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Adaptive change-point mixed models applied to data on outpatient tetracycline use in Europe

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Abstract: In this paper, we propose a change-point mixed model to assess the change in the trend of outpatient antibiotic use in a Bayesian framework, where the change-points are unknown parameters of the model. Model selection using DIC indicates that the data supports the model with a country-specific change-point. The location of the change-points may be related to points in time where public health strategies aiming at increasing the awareness of the public to a more rational use of antibiotics or targeting to reduce overconsumption of antibiotics were initiated.

Key words: amplitude; antibiotic use; change-point model; non-linear model; phase shift; seasonal variation

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1 Introduction

Antibiotics are drugs that inhibit or abolish the growth of bacteria. Antibiotic resistance is a major European and global public health problem and international efforts

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are needed to counteract the emergence of resistance. The increase in resistance rate of many important 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 suggest that this increase is directly related to the actual use of antibiotics. Antibiotic use is increasingly recognized as the main driver for resistance and differential selection pressure of antibiotic agents may be responsible for some of the observed differences (Goossens *et al*., 2005; Davey *et al*., 2008; Huttner *et al*., 2010).

Specific actions such as campaigns aimed at the public and general practitioners appeared essential, because antibiotic use in outpatients accounts for the main part of the overall antibiotic usage (>90%) (Goossens *et al*., 2005; Adriaenssens *et al*., 2011). Campaigns directed to the public in order to (*i*) inform about antibiotic resistance and to warn about the medical and general health issues related to the inappropriate use of antibiotics and (*ii*) foster the patient–physician and patient–pharmacist dialogue about the appropriate use of antibiotics, will increase the awareness of the public to a more rational use of antibiotics. In some European countries (e.g., in Belgium, France, Germany, Greece, Iceland, Italy, Luxembourg, Portugal, Spain and United Kingdom), campaigns were planned as part of a national strategy to reduce resistance to antimicrobial drugs. These strategies also included measures to promote appropriate use of antimicrobial drugs in hospitals, long-term care facilities and the agricultural sector (Huttner *et al*., 2010).

Longitudinal data on outpatient antibiotic use were available from 27 European countries for the period 1997–2009 within the European Surveillance of Antimicrobial Consumption (ESAC) project (Adriaenssens *et al*., 2011; Coenen *et al*., 2011; Minalu *et al*., 2011). Given that repeated measures were taken for each country, intra-country correlation has to be taken into account when analyzing the data. The main objective of the study is to develop an appropriate statistical model to assess the significance of country-specific trends in Europe and to identify possible change-points, while accounting for country-specific global use as well as seasonal effects.

In common regression, time series or longitudinal data analysis, the outcome variable is modelled as a linear function of explanatory variables and/or time. Sometimes it may happen that the relationship between the outcome and some explanatory variables and/or time is non-smooth (non-differentiable), showing one or more points where the effect on the response changes abruptly. These points are called break-points, change-points, transition-points or switch-points. To estimate the change-points, Bayesian (Smith, 1975; Carlin *et al*., 1992; Lange *et al*., 1992; Kiuchi *et al*., 1995; Slate and Turnbull, 2000; Ghosh and Vaida, 2007; Dominicus *et al*., 2008) or likelihood (Pastor and Guallar, 1998; Hall *et al*., 2000; Hall *et al*., 2003; Muggeo, 2003; Jacqmin-Gadda *et al*., 2006; Hens *et al*., 2010) methods may be used.

Within the likelihood framework, Pastor and Guallar (1998) used a two-segmented logistic regression model to estimate a change-point in the context of dose–response analysis in epidemiological studies. Muggeo (2003) proposed an approach to estimate broken line models reducing the problem to a linear framework. Jacqmin–Gadda

et al. (2006) proposed a random change-point model which combines a piecewise polynomial mixed model with a random change-point for the evolution of the cognitive test and a log-normal model depending on the random change-point for the time to dementia.

A fully Bayesian hierarchical structure for a mixed effects segmented regression model with one change-point was considered by Slate and Turnbull (2000), and applied to large data sets concerning prostate specific antigen as a serial marker for prostate cancer. Ghosh and Vaida (2007) proposed a change-point model with one random change-point for the analysis of longitudinal CD4 T-cell counts for HIV infected subjects following highly active antiretroviral treatment. And Dominicus *et al.* (2008) studied a Bayesian random change-point model with one random change-point to capture variability in measures of cognitive function. Hall *et al.* (2003) compared the Bayesian approach with the likelihood approach for modelling cognitive function over time, and pointed out that the Bayesian method has an advantage over the likelihood method in that it does not require all subjects to have the same change-point.

In this paper, an adaptive Bayesian linear spline model is proposed, where the number of knots (change-points) and their location are data driven and determined by the deviance information criterion (DIC). The presence and the location of the change-points is data driven and can vary across countries as random change-points. Latent country-specific indicators allow the model to switch off the change-points for particular countries.

The application of the model may yield new and important insights in the evolution of outpatient antibiotic use in Europe. We employ a fully Bayesian approach. The models are implemented in R using the R-package R2WinBUGS (Sturtz *et al.*, 2005). The programs used for the analyses are available upon request from the first author. The program used to fit the change-point model with one unknown common change-point, one country-specific random change-point and a country-specific latent indicator for the change-point is included in Appendix III.

The paper is organized as follows. In Section 2, we describe the data on the total outpatient antibiotic use analyzed in the paper. In Section 3, we describe the models, the prior distributions for the parameters and we discuss how model comparison was applied. Results are presented in Section 4. Finally, discussions and concluding remarks are included in Section 5.

2 Outpatient antibiotic use data

Quarterly ESAC-NET data on total outpatient antibiotic use from 27 European countries were collected for the period 1997–2009 within ESAC-NET, an international network of surveillance systems. The methods of data collection and processing for the ESAC-NET project have been described in detail elsewhere (Adriaenssens *et al.*, 2011; Coenen *et al.*, 2011), and are also available on the ESAC-NET website (www.esac.ua.ac.be). Antibiotic use data is expressed as the number of defined

