2011
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FACULTY OF SCIENCES

Master of Statistics: Biostatistics

Masterproef

Longitudinal data analysis of data on outpatient antibiotic use in Europe

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

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Summary

Antibiotics are drugs used to treat bacterial infections. The use and misuse of antibiotics has over time lead to resistance of bacteria to several antibiotics. This is a major public health problem and as a start to face this problem trustworthy information related to antibiotics consumption needs to be gathered. This is done by both ESAC and IMS Health. In this study the IMS Health data, expressed in both DID and PID and measured from 2000 until 2008, were used to analyze the global trend and seasonal fluctuations in antibiotic consumption. Nonlinear mixed models were constructed assessing both the change of antibiotic consumption over time and the change in seasonal fluctuation. To assess whether both models were in agreement a joint nonlinear mixed model was built containing information on both DID and PID. The change in DDD per package over time was assessed through a linear mixed model.

While for some subgroups the average antibiotic consumption decreased over time, others showed an increasing consumption over time; and while for some subgroups the seasonal fluctuation diminished over time, it was enlarged for others. The conclusions based on DID and PID were not always in agreement as an increase in PID went together with no significant change in DID or vice versa. In all subgroups and for both DID and PID we saw a high positive correlation between the random intercept and the random amplitude indicating that a country with a high antibiotic consumption at baseline has a strong seasonal effect in absolute terms. The joint model showed that there was a positive correlation between all random effects, indicating that when a random effect is above average for DID it will also be above average for PID and vice versa. From the analysis of DP we learned that the DDD per package is substantially different among subgroups and among countries and that the average DP is increasing over time (except for J01M which has a non-significant quarterly increase).

Content

1 Introduction

Antibiotics are drugs that are used to treat bacterial infections. One prominent example is penicillin, which was discovered by Fleming in 1929. He observed that some bacteria were sensitive to penicillin, while many others were insensitive (1). In his Nobel lecture, Fleming noted that the sensitive bacteria could easily develop resistance by exposure to low doses of the antibiotic (2). Meanwhile both ecological studies and randomized controlled trials in individual patients have demonstrated a link between antibiotic use and resistance (3-5). Unfortunately, the use and misuse of antibiotics has lead to resistance of bacteria to several antibiotics (6-9). This is a major public health problem as resistance in the infecting organisms is related to treatment failure, prolonged hospitalization, increased costs of care and increased mortality (10). In order to fight this problem an effective national and international approach is needed urgently. One part of the solution is to gather trustworthy information on the consumption of antibiotics in Europe (11).

The European Surveillance of Antimicrobial Consumption (ESAC) project - currently ESAC-NET coordinated by the European Centre for Disease Prevention and Control (ECDC; http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net) - consisted of a network of surveillance systems that enabled the collection of data on European antibiotic consumption. An analysis of these ESAC data, ranging between 1997 and 2009, revealed that total outpatient antibiotic use expressed in the number of defined daily doses (DDD) per 1000 inhabitants per day (DID) increased significantly over time while it showed a significant seasonal fluctuation with a high winter peak, that decreased over time (12). More detailed analyses of major antibiotic subgroups were described in separate papers (13-17). For a better understanding of outpatient antibiotic use, another outcome measure was suggested, i.e. the number of packages per 1000 inhabitants per day (PID). The ESAC database only contains data expressed in PID for 2009 from 17 European countries.

Yearly and quarterly data on outpatient antibiotic use expressed in DID and PID between 2000 and 2008 were available within ESAC through IMS Health (18). These data allowed to express antibiotic use in DID as well as in PID. In the present study IMS Health data were used to analyze the global trend and seasonal fluctuations in antibiotic consumption expressed in DID and PID separately. To assess whether the separate models were in agreement, a joint model was build containing both information on DDD and on packages. Next, the change in DDD per package over time was assessed. In a last section the resulting model for the IMS Health data was applied to the ESAC data and conclusions were compared, given that only common measurement points and countries were used in this comparison.

2 Methods

All statistical analyses were conducted using SAS 9.2, SPSS 16.0 and R 2.13.2.

2.1 Data

The IMS Health data contain information on 31 countries, being 25 EU member states (all but Cyprus and Malta), 2 candidate countries (Croatia and Turkey), 2 founding members of the European Free Trade Association (EFTA) (Norway and Switzerland) and 2 other countries (Israel and Russian Federation).

For most countries information is given on ambulatory care (AC), while for some only information on total care (TC) was available (Denmark, Netherlands, Russian Federation, Sweden and Slovenia). Data on TC were also used as AC represents over 90% of TC. Data were measured quarterly from 2000 until 2008 and are aggregated at the level of the active substance in accordance to the Anatomical Therapeutic Chemical (ATC) classification system (WHO version 2011 (19)). In this study information on consumption of antibiotics in group J (antiinfectives for systemic use), more particularly the J01 subgroup (antibacterials for systemic use) was used. This subgroup is further divided into eight pharmacological subgroups (ATC3 level) being penicillins (J01C), macrolides (J01F), quinolones (J01M), cephalosporins (J01D), tetracyclines (J01A), sulphonamides (J01E), urinary antiseptics (J01X) and other antibiotics (concatenation of J01B, J01G and J01R). The pharmacological subgroups are further divided into chemical subgroups (ATC4 level) and chemical substances (ATC5 level). All ATC3 level subgroups and two ATC4 level subgroups are considered in this study, the latter being penicillins with extended spectrum (J01CA) and combinations of penicillins (J01CR).

Consumption data were expressed in DID and in PID. The DDD per package (DP) was calculated by dividing DID by PID per country per quarter.

