Hyper priors ####
tau  ~        dgamma(0.001, 0.001)
b1.tau  ~    dgamma(0.001, 0.001)
bs.tau  ~    dgamma(0.001, 0.001)
bc1.tau  ~  dgamma(0.001, 0.001)
b.tau[1:2, 1:2] ~  dwish(R[1:2,1:2],2)

sigma <-        1/tau
sigma_b1<-    1/b1.tau
sigma_bs<-    1/bs.tau
sigma_bc1<-  1/bc1.tau
```

```
sigma_b[1:2,1:2] <- inverse(b.tau[1:2, 1:2])

}


########## For R############

####The remove the contents of the workspace ####
rm(list=ls(all=TRUE))

####R2WinBUGS package####
library(R2WinBUGS)

#####Set the directory####
setwd("C:\\Users\\tadele\\Desktop\\thesis\\Results\\results for total antibiotic use J01C")
BugsPath = "C:/Users/tadele/Desktop/deskttop/WinBUGS14"
setwd("C:\\Users\\tadele\\Desktop\\thesis\\Results\\results for total antibiotic use J01C\\last ok")

####Import the original data####
dat = read.table("data_J01C.txt",header=TRUE)
names(dat)
dat<-dat[order(dat[,3],dat[,1]), ]
attach(dat)

####Create the data for the WinBUGS model####
country=as.data.frame(unique(dat[,2]))
Y=dat$DID
T=dat$time
ID=dat$country_ID
M=length(unique(dat$country_ID))
N=length(T)
data<-list(N=N, M=M, Y=Y, ID=ID, T=T,R = structure(
  .Data = c(0.1, 0,
                0, 0.1), .Dim = c(2,2)), omega=1.570796, mean = c(0,0))

####Give initial values #####
inits1=list(B0=8.1027, B1=0.0131, B2=0.0324, alpha=1.9587, alphaTime=-0.0035, delta=0.3830,
        tau=(1/0.8205), b1.tau=(1/0.0050), bs.tau=(1/0.0004), bc1.tau =(1/0.0124),
        b.tau = structure(
          .Data = c((1/9.8328), (1/2.2592),
                (1/2.2592), (1/1.4182)), .Dim = c(2, 2)),
        b=structure(.Data=c(rep(0,each=5,times=M)),.Dim=c(M,5)),
        C1=structure(.Data=c(rep(26,each=1,times=M)),.Dim=c(M,1)))
inits2=list(B0=8.1077, B1=0.0134, B2=0.0327, alpha=1.9581, alphaTime=-0.0039, delta=0.3825,
        tau=(1/0.8221), b1.tau=(1/0.0051), bs.tau=(1/0.000405), bc1.tau =(1/0.0126),
        b.tau = structure(
          .Data = c((1/9.9328), (1/2.3592),
                (1/2.3592), (1/1.4152)), .Dim = c(2, 2)),
        b=structure(.Data=c(rep(0,each=5,times=M)),.Dim=c(M,5)),
        C1=structure(.Data=c(rep(26,each=1,times=M)),.Dim=c(M,1)))
inits=list(inits1,inits2)

####Give the parameters you want to monitor#####
parameters=c("B0","B1","B2","C1","alpha","alphaTime","delta","sigma","sigma_b","sigma_b1", "sigma_bs",
                "sigma_bc1","b")

#### Give the model (.txt file) ####
modelex="Model 1c-rand.txt"

#### MCMC parameters ####
```

```
nchainex=length(inits)
niterex=410000
nburninex=10000
nthinex=40


####Call the bugs function####
sims1<-bugs(data, inits, parameters, modelex, nchainex, niterex, nburninex, nthinex, digits=4,
                bugs.directory=BugsPath, debug=T)

#### display the output####
print(sims1,digits=4)
```

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adaptive change-point mixed models to data on outpatient antibiotic use in Europe

Richting: **Master of Statistics-Biostatistics**
Jaar: **2012**

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Datum: **14/09/2012**