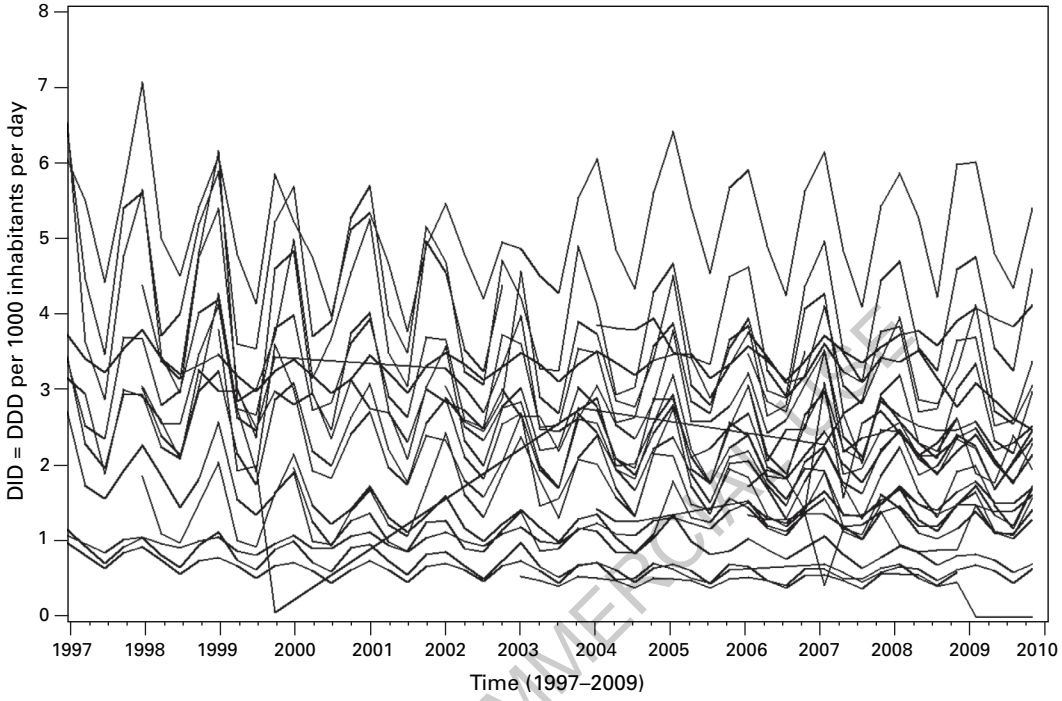


Figure 1 Observed country-specific evolutions for the quarterly use of tetracycline expressed in DID in 27 European countries

daily doses (DDD) per 1000 inhabitants per day (DID). This paper focuses on the outpatient use of tetracycline for the period 1997–2009, with the observed country-specific trends for the quarterly tetracycline use in DID shown in Figure 1.

As can be seen in Figure 1, there is variability across repeated measurements from the same country (i.e., within-country variability) as well as variability between countries (i.e., between-country variability), which suggests that country-specific intercepts and slopes should be incorporated into the model to account for heterogeneity across countries. The longitudinal profiles show clear seasonal variation of outpatient tetracycline use in all countries, with upward peaks in the winter season. Thus, a non-linear model needs to be adopted to take the seasonality into account. From the longitudinal profiles it can clearly be seen that countries with higher tetracycline use at the baseline (in 1997) have a higher amplitude (higher seasonal variation). Figure 1 also shows that not all longitudinal profiles are complete for all countries. Some profiles start later in time and others show intermediate missing parts. As the missingness mechanism is assumed to be missing completely at random (MCAR), all analyses were based on all available cases.

3 Adaptive change-point models

We start by introducing a non-linear mixed model with a sinusoidal component over time to account for the seasonal variation. We extend the non-linear mixed model by including fixed and random change-points to identify possible changes in the trend of tetracycline use in DID. We extend the existing approaches for random change-point models (e.g., Kiuchi *et al*., 1995; Ghosh and Vaida, 2007; Dominicus *et al*., 2008) by a general model building procedure where the number of knots and their location are data driven, and by taking into account a country-specific seasonal variation. The change-point models were also extended by including country-specific latent indicators, allowing the model to switch off the change-points for particular countries. All models are fitted in a fully Bayesian paradigm.

3.1 Non-linear mixed model

We applied the non-linear mixed model (3.1) to model the use of tetracycline in DID. An extension with known common change-points, unknown common change-points and country-specific random change-points is then considered. The non-linear mixed model is formulated as

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + (\beta_0^S + b_{0i}^S + \beta_1^S t_{ij}) \sin(\omega t_{ij} + \delta) + \varepsilon_{ij}, \qquad (3.1)$$

where Y_{ij} is the total outpatient tetracycline use in DID for country i ($i = 1, 2, \ldots, N$) at time points t_{ij} ($j = 1, 2, \ldots, n_i$), n_i is the number of observations from the ith country, time = 1 corresponds to the start of the study (first quarter of 1997), $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_0^S, \beta_1^S, \delta)$ is a vector of fixed effects, β_0 is the intercept, β_1 is the regression coefficient describing the marginal linear time trend (t), β_0^S is the fixed amplitude, β_1^S is the amplitude varying over time, ω (in radians) is the frequency which is a known constant ($= 2\pi/T$) where T (= 4) is the period for the sine curve, δ (in radians) is the phase shift or phase angle which is an unknown parameter, $\boldsymbol{b_i} = (b_{0i}, b_{1i}, b_{0i}^S)$ 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 and b_{0i}^S is the country-specific random slope for amplitude and we assume $\boldsymbol{b_i} \sim N(0, \boldsymbol{D})$. The matrix $\boldsymbol{D}$ is a general covariance matrix with elements $d_{ij} = d_{ji}$. $\boldsymbol{\varepsilon}_i$ is an n_i-dimensional vector of unexplained error terms ε_{ij}. It is usually assumed that all $\boldsymbol{\varepsilon}_i$ are independent and normally distributed with mean vector zero and covariance matrix $\boldsymbol{\Sigma}_i$. Often, $\boldsymbol{\Sigma}_i$ is assumed equal to $\sigma_\varepsilon^2 \boldsymbol{I}_{n_i}$, where $\boldsymbol{I}_{n_i}$ is the n_i-dimensional identity matrix.

Since no convergence was obtained when using an unstructured covariance matrix for the random effects, a diagonal covariance matrix was used.

3.2 Adaptive change-point model

Since there is no prior knowledge on the number of change-points, we gradually build up the model by first considering a change-point model with a known common change-point and then extending it by including unknown common and country-specific random change-points.