2.2 Longitudinal data analysis

The use of quarterly data implies that multiple measurements were taken on the same country. This suggests that these measurements are not independent but are correlated within the country. For that reason mixed effects models are the most appropriate tool to study the trends in the data. Mixed effects models consist of a fixed component, which reflects the average trend in the data, and a random component, which represents the deviation of individual countries from this average trend (20,21). Individual profiles were constructed to assess the variability across measurements within one country and between different countries. This gives an indication whether random effects are required in the mixed model or not. The seasonal trend in quarterly data can be modeled by a nonlinear term, which can be included when using a nonlinear mixed model. On top of the features from the linear mixed model, the nonlinear mixed model has the ability to incorporate a nonlinear term in the model (21).

A nonlinear mixed model, previously applied in the analysis of the ESAC data, was used as a starting model (22). The model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + (\beta_3 + b_{3i})*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij},$$

where Y_{ij} is the use of antibiotics in country i at quarter j (expressed as DID or PID), β_0 and b_{0i} are respectively fixed and random intercepts, β_1 and b_{1i} are fixed and random slopes, β_2 and b_{2i} are fixed and random amplitudes for the sine function, β_3 and b_{3i} are fixed and random changes in the amplitude over time, ω is the frequency in which the sine function repeats itself (= $2\pi/T$ with T = 4 quarters), δ is the phase shift, ε_{ij} is the measurement error and time = 1 corresponds to the first measurement (first quarter of 2000). We assume that the vector of random effects follows a normal distribution with mean zero and covariance matrix D(4x4). Convergence could not be obtained when fitting the model with an unstructured covariance structure for the random effects, hence the covariance structure was simplified by setting the covariances between b_{3i} (random change in amplitude) and all other random effects equal to zero (illustrated below with '*var*' representing a variance and '*cov*' representing a covariance).

$$\begin{pmatrix} \text{var}(b_{0i}) & \text{cov}(b_{0i}, b_{1i}) & \text{cov}(b_{0i}, b_{2i}) & 0 \\ & \text{var}(b_{1i}) & \text{cov}(b_{1i}, b_{2i}) & 0 \\ & & \text{var}(b_{2i}) & 0 \\ & & & \text{var}(b_{3i}) \end{pmatrix}$$

If fitting the model with this simplified covariance matrix for the random effects still resulted in convergence problems, the covariance matrix was simplified further by setting the covariances between all random effects equal to zero (illustrated below with '*var*' representing a variance).

$$\begin{pmatrix} \text{var}(b_{0i}) & 0 & 0 & 0 \\ & \text{var}(b_{1i}) & 0 & 0 \\ & & \text{var}(b_{2i}) & 0 \\ & & & \text{var}(b_{3i}) \end{pmatrix}$$

From this starting model the final model was obtained by removing random and fixed effects when possible. To check whether a random effect could be removed, we used a likelihood ratio test which is based on the comparison of the maximized likelihoods for the model with and without the random effect of interest. The corresponding null hypothesis of interest for the removal of the random change in slope (b_{4i}) would be $H_0 : \text{cov}(b_{1i},b_{4i}) = \text{cov}(b_{2i},b_{4i}) = \text{cov}(b_{3i},b_{4i}) = \text{var}(b_{4i}) = 0$.

As the variance is required to be positive, this null hypothesis is clearly on the boundary of the parameter space. For this reason the classical likelihood inference based on a single χ^2 distribution cannot be applied and a mixture of two equally weighted (weight = 0.5) χ^2 distributions with k and k+1 degrees of freedom has to be used instead (20).

When a random effect could be excluded from the model, we tested whether the accompanying fixed effect could be left out by using a regular likelihood ratio test (based on a single χ^2 distribution).

In order to assess whether the majority of the total variation is explained well by the random effects and the sinusoidal component, a plot of the smoothed average trend of the residuals over time was constructed.

The overall fit of the model was evaluated by plotting the observed and predicted values over time for all countries. In order to present a clear figure the fit was plotted for the average and only two countries of our choice (i.e. Belgium and the Netherlands).

2.3 Joint model DID and PID

Previously a nonlinear mixed model was constructed separately for antibiotic consumption data expressed in DID and expressed in PID, respectively. In order to see whether both models were in agreement, a joint nonlinear mixed model was constructed combining both final models for DID and PID. In this joint model we were able to study the relationship between the random effects of the separate models (for DID and PID) through correlations between the random effects. Correlations were calculated based on the covariance matrix. Due to computational difficulty, the covariance matrix for the joint model only contained estimates for the covariances between matching random effects for both models (for DID and PID). All other covariances were set equal to zero in order to reach convergence (illustrated below).

$$\begin{pmatrix} \text{var}(b_{0iD}) & \text{cov}(b_{0iD}, b_{0iP}) & 0 & 0 & 0 & 0 \\ & \text{var}(b_{0iP}) & 0 & 0 & 0 & 0 \\ & & \text{var}(b_{1iD}) & \text{cov}(b_{1iD}, b_{1iP}) & 0 & 0 \\ & & & \text{var}(b_{1iP}) & 0 & 0 \\ & & & & \text{var}(b_{2iD}) & \text{cov}(b_{2iD}, b_{2iP}) \\ & & & & & \text{var}(b_{2iP}) \end{pmatrix}$$

However, the estimates for the variances of the random effects for DID and PID were one a different scale, which could prevent the model from converging. To improve stability, the data for PID were rescaled by multiplying with factor 10. This resulted in variance estimates for the PID model that were on the same scale as the variance estimates for the DID model, which eased convergence for the joint model. It should however be kept in mind that this rescaling also results in rescaled final estimates.

To know whether there was a perfect correlation between the matching random effects, we used a Wald test to check if the correlation was equal to one. From the SAS procedure NLMIXED the asymptotically normally distributed Wald statistic could be achieved by specifying a large number of degrees of freedom (df = 1E6) for the t statistic. In this study the squared version of the Wald statistic, which is based on a chi-square distribution with one degree of freedom, was used (21,23). As the correlation is restricted to lie between -1 and +1, the null hypothesis for this test was situated on the boundary of the parameter space and hence an equally weighted mixture of two χ^2 distributions with zero and one degrees of freedom was used to compute the correct p-value (20).