A general mixed model with country-specific mean can be written as

$$Y_{ij} = \mu_i(t_{ij}) + \varepsilon_{ij}, \quad i = 1, 2, \ldots, N; \; j = 1, 2, \ldots, n_i,$$
$$\mu_i(t_{ij}) = \mu_i^T(t_{ij}) + \mu_i^S(t_{ij}), \tag{3.2}$$

where Y_{ij} is the tetracycline use in DID for country i at time points 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 which is assumed to be normally distributed with mean zero and constant variance σ_ε^2. The country-specific mean components $\mu_i^T(t_{ij})$ and $\mu_i^S(t_{ij})$ are modelled as

$$\mu_i^T(t_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \mu_i^{CP}(t_{ij}),$$
$$\mu_i^S(t_{ij}) = (\beta_0^S + b_{0i}^S + \beta_1^S t_{ij})\sin(\omega t_{ij} + \delta), \tag{3.3}$$

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

$$\mu_i^{CP}(t_{ij}) = \sum_{k=1}^{K} (\beta_{(k+1)} + b_{(k+1)i})(t_{ij} - K_{ki})_+, \tag{3.4}$$

where $x_+ = \max(x, 0)$, K is the number of unknown change-points, $K_{ki} = C_k$ or $K_{ki} = C_k + c_{ki}$ or $K_{ki} = c_{ki}$ where C_k denotes a global change-point and c_{ki} a country-specific random change-point. If $\mu_i^{CP}(t_{ij}) = 0$ then there are no change-points and the model reduces to model (3.1).

Substituting equations (3.3) and (3.4) in equation (3.2) yields the model

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \sum_{k=1}^{K} (\beta_{(k+1)} + b_{(k+1)i})(t_{ij} - K_{ki})_+ + (\beta_0^S + b_{0i}^S + \beta_1^S t_{ij})\sin(\omega t_{ij} + \delta) + \varepsilon_{ij}, \tag{3.5}$$

where the fixed effects β_0, β_1, β_0^S, β_1^S, ω and δ, and the random effects b_{0i}, b_{1i} and b_{0i}^S are defined as before, K is the number of change-points, for $k = 1, 2, \ldots, K$, $\beta_{(k+1)}$ is the global difference in the linear trend before and after the change-point, $b_{(k+1)i}$ is the country-specific difference in the linear trend before and after the change-point and ε_{ij} is an unexplained error term. Random effects for the 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 countries. The number of change-points K and the location of the change-point(s) are data driven.

In Equation (3.5) all countries are assumed to have a change in the trend of tetracycline use in DID, but this might not be true because some countries might not have a change in the trend of tetracycline use. To relax this assumption, we extend (3.5) by including country-specific latent indicators for the change-points,

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \sum_{k=1}^{K}\{(\beta_{(k+1)} + b_{(k+1)i})(t_{ij} - K_{ki})_+\}I_{ki} + (\beta_0^S + b_{0i}^S + \beta_1^S t_{ij})\sin(\omega t_{ij} + \delta) + \varepsilon_{ij}, \quad (3.6)$$

where I_{ki} is an unknown country-specific indicator for the change in the trend of tetracycline use in DID for country i for the kth change-point, $k = 1, 2, \ldots, K$ where K is the number of change-points. Here, $I_{ki} = 1$ if there is a change at knot K_{ki} in the use of tetracycline over time in country i, or $I_{ki} = 0$ if there is no change in the use of tetracycline over time in country i.

As there are no prior information on the number of change-points in the study, the number of change-points K in Equations (3.5) and (3.6) has to be chosen prior to the data fitting, $k = 1, \ldots, K$. We first start from the simplest model where there is only a known common change-point, i.e., $K = 1$. We gradually extend the model by including a known and an unknown common change-point. And later, we extended the model by including an additional unknown common change-point. Next to the common change-points, country-specific random change-points have also been included in the model.

3.3 Prior specification

The following uninformative prior distributions were used for the fixed effects:

$$\begin{aligned}\beta_0, \beta_1, \beta_{(k+1)}, \beta_0^S, \quad \beta_1^S, \delta &\sim \text{Normal}(0, 1000), \text{ independently where } k = 1, \ldots, K,\\ C_1 &\sim \text{Uniform}(1, 52),\\ C_2 &\sim \text{Uniform}(C_1, 52).\end{aligned} \quad (3.7)$$

The normal priors on $\beta_0, \beta_1, \beta_{(k+1)}, \beta_0^S, \beta_1^S$ and δ have large variances, expressing our lack of knowledge about the regression coefficients. For the random effects, a normal prior distributions was used:

$$\begin{aligned}b_{0i} &\sim \text{Normal}(0, \sigma_{b_0}^2),\\ b_{1i} &\sim \text{Normal}(0, \sigma_{b_1}^2),\\ b_{(k+1)i} &\sim \text{Normal}(0, \sigma_{b_{(k+1)}}^2),\\ b_{0i}^S &\sim \text{Normal}(0, \sigma_{b_0^S}^2),\\ c_{ki} &\sim \text{Normal}(C_k, \sigma_{c_k}^2)I(1, 52).\end{aligned} \quad (3.8)$$

A uniform prior distribution over the total range of time was also assumed for the country-specific random change-point:

$$c_{ki} \sim \text{Uniform}(1, 52). \tag{3.9}$$

The country-specific indicator for the kth change-point (I_{ki}) is Bernoulli-distributed with probability P_k, where the probability P_k is beta-distributed with shape parameters α_p (=1) and β_p (=1):

$$\begin{aligned} I_{ki} &\sim \text{dbern}(P_k), \\ P_k &\sim \text{dbeta}(1,1). \end{aligned} \tag{3.10}$$

The hyperparameters in the prior distributions were chosen so that the priors are uninformative. An independent inverse gamma distribution with a shape parameter α (=0.001) and a scale parameter β (=0.001) was used for the variance parameters.

$$\sigma^2_{b_0}, \sigma^2_{b_1}, \sigma^2_{b_{(k+1)}}, \sigma^2_{b_0^s}, \sigma^2_{c_k}, \sigma^2_{\varepsilon} \sim \text{IGamma}(0.001, 0.001), \text{ independently,} \tag{3.11}$$

where $x \sim \text{IGamma}(\alpha, \beta)$ means that $1/x$ has the Gamma distribution with mean α/β and variance α/β^2 (Ntzoufras, 2009).

3.4 Model selection

We use the DIC for model comparison (Spiegelhalter *et al*., 2002). The DIC can be represented as:

$$DIC = p_D + \bar{D}. \tag{3.12}$$

DIC is a Bayesian equivalent to Akaike's information criterion (AIC) and consists of two components, a term that measures goodness-of-fit ($\bar{D}$, defined as the posterior expectation of the deviance) and a penalty term for model complexity (p_D, defined as the difference between the posterior mean of deviance and the deviances evaluated at the posterior mean $\bar{\theta}$ of the parameters). $p_D = \bar{D} - D(\bar{\theta})$. The smaller the DIC, the better the fit (Spiegelhalter *et al*., 2002; Gelman *et al*., 2004; Ghosh and Vaida, 2007; Dominicus *et al*., 2008).