2.4 Comparison IMS Health – ESAC

In this study we used data from IMS Health, expressed in both PID and DID, to analyze the trend and seasonal fluctuation in antibiotic consumption over time for different subgroups at the ATC3 level. For the same purpose, data expressed in DID from the ESAC project have been used. As both sources render information on the same topic, we wanted to compare the obtained results. The comparison was made by fitting the final models (built for the IMS Health data) on both the IMS Health and the ESAC data.

To reach an optimal comparison, only common timepoints and countries were used in this analysis. This implied leaving out the countries Bulgaria, Switzerland, France, Norway, Romania and Turkey from the IMS Health data analysis, and the countries Iceland and Israel from the ESAC data analysis.

2.5 Change in DDD per package

A link between DID and PID is the DDD per package (DP), which is calculated by dividing DID by PID. As both outcomes are measured quarterly between the first quarter of 2000 and the last quarter of 2007, also DP has quarterly measurements. As this implies that measures are again correlated within the country, a mixed-effects model is an appropriate tool to model these data.

Individual profiles were constructed to show the variability within and between countries, and are used to assess the necessity of random intercepts and slopes. As both DID and PID measure the same seasonal fluctuation, dividing DID by PID cancels out most of this seasonality. For this reason the individual profiles can be approximated well by a straight line and hence a linear mixed model is an appropriate tool to model the DP data.

A linear mixed model with fixed and random intercepts and fixed and random slopes was used as a starting model. This model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + \varepsilon_{ij}$,

where Y_{ij} is the DDD per package in country i at quarter j, β_0 and b_{0i} are the fixed and random intercepts, β_1 and b_{1i} are the fixed and random slopes, ε_{ij} is the measurement error and time = 1 corresponds to the first measurement (first quarter of 2000). We assumed the vector of random effects follows a normal distribution with mean zero and an unstructured covariance matrix D(2x2). It was also assumed that the error terms are independent and normally distributed with mean zero and covariance matrix Σ_i. As there are 32 repeated measures per country, an unstructured covariance matrix could not be used. Instead a first order autoregressive (AR(1)) covariance matrix was used which implies that the covariance of the errors at timepoints i and j are autocorrelated and equals $\sigma^2\rho^{|i-j|}$, where σ^2 is the error variance and ρ is an autocorrelation coefficient.

The need for random effects is checked through a likelihood ratio test based on an equally weighted mixture of two χ^2 distributions with k and k+1 degrees of freedom. The need for the fixed effects was tested with a likelihood ratio test based on a single χ^2 distribution.

3 Results

Individual profiles were constructed for DID and PID outcomes in all antibiotic groups studied (profiles for subgroup J01 are shown in Figure 1 and Figure 2). Both profiles showed that there is considerable within country variability, as well as between country variability, which indicates the need for random intercepts and slopes. It can also be seen that there is a clear seasonal fluctuation which could be approximated well by a sine wave and verifies the need for a nonlinear term. The profiles also showed that countries with a higher antibiotic consumption at baseline have a higher amplitude and hence a stronger seasonal effect. Profiles for all other subgroups resulted in similar conclusions (appendix Figure 1 for DID and Figure 2 for PID). Only profiles for urinary antiseptics (J01X) differed slightly as they showed only minor seasonal variation (appendix Figure 3).

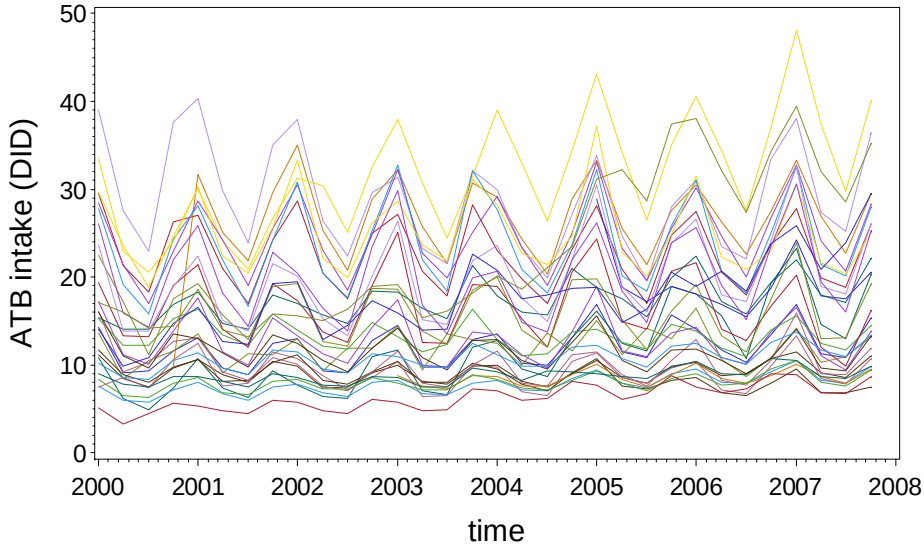

Figure 1. Observed country-specific changes in quarterly antibiotics consumption (J01) expressed in DID in 31 European countries.

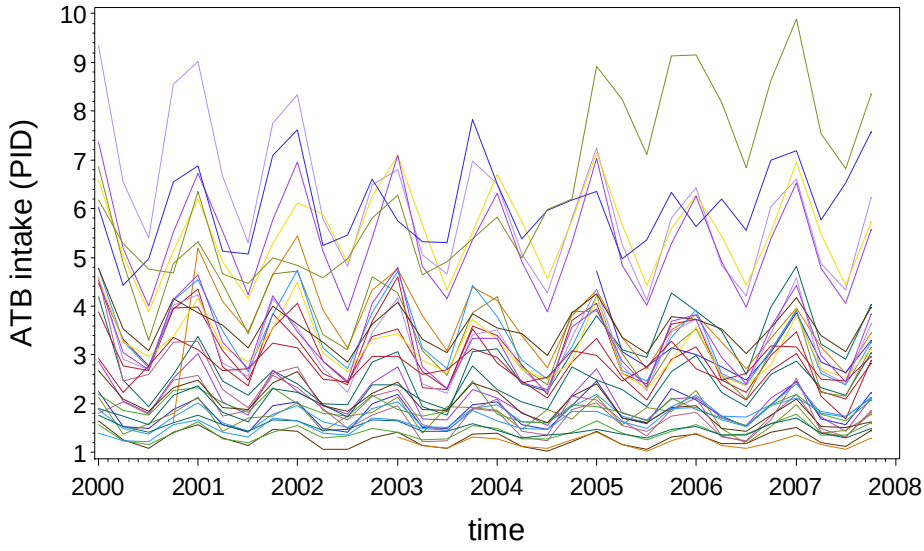

Figure 2. Observed country-specific changes in quarterly antibiotics consumption (J01) expressed in PID in 31 European countries.

3.1 Antibacterials (for systemic use) (J01)

Antibacterial consumption ranges from 3.24 to 48.06 DID. Likelihood ratio tests indicated that the random change in amplitude could be removed from the starting model. The final model is defined as $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.

The plot of the residuals over time (Figure 3) confirms that there is no clear systematic structure, hence we assume that the variation is explained by the random effects and the sinusoidal component in the model.

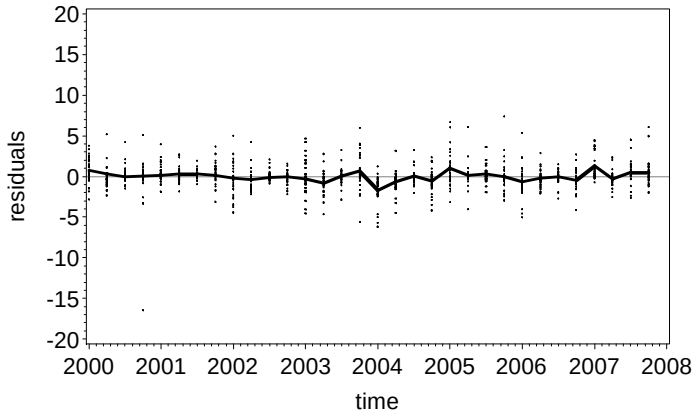

Figure 3. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for total antibacterial consumption in DID and the smoothed average trend of the residuals (solid line).

Parameter estimates for the final model are given in Table 1. On Figure 4 it is shown that the model fits the data well as both the average and country specific lines approximate the observed data well.

Table 1. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for total antibacterial consumption measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and * : p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01	14.2404 (1.2288)**	0.1037 (0.0330)**	3.0858 (0.3909)**	0.0187 (0.0087)*

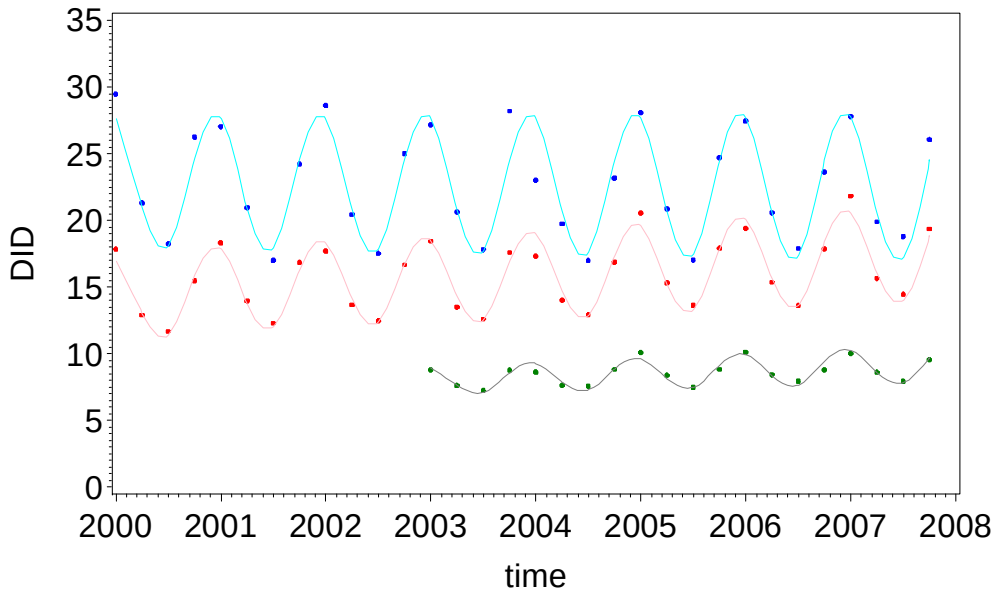

Figure 4. Average (red) and country-specific (blue: Belgium and green: Netherlands) predicted (lines) and observed (dots) total antibacterial consumption expressed in DID.

The estimates for the variance components are:

$$D = \begin{pmatrix} 46.1383 & -0.1754 & 12.0934 \\ & 0.0323 & 0.0667 \\ & & 3.8900 \end{pmatrix} \text{ and } \sigma^2 = 2.9932.$$

This covariance structure implies that the correlation between the random effects equals -0.1438 (between random intercept and random slope), 0.9027 (between random intercept and random amplitude) and 0.0570 (between random slope and random amplitude).

Antibacterial consumption varies from 1.024 to 9.899 PID. Likelihood ratio tests indicated that the random change in amplitudes could be removed from the model. The likelihood ratio test that checked the need of the fixed change in amplitude was borderline non-significant, hence it was kept. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.
The residuals plot suggests that there is no clear structure and hence we assume that the total variation in the data is well explained by the remaining random effects and the sine wave (Figure 5).