There has been and there still is discussion on Bayesian model selection in general and on the specification of the prior for model selection and hypothesis testing, related to the Jeffreys-Lindley paradox (Lindley, 1957). See, for instance, Spiegelhalter *et al*. (2002) in which pros and cons of several approaches to Bayesian model selection are discussed by the authors and several discussants. Posterior model probabilities and Bayes factors might be considered to represent the gold standard in fully Bayesian model determination, but these quantities are sensitive to the choice of prior distribution in the case of specifying a default prior under weak prior information (Overstall and Forster, 2010). Criterion-based methods such as BIC or DIC do not give posterior model probabilities, and as such the issue of default prior specification is avoided. Here we opted for DIC as a criterion for model selection. An in-depth analysis of this issue with a comparison of the performance and characteristics of

different model selection criteria is considered beyond the scope of this paper. For more details and some recent developments on this issue related to Lindley's paradox, we refer to Casella *et al*. (2009), Mulder *et al*. (2009), Overstall and Forster (2010), and references therein.

Plummer (2008) provided a justification for the DIC by demonstrating the link between DIC and cross-validation. In his paper, DIC is shown to be an approximation to a penalized loss function based on the deviance, with a penalty derived from a cross-validation argument. This approximation is valid only when the effective number of parameters in the model is much smaller than the number of independent observations (i.e., $p_D << n$). A corrected DIC, $DIC_c = \bar{D} + \sum_{i=1}^{n} p_{D_i}/(1 - p_{D_i})$, was suggested for generalized linear mixed models when the DIC cannot be justified as approximation to the penalized plug-in deviance. To the best of our knowledge, the use of the corrected DIC has not been studied for non-linear mixed models and requires further research. Therefore, we do not pursue its use in this paper.

The quarterly tetracycline use data was analyzed in Minalu *et al*. (2011) using the non-linear mixed model. The results of the non-linear mixed models were used as a starting value for the MCMC algorithm. And for the additional change-point parameters, the locations of campaigns or policy changes in antibiotic use in most European countries were used as starting values. To ensure adequate convergence all results were obtained using two chains of 110 000 iterations, of which we discarded the first 10 000 (burn-in) and the chain was then thinned to every 5th sample as there was autocorrelation for some parameters. Trace plots and the potential scale reduction $\hat{R}$ were used to check convergency of the MCMC algorithm (Gelman *et al*., 2004).

4 Results

We considered the following models, within the family (3.5):

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

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

Model 2: Non-linear mixed model with a known common change-point ($C_1 = 17$),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - 17)_+,$$

Model 3: Non-linear mixed model with a known common change-point ($C_1 = 29$),

$$\mu_i^{CP}(t_{ij}) = (\beta_2 + b_{2i})(t_{ij} - 29)_+,$$

Model 4: 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 5: Non-linear mixed model with two unknown common change-points (C_1 and C_2),

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

where ordering restriction was imposed for the common change-points (i.e., $C_1 < C_2$).

Model 6: Non-linear mixed model with one country-specific random change-point (c_i),

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

where the country-specific random change-point is centred around the unknown point C_1 and is restricted to lay within [1,52], $c_i \sim N(C_1, \sigma_c^2)(1, 52)$.

Model 7: Non-linear mixed model with one country-specific random change-point (c_i),

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

where the country-specific random change-points are $U(1, 52)$ distributed.

Model 1 without a change-point is first extended with known common change-points (Models 2 and 3). Because there were public campaigns in some of the European countries during the year 2000–01 (e.g., in Belgium, Germany and Greece) and during the year 2004–05 (e.g., in Portugal and United Kingdom), we used time = 17 (first quarter of 2001) and time = 29 (first quarter of 2004) as known common change-points in the trend of tetracycline use in DID, respectively, in Model 2 and Model 3. Next, we estimate the change-points by including unknown common and/or country-specific random change-points (Models 4–7). The non-linear mixed model (Model 1) was extended by including a non-linear trend and secondly an amplitude varying non-linearly over time (expressed as t_{ij}^{α}). As these extended models did not outperform the change-point models, we only presented the results of the original non-linear and the change-point models (Models 1–7). Various models with three change-points were applied too, but convergence could not be reached for any of these models.

For the unknown common change-points in Models 4–6, uniform prior distributions over the total range of time were used. A normal prior distribution with mean zero and variance $\sigma_{c_k}^2$ was used for the country-specific random change-point in Model 6, while in Model 7 a uniform prior distribution over the total range of time was assumed for the country-specific random change-point. A summary of the posterior distributions of the model parameters in Models 1–7 is given in Table 1.

The results in Table 1 clearly indicate the need for one or more change-points. Indeed, Model 1 (no change-points) gets little support with the highest DIC = 391.6500. Including a known common change-point reduces the DIC considerably (Models 2

Table 1 Parameter estimates: posterior means (and standard errors), and model comparison ($\bar{D}$, p_D and DIC values)

Parameters	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
β_0	2.6399 (0.2630)	2.7620 (0.3121)	2.5814 (0.2941)	2.6367 (0.2505)	2.7240 (0.2770)	2.5937 (0.2986)	2.6330 (0.2815)
β_1	−0.0087 (0.0041)	−0.0253 (0.0074)	−0.0118 (0.0067)	−0.0115 (0.0065)	−0.0212 (0.0078)	−0.0133 (0.0064)	−0.0146 (0.0071)
β_2	-	0.0202 (0.0076)	0.0093 (0.0089)	0.0098 (0.0088)	0.0213 (0.0119)	0.0112 (0.0102)	0.0118 (0.0109)
β_3	-	-	-	-	−0.0048 (0.0142)	-	-
C_1	-	17*	29*	29.3975 (1.2912)	20.2353 (3.1875)	29.4144 (2.8802)	-
C_2	-	-	-	-	31.9461 (1.4710)	-	-
β_0^S	0.6176 (0.0629)	0.6098 (0.0622)	0.6112 (0.0614)	0.6109 (0.0618)	0.6083 (0.0616)	0.6100 (0.0612)	0.6113 (0.0618)
β_1^S	−0.0064 (0.0010)	−0.0062 (0.0009)	−0.0062 (0.0008)	−0.0062 (0.0008)	−0.0062 (0.0008)	−0.0062 (0.0008)	−0.0062 (0.0008)
δ	0.4972 (0.0245)	0.5041 (0.0228)	0.4989 (0.0217)	0.4988 (0.0216)	0.5016 (0.0211)	0.5002 (0.0213)	0.5004 (0.0212)
$\sigma^2_{b_0}$	1.8174 (0.5703)	2.0457 (0.6508)	1.9518 (0.6247)	1.9091 (0.5979)	1.8666 (0.5975)	1.9835 (0.6359)	2.0599 (0.6536)
$\sigma^2_{b_1}$	0.0004 (0.0001)	0.0009 (0.0003)	0.0009 (0.0003)	0.0009 (0.0003)	0.0008 (0.0003)	0.0009 (0.0003)	0.0009 (0.0004)
$\sigma^2_{b_2}$	-	0.0010 (0.0004)	0.0016 (0.0006)	0.0016 (0.0006)	0.0009 (0.0004)	0.0020 (0.0008)	0.0024 (0.0010)
$\sigma^2_{b_3}$	-	-	-	-	0.0018 (0.0007)	-	-
σ^2_c	-	-	-	-	-	51.3065 (32.6960)	-
$\sigma^2_{b_0^S}$	0.0777 (0.0249)	0.0782 (0.0248)	0.0788 (0.0246)	0.0790 (0.0252)	0.0792 (0.0250)	0.0791 (0.0250)	0.0791 (0.0249)
σ^2_e	0.0806 (0.0038)	0.0691 (0.0033)	0.0623 (0.0030)	0.0625 (0.0030)	0.0597 (0.0029)	0.0605 (0.0029)	0.0603 (0.0030)
$\bar{D}$	313.8719	162.3209	60.6070	62.9339	17.5635	30.5115	28.6827
p_D	77.7781	91.7648	96.3882	97.7551	102.4649	95.3957	56.2395
DIC	391.6500	254.0857	156.9952	160.6891	120.0285	125.9073	84.9222

Note: *Because there were public campaigns in some of the European countries during the year 2000–01 (e.g., in Belgium, Germany and Greece) and during the year 2004–05 (e.g., in Portugal and UK), time = 17 and time = 29 are used as known common change-points.

Source: Authors' own.

and 3). There is no improvement when the known change-point 29 is replaced by an unknown common change-point (Model 4). There is, however, a further improvement when two unknown common change-points are included in the model (Model 5). In Models 2–5 all countries are assumed to have the same common change-point, while in Models 6–7 all countries have different change-points. Comparing Model 6 with Model 4 shows a reduction in DIC when including a country-specific random change-point next to the global change-point. A large improvement is achieved when a uniform prior distribution over the total range of time was used for the country-specific random change-point (Model 7). Scatter plots of country-specific estimates for the change-points in Models 6 and 7 are shown in Figures A1 and A2 of Appendix I.

The estimate for the unknown common change-point (C_1) obtained from fitting Model 4 is 29.3975 (fourth quarter of 2003), which is quite close to the estimates for the common change-point obtained from fitting Model 6 ($C_1 = 29.4144$). The average for the estimated country-specific random change-points in Model 7 is 28.7451, which is very close to the estimate for the unknown common change-points in Models 4 and 6. From Model 5, the estimate for the first common change-point (C_1) is 20.2353 (fourth quarter of 2001) and 31.9461 (fourth quarter of 2004) for the second common change-point (C_2).

The 95% quantile-based credible interval for β_1 $(-0.0270, -0.0003)$ indicates that there is a significant decrease in the global trend of tetracycline use in DID. The credible intervals for β_0^S and β_1^S do not include zero, indicating a significant overall seasonal variation and a significant overall seasonal variation trend over time, respectively.

The estimated linear trend (dashed line), the estimated change-point model (solid line) from Model 7 and the observed average DID for Europe are shown in Figure 2. The predicted mean is based on the predicted outcomes from the posterior distribution of the country-specific random effects. Figure 2 indicates that the model describes the data very well.

Models 2–7 assume that there are one or more trend changes of tetracycline use in all countries, but for some countries it might be better to have only one or even no change-point. To allow a data-adaptive selection of the number and location of the country-specific change-points, we extend Models 4–7 by including a latent country-specific indicator I_{ki} for the kth change-point, $k = 1, 2, \ldots, K$ for country i ($i = 1, 2, \ldots, N$).

*Model 4**: Non-linear mixed model with one unknown common change-point (C_1) and a country-specific indicator I_{1i},

$$\mu_i^{CP}(t_{ij}) = \{(\beta_2 + b_{2i})(t_{ij} - C_1)_+\} I_{1i},$$

where I_{1i} is an unknown country-specific indicator for the change in the trend of DID for country i. Here, $I_{1i} = 1$ if a change at C_1 in the use of tetracycline over time in country i is needed, or $I_{1i} = 0$ if no change in the use of tetracycline over time in country i is needed,

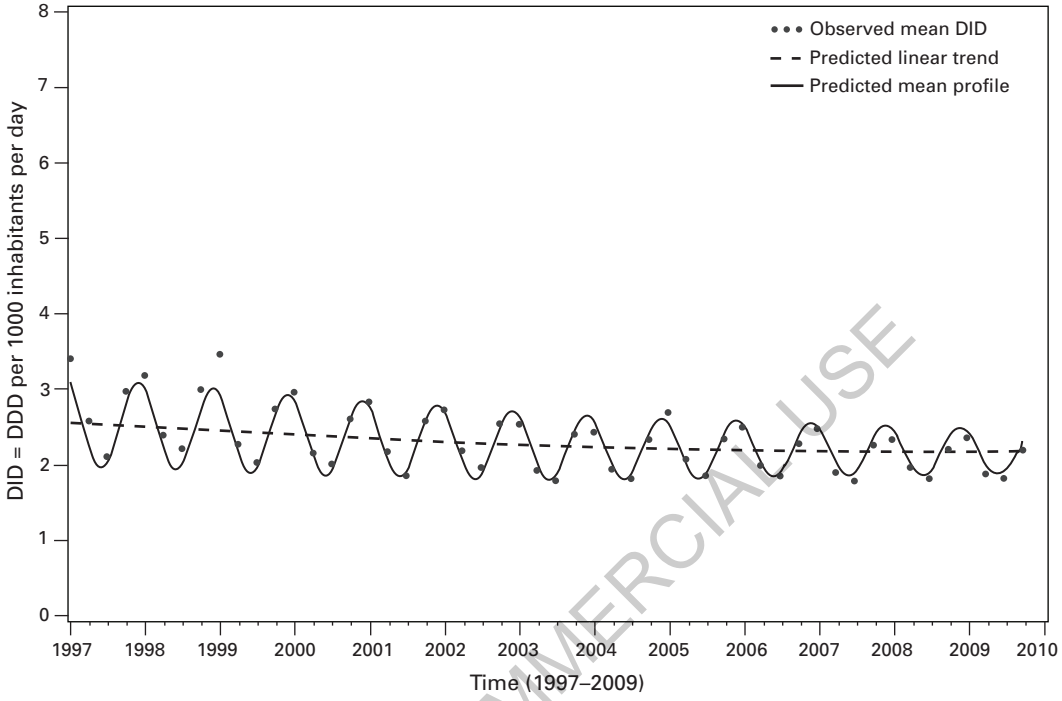


Figure 2 The observed mean DID (dots), the predicted mean profile (solid line) and the predicted linear trend (dashed line) obtained from fitting Model 7
Source: Authors' own.