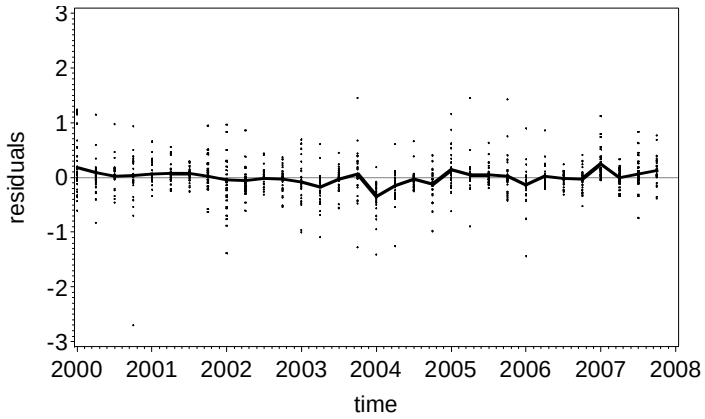

Figure 5. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for total antibacterial consumption in PID and the smoothed average trend of the residuals (solid line).

Parameter estimates for the final model are given in Table 2. The model fits the data well as can be seen from Figure 6, since observed and predicted outcomes lie close together.

Table 2. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for total antibacterial consumption measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001).**

	β_0	β_1	β_2	β_3
J01	3.1006 (0.2714)**	-0.0061 (0.0066)	0.6608 (0.0699)**	-0.0033 (0.0017)

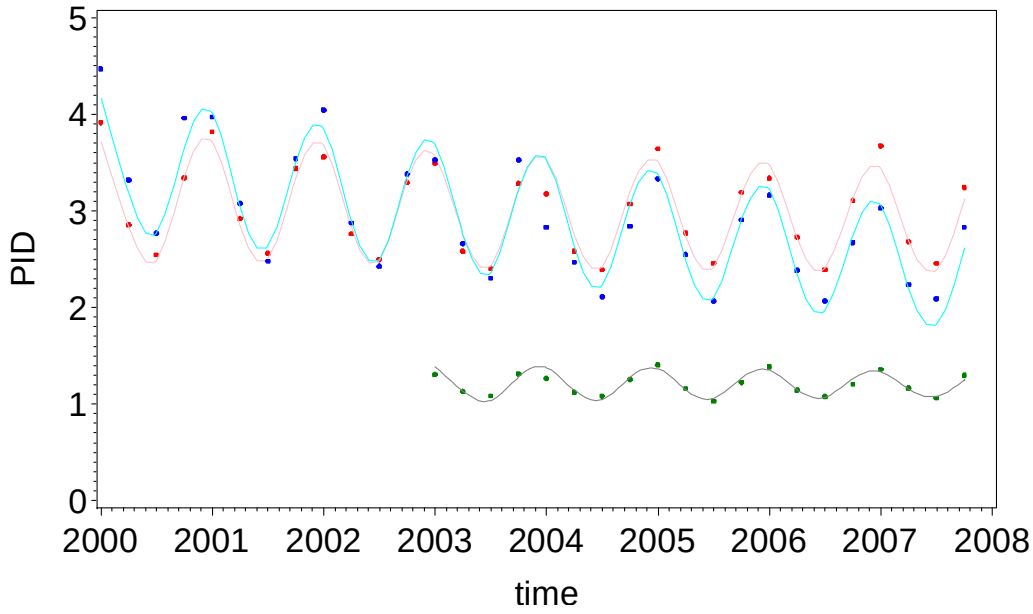

Figure 6. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) total antibacterial consumption expressed in PID.

The estimates for the variance components are:

$$D = \begin{pmatrix} 2.2574 & -0.0133 & 0.4839 \\ & 0.0013 & -0.0029 \\ & & 0.1193 \end{pmatrix} \text{ and } \sigma^2 = 0.1152.$$

The covariance structure implies that the correlation between the random effects equals -0.2455 (between random intercept and random slope), 0.9325 (between random intercept and random amplitude) and 0.2329 (between random slope and random amplitude).

A joint model was fitted to the data by using the rescaled outcomes (DID and 10*PID). The correlations between random effects for DID and PID are 0.7743 (between random intercepts), 0.8647 (between random slopes) and 0.9571 (between random amplitudes). Only the correlation between the random amplitudes appeared to be not significantly different from 1 (corrected p-value = 0.095).

3.2 Penicillins (J01C)

The consumption of penicillins ranges from 0.59 to 22.87 DID. The starting model could be reduced by removing the random change in amplitudes. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

There is no clear structure in the residuals, as can be seen on the residuals plot (appendix figure 4 (left)). Parameter estimates for the final model are given in Table 3. The model appears to fit the data well, as can be seen on Figure 7.

Table 3. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for penicillin consumption measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and * : p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01C	5.9694 (0.6597)**	0.0649 (0.0157)**	1.3531 (0.1956)**	0.0116 (0.0046)*

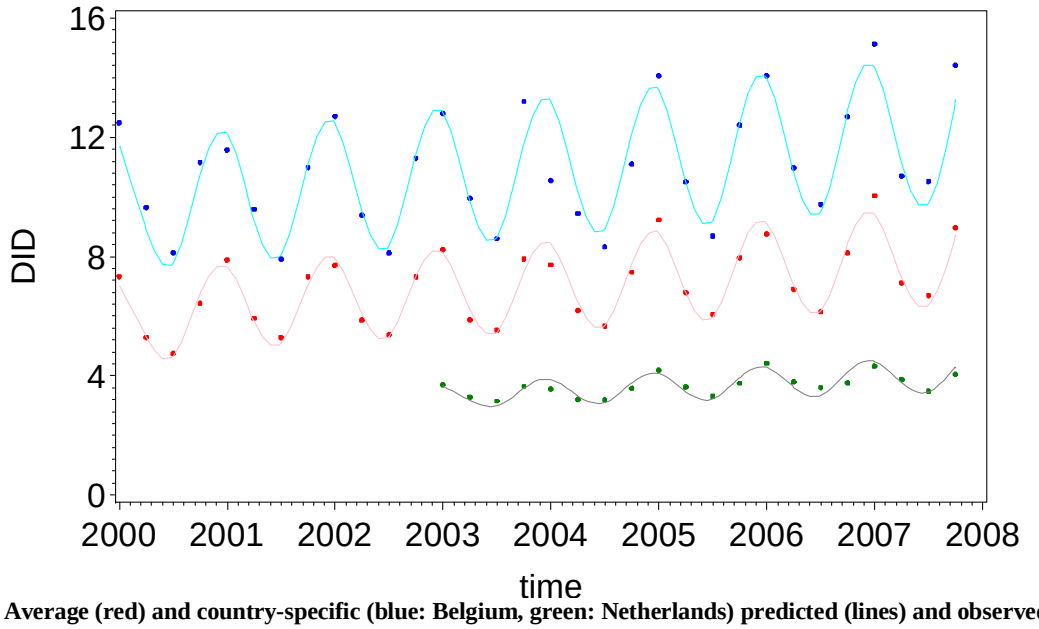

Figure 7. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) penicillin consumption expressed in DID.

The estimates for the variance components are:

$$D = \begin{pmatrix} 13.2967 & -0.0169 & 3.0888 \\ & 0.0072 & 0.0115 \\ & & 0.9458 \end{pmatrix} \text{ and } \sigma^2 = 0.8476.$$

This covariance structure implies that the correlation between the random effects equals -0.0546 (between random intercept and random slope), 0.8710 (between random intercept and random amplitude) and 0.1394 (between random slope and random amplitude).

Penicillin consumption ranges from 0.33 to 5.54 PID. According to likelihood ratio tests, the starting model could not be simplified and hence all random effects are kept in the model. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + (\beta_3 + b_{3i})*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.
There is no systematic structure in the residuals, as can be seen in the residuals plot (appendix Figure 4 (right)). Parameter estimates for the fixed effects in the final model are given in Table 4. The good model fit is presented in Figure 8.

Table 4. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for penicillin consumption measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001).**

	β_0	β_1	β_2	β_3
J01C	1.3529 (0.1362)**	-0.0037 (0.0031)	0.2866 (0.0310)**	-0.0016 (0.0010)

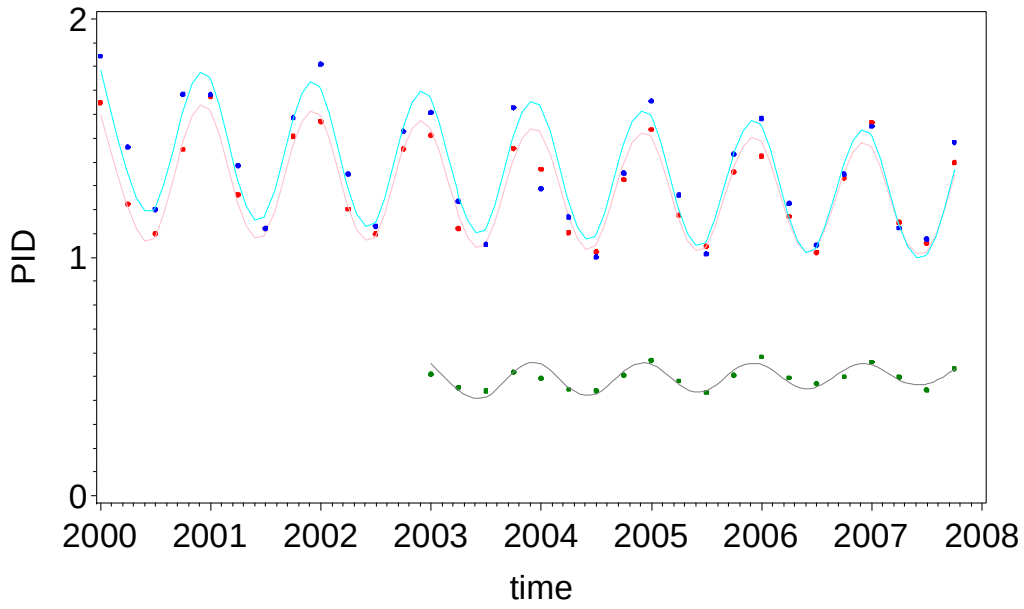

Figure 8. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) penicillin consumption expressed in PID.

The estimates for the variance components are:

$$D = \begin{pmatrix} 0.5691 & -0.0029 & 0.1063 & 0 \\ & 0.0003 & -0.0007 & 0 \\ & & 0.0223 & 0 \\ & & & 0.000008 \end{pmatrix} \text{ and } \sigma^2 = 0.0267.$$

This covariance structure implies that the correlation between the random effects equals -0.2219 (between random intercept and random slope), 0.9436 (between random intercept and random amplitude) and -0.2706 (between random slope and random amplitude).

A joint model was fitted to the data using the rescaled outcomes (DID and 10*PID). The correlations between the matching random effects are 0.5466 (between random intercepts), 0.6981 (between random slopes) and 0.8504 (between random amplitudes). All correlations were significantly different from 1.

3.3 Penicillins with extended spectrum (J01CA)

The consumption of penicillins with extended spectrum ranges from 0.55 to 15.22 DID. Likelihood ratio tests showed that the random change in amplitude as well as the fixed change in amplitude could be removed from the starting model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

The residual plot (appendix Figure 5 (left)) shows that there is no clear structure in the residuals. Parameter estimates for the final model are given in Table 5. The good fit of the model can be seen in Figure 9.