*Model 5**: Non-linear mixed model with two unknown common change-points (C_1 and C_2) and two country-specific indicators (I_{1i} and I_{2i}),

$$\mu_i^{CP}(t_{ij}) = \{(\beta_2 + b_{2i})(t_{ij} - C_1)_+\}I_{1i} + \{(\beta_3 + b_{3i})(t_{ij} - C_2)_+\}I_{2i},$$

where ordering restriction was imposed for the common change-points (i.e., $C_1 < C_2$).

*Model 6**: Non-linear mixed model with one country-specific random change-point (c_i) and a country-specific indicator I_{1i},

$$\mu_i^{CP}(t_{ij}) = \{(\beta_2 + b_{2i})(t_{ij} - c_i)_+\}I_{1i},$$

where the country-specific random change-point is centred around the unknown point C_1 and is restricted to lay within [1,52], $c_i \sim N(C_1, \sigma_c^2)(1, 52)$.

*Model 7**: Non-linear mixed model with a country-specific random change-point (c_i) and a country-specific indicator I_{1i},

Table 2 Parameter estimates: posterior means and standard errors, and model comparison: $\bar{D}$, p_D and DIC values obtained from fitting Models 4*, 6* and 7*

Parameters	Model 4*	Model 6*	Model 7*
β_0	2.6488 (0.2734)	2.6618 (0.2890)	2.6322 (0.2527)
β_1	−0.0120 (0.0064)	−0.0140 (0.0066)	−0.0139 (0.0065)
β_2	0.0108 (0.0105)	0.0130 (0.0111)	0.0126 (0.0126)
C_1	29.4560 (1.2975)	29.1115 (2.8179)	-
β_0^S	0.6113 (0.0630)	0.6104 (0.0613)	0.6120 (0.0615)
β_1^S	−0.0062 (0.0008)	−0.0062 (0.0008)	−0.0062 (0.0008)
δ	0.4985 (0.0218)	0.4999 (0.0214)	0.5002 (0.0213)
P_1	0.8407 (0.1222)	0.8651 (0.1091)	0.8861 (0.1008)
σ^2_{b0}	1.9527 (0.6229)	2.0181 (0.6382)	2.0580 (0.6472)
σ^2_{b1}	0.0009 (0.0003)	0.0009 (0.0003)	0.0009 (0.0003)
σ^2_{b2}	0.0018 (0.0008)	0.0022 (0.0009)	0.0026 (0.0011)
σ^2_c	-	46.3954 (30.8729)	-
$\sigma^2_{b0^S}$	0.0791 (0.0252)	0.0788 (0.0248)	0.0790 (0.0251)
σ^2_e	0.0626 (0.0030)	0.0606 (0.0030)	0.0605 (0.0030)
$\bar{D}$	65.1738	32.7773	31.0169
p_D	87.6091	92.3128	54.7426
DIC	152.7831	125.0902	85.7595

Note: * Models 4, 6 and 7 are fitted with a country-specific latent indicator I_{ki}

Source: Authors' own.

$$\mu_i^{CP}(t_{ij}) = \{(\beta_2 + b_{2i})(t_{ij} - c_i)_+\} I_{1i},$$

where the country-specific random change points are $U(1, 52)$ distributed.

The parameter estimates for all parameters in Models 4*, 6* and 7* are given in Table 2. No convergence was obtained for Model 5*.

From the results given in Table 2, Model 7* has the lowest DIC value which is quite close to the DIC value of Model 7 (in Table 1). The parameter estimates given in Table 2 are also close to the corresponding parameter estimates given in Table 1. The parameter estimates for the country-specific latent indicators I_{ki} are given in Table A1 in Appendix II. The posterior means for the change-point indicator I_{ki} is greater than 0.5 for all countries, which indicates a change in the trend of tetracycline use for all countries.

The observed country-specific profiles and the predicted country-specific profiles from Model 7 for three selected countries (Iceland, Belgium and Austria) are shown in Figure 3. As can be seen from Figure 3, the predicted country-specific profiles follow closely the observed country-specific DID values. The bold dots indicate the estimated country-specific random change-points obtained from fitting Model 7.

A visual inspection of convergence diagnostics graphs for various model parameters showed that the posterior densities are smooth and unimodal shapes. The trace

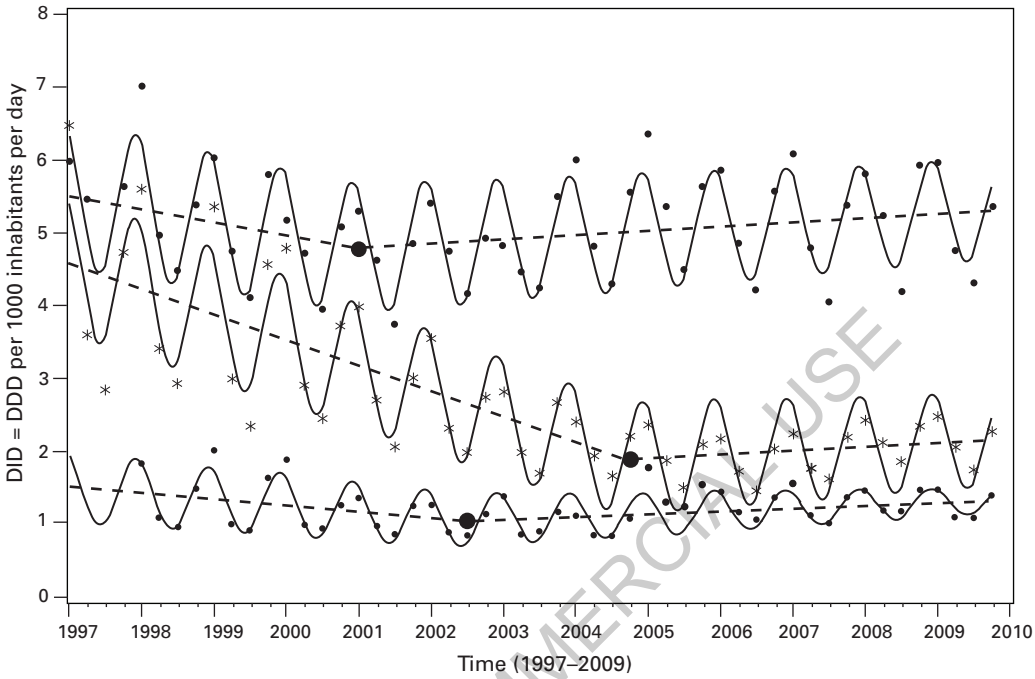


Figure 3 The observed country-specific DID (dots and stars), the predicted country-specific profiles (solid lines) and the country-specific predicted linear trends (dashed lines) obtained from fitting Model 7 for three selected countries (Iceland, Belgium and Austria from top to bottom)

Source: Authors' own.

plots indicate that chains appear to have reached a stationary distribution. The chain also has good mixing and is dense.