Table 5. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for penicillins with extended spectrum consumption measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope and β_2 the fixed amplitude for the sine wave (: p-value < 0.0001).**

	β_0	β_1	β_2
J01CA	3.6967 (0.3822)**	0.0113 (0.0103)	0.9633 (0.1148)**

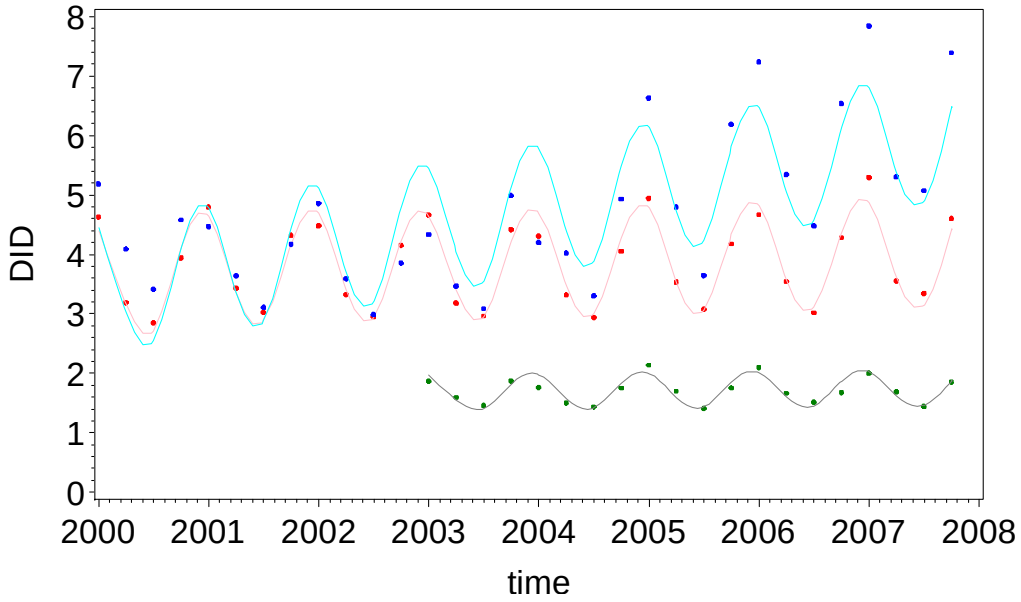

Figure 9. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) penicillins with extended spectrum consumption expressed in DID.

The estimates for the variance components are:

$$D = \begin{pmatrix} 4.4371 & -0.0273 & 1.1456 \\ & 0.0031 & 0.0025 \\ & & 0.3818 \end{pmatrix} \text{ and } \sigma^2 = 0.3980.$$

This covariance structure implies that the correlation between the random effects equals -0.2328 (between random intercepts), 0.8802 (between random slopes) and 0.0727 (between random amplitudes).

The consumption of penicillins with extended spectrum lies between 0.075 and 3.39 PID. Likelihood ratio tests indicated that none of the random effects could be removed from the model. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + (\beta_3 + b_{3i})*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.
There is no clear structure in the residuals, as is shown in the residuals plot (appendix Figure 5 (right)). Parameter estimates for this model are given in Table 6 and the good model fit is shown in Figure 10.

Table 6. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for penicillins with extended spectrum consumption measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01CA	0.6533 (0.0849)**	-0.0040 (0.0016)*	0.1645 (0.0209)**	-0.0015 (0.0005)*

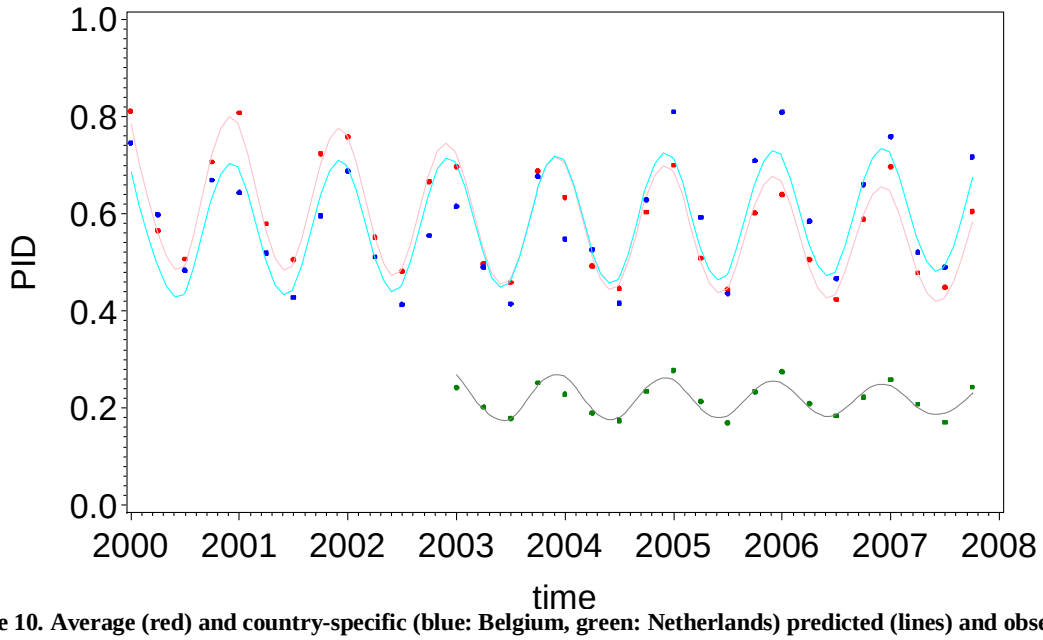

Figure 10. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) penicillins with extended spectrum consumption expressed in PID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.2219 & -0.0014 & 0.0498 & 0 \\ & 0.00008 & -0.0003 & 0 \\ & & 0.0113 & 0 \\ & & & 0.000002 \end{pmatrix} \text{ and } \sigma^2 = 0.0079.$$

This covariance structure implies that the correlation between the random effects equals -0.3323 (between random intercept and random slope), 0.9945 (between random intercept and random amplitude) and -0.3155 (between random slope and random amplitude).

A joint model was fitted to the data by using the rescaled outcomes (DID and 10*PID). The correlations between matching random effects for DID and PID are 0.6443 (between random intercepts), 0.6010 (between random slopes) and 0.8195 (between random amplitudes). All correlations were significantly different from 1.