5 Discussion

This study was motivated by the need to assess the use of tetracycline in 27 European countries, to assess the change in the trend of tetracycline use over time, and to possibly relate any changes in antibiotics use due to campaigns and policy changes. The data have previously been analyzed based on a non-linear mixed model while taking into account the seasonal effects (Minalu *et al*., 2011). From the analysis, we have identified significant variation in total outpatient tetracycline use in Europe. Differences in tetracycline use between countries might be explained by variations in incidence of community acquired infections, culture and education, and differences in drug regulations and in the structure of the national pharmaceutical market (Goossens *et al*., 2005).

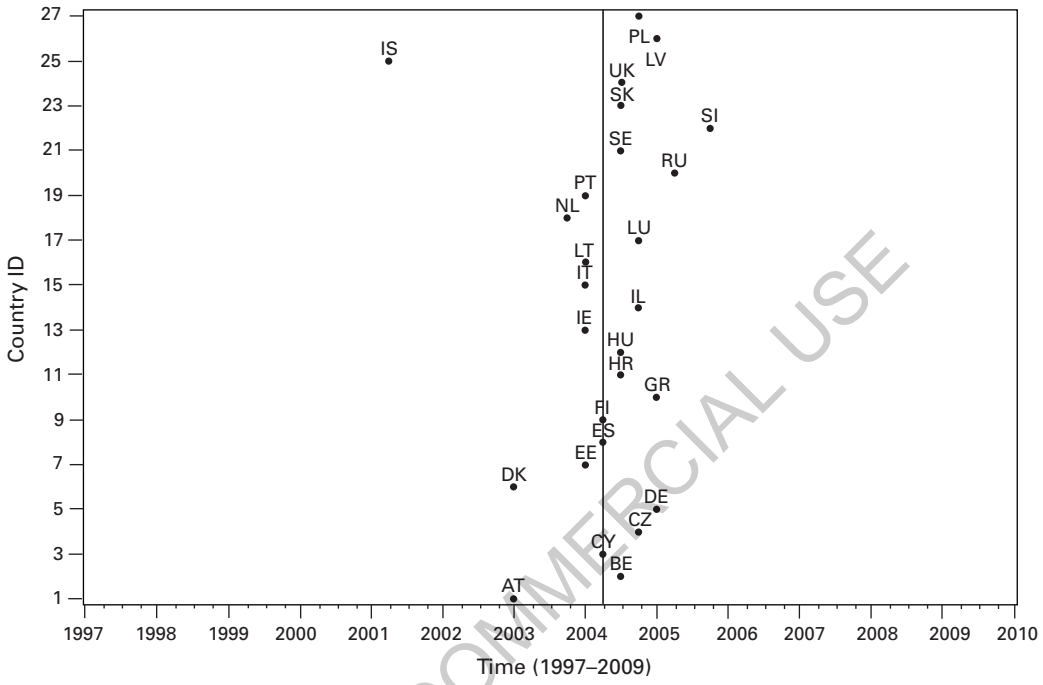
In this paper, we presented and discussed adaptive change-point Bayesian models to analyze the outpatient tetracycline use from 1997 to 2009. We considered the non-linear mixed model extended with known common change-points, unknown common change-points and country-specific random change-points. The change-point mixed model was also extended by including country-specific indicators for the change-points. A widely used statistic for comparing models in a Bayesian framework, the DIC, was used for model comparison. The model with country-specific change-points (Model 7) has the lowest value of DIC. There is some controversy on which criterion to use to compare Bayesian models. Gelman *et al*. (2004) suggested p_V = Var(Deviance)/2 as an estimate of the effective number of parameters in the model as an alternative to p_D. Note that using p_V as an alternative measure of complexity, the change-point model with two unknown common change-points (Model 5) has the lowest DIC value.

The random change-point models have been applied in many applications (Kiuchi *et al*., 1995; Ghosh and Vaida, 2007; Dominicus *et al*., 2008). In this paper, we extended the existing approaches by a general model building procedure where the number of knots and their location are data driven. We also extended the previously proposed change-point models by taking into account a country-specific seasonal variation. The change-point models were also extended by including country-specific latent indicators, allowing the model to switch off the change-points for particular countries.

From the results obtained from fitting the change-point model with a country-specific change-point (Model 7), there is a significant decrease in the trend of tetracycline use in DID. There is a significant seasonal variation in the use of tetracycline and also a significant seasonal variation trend over time.

The adaptive change-point models can be extended with more change-points. But for the tetracycline use data, convergence was not reached by including more than two common change-points or more than one country-specific random change-point. We have conducted a small-scale simulation study under different scenarios to investigate the change-point model in more detail. The results of this small-scale simulation study show that the change-point model with two (resp. three) change-points fits the data best when the data are generated under the change-point model with two (resp. three) change-points. As for the analyses of the case study, the change-point model with three (resp. four) change-points did not converge. This simulation experiment confirms that the convergence issues we encountered in our data application for the model with three or more change-points are very likely attributable to the absence of three or more change-points.

Appendix I: Estimates for the country-specific change-point

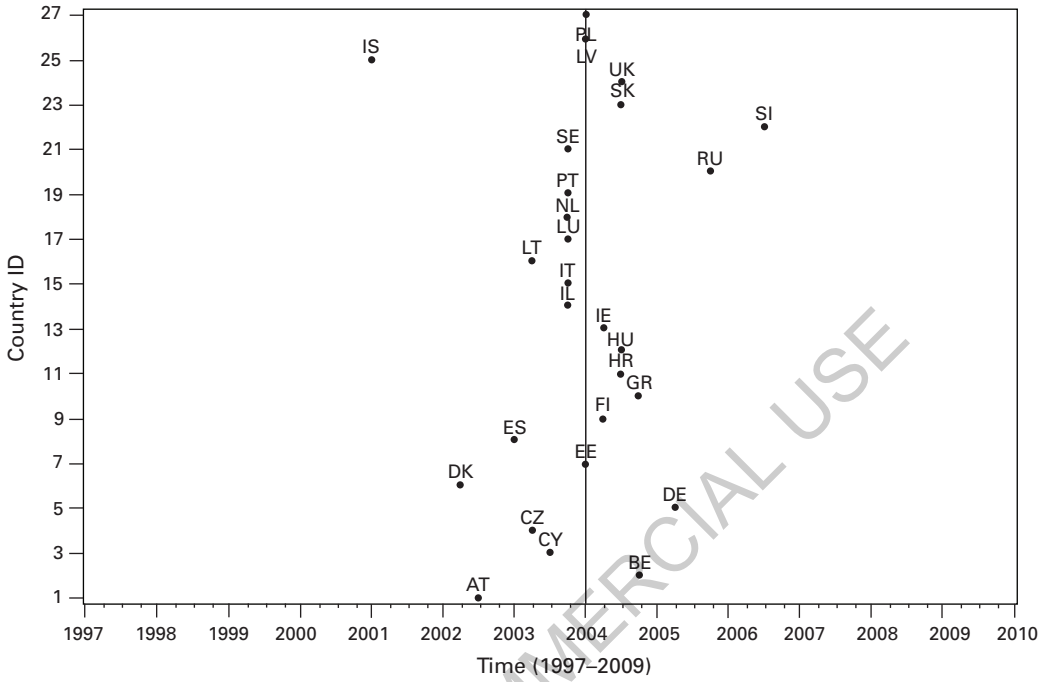


Country abbreviations:

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 A1 Scatter plot of estimates for the country-specific change-points obtained from fitting Model 6. The vertical line indicates the estimated global change-point.

Source: Authors' own.



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 A2 Scatter plot of estimates for the country-specific change-points obtained from fitting Model 7. The vertical line indicates the average for the estimated country-specific random change-points.
Source: Authors' own.

Appendix II: Estimates for the country-specific change-point indicators

Table A1 Parameter estimates: posterior means (and standard errors) for the country-specific indicators (I_{ki}) obtained from fitting Models 4*, 6* and 7*

Country	Parameters	Model 4*	Model 6*	Model 7*
Austria	I_1	0.9516(0.2147)	0.9693(0.1724)	0.9629(0.1890)
Belgium	I_2	1.0000(0.0000)	1.0000(0.0000)	1.0000(0.0000)
Cyprus	I_3	0.8434(0.3635)	0.8706(0.3356)	0.8794(0.3257)
Czech Republic	I_4	0.8026(0.3980)	0.8746(0.3311)	0.8963(0.3048)
Germany	I_5	0.9696(0.1718)	0.9785(0.1450)	0.9740(0.1592)
Denmark	I_6	0.9054(0.2926)	0.9194(0.2722)	0.9241(0.2648)
Estonia	I_7	0.7104(0.4536)	0.7515(0.4321)	0.8006(0.3996)
Spain	I_8	0.6616(0.4732)	0.7266(0.4457)	0.8132(0.3898)
Finland	I_9	1.0000(0.0000)	1.0000(0.0000)	1.0000(0.0000)
Greece	I_{10}	0.8278(0.3776)	0.8634(0.3434)	0.8869(0.3167)
Croatia	I_{11}	0.9932(0.0819)	0.9930(0.0834)	0.9885(0.1066)
Hungary	I_{12}	0.9576(0.2016)	0.9656(0.1823)	0.9557(0.2057)
Ireland	I_{13}	0.8520(0.3551)	0.8604(0.3466)	0.8823(0.3222)
Israel	I_{14}	0.7719(0.4196)	0.8041(0.3969)	0.8389(0.3677)
Italy	I_{15}	0.8299(0.3757)	0.8457(0.3613)	0.8665(0.3401)
Lithuania	I_{16}	0.9705(0.1692)	0.9773(0.1489)	0.9756(0.1543)
Luxembourg	I_{17}	0.7520(0.4318)	0.7994(0.4004)	0.8286(0.3769)
Netherlands	I_{18}	0.9996(0.0194)	0.9996(0.0212)	0.9990(0.0308)
Portugal	I_{19}	0.8623(0.3446)	0.8908(0.3119)	0.8903(0.3125)
Russian Federation	I_{20}	0.8067(0.3949)	0.8569(0.3502)	0.9025(0.2967)
Sweden	I_{21}	0.5890(0.4920)	0.6698(0.4703)	0.8136(0.3894)
Slovenia	I_{22}	0.7065(0.4554)	0.8022(0.3983)	0.9013(0.2982)
Slovakia	I_{23}	1.0000(0.0071)	1.0000(0.0000)	0.9997(0.0166)
United Kingdom	I_{24}	0.9998(0.0158)	0.9997(0.0180)	0.9996(0.0200)
Iceland	I_{25}	0.9768(0.1505)	0.9999(0.0087)	1.0000(0.0000)
Latvia	I_{26}	0.7986(0.4011)	0.8164(0.3872)	0.8408(0.3659)
Poland	I_{27}	0.8389(0.3677)	0.8594(0.3476)	0.8678(0.3387)

Note: *Models 4, 6 and 7 are fitted with a country-specific latent indicator I_{ki}.

Source: Authors' own.

Appendix III: R code

The following WinBUGS code were used in R using the R-package R2WinBUGS to fit the change-point model with one unknown common change-point, one country-specific random change-point and a country-specific latent indicator for the change-point.

```
#Model
model{
# Basic model
for (i in 1:N){
Y[i] ~ dnorm(mu[i],tau)
mu[i]<- (B0 + b1[ID[i]]) + (B1 + b2[ID[i]])*T[i] + (B2 + b3[ID[i]])*
```

```
      (T[i]-(C1 + c1[ID[i]]))*step(T[i]-(C1 + c1[ID[i]]))*change[ID[i]] +
      (alpha + b4[ID[i]] + alphaTime*T[i])*sin(omega*T[i] + delta)
        }
# Priors for random effects
for (j in 1:M){
b1[j]~ dnorm(0,b0.tau)
b2[j]~ dnorm(0,b1.tau)
b3[j]~ dnorm(0,b2.tau)
b4[j]~ dnorm(0,b3.tau)
c1[j]~ dnorm(0,c1.tau)
change[j] ~ dbern(changemean)
                    }
# 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)
C1~ dunif(1,52)
changemean ~ dbeta(1,1)

#Hyper priors
tau  ~   dgamma(0.001, 0.001)
b0.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)
c1.tau~ dgamma(0.001, 0.001)

sigma     <- 1/tau
sigma_b0 <- 1/b0.tau
sigma_b1 <- 1/b1.tau
sigma_b2 <- 1/b2.tau
sigma_b3 <- 1/b3.tau
sigma_c1 <- 1/c1.tau
}
```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