3.4 Combinations of penicillins (J01CR)

Consumption of combinations of penicillins lies between 0.000169 and 11.92 DID. The most complex starting model that could be fitted to these data was a model with fixed intercept, slope, amplitude and change in amplitude and random intercept, slope and amplitude. Likelihood ratio tests indicated that none of the random effects could be removed from the model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

The residuals plot (appendix Figure 6 (left)) shows that there is no systematic structure in the residuals. Parameter estimates for this model are given in Table 7 and the good fit is illustrated in Figure 11.

Table 7. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for consumption of combinations of penicillins measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001).**

	β_0	β_1	β_2	β_3
J01CR	2.0284 (0.3575)**	0.0506 (0.0111)**	0.4515 (0.0991)**	0.0098 (0.0022)**

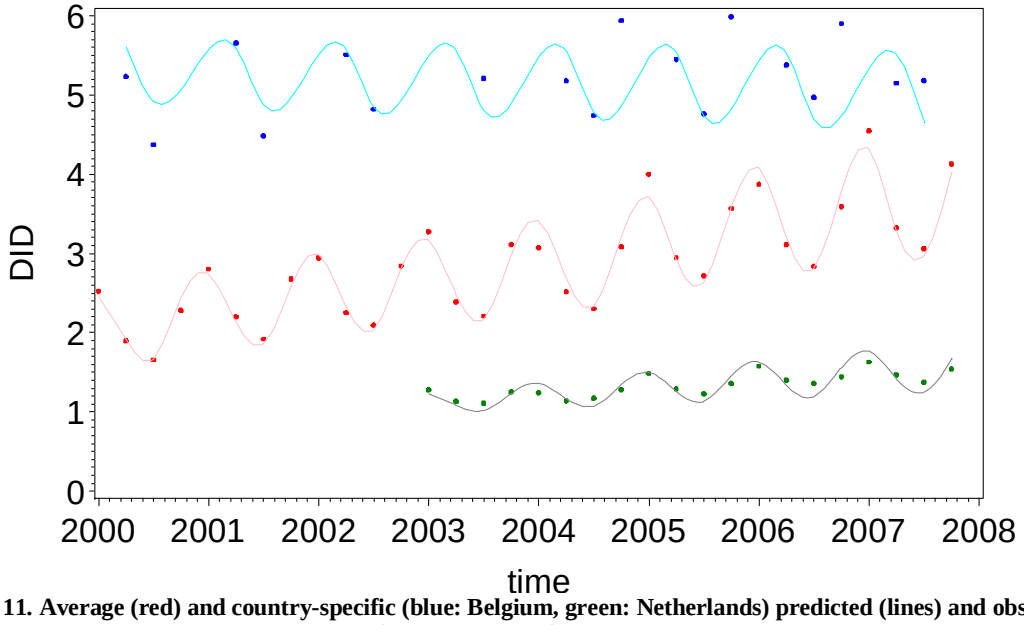

Figure 11. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) consumption of combinations of penicillins expressed in DID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 3.9117 & 0.0203 & 0.8748 \\ & 0.0037 & 0.0149 \\ & & 0.2486 \end{pmatrix} \text{ and } \sigma^2 = 0.1947.$$

This covariance structure implies that the correlation between the random effects equals 0.1687 (between random intercept and random slope), 0.8871 (between random intercept and random amplitude) and 0.4913 (between random slope and random amplitude).

Consumption of combinations of penicillins ranges from 0.0000146 to 2.38 PID. The most complex starting model that could be fitted to these data was a model containing both random and fixed intercepts, slopes and amplitudes and a fixed but no random change in amplitude. Likelihood ratio tests indicated that none of the random effects could be removed. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

A plot of the residuals (appendix Figure 6 (right)) indicates that there is no systematic structure. Parameter estimates are given in Table 8 and the good model fit is illustrated in Figure 12.

Table 8. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for consumption of combinations of penicillins measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01CR	0.3486 (0.0538)**	0.0037 (0.0017)*	0.0797 (0.0141)**	0.0007 (0.0003)*

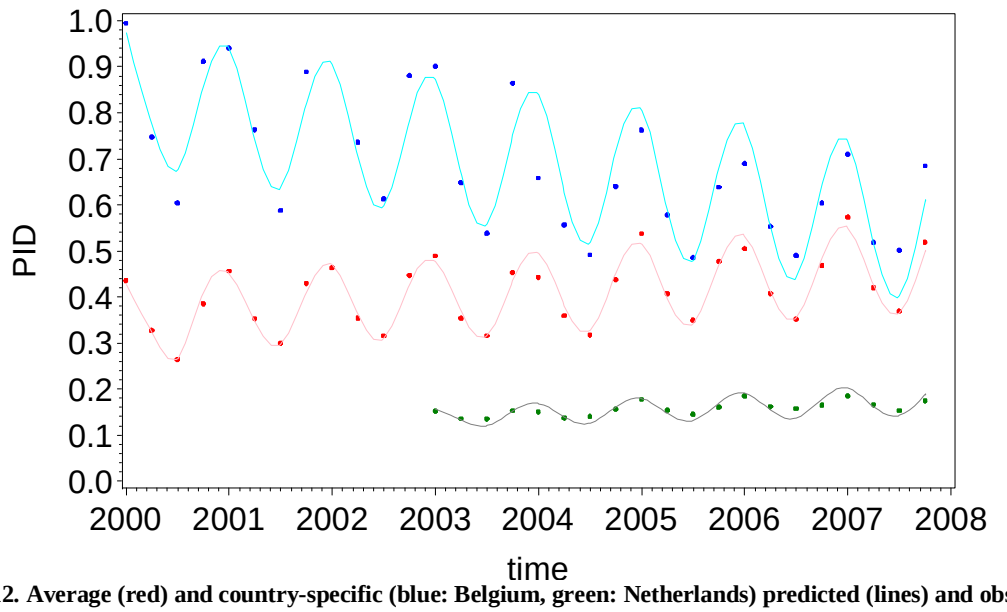

Figure 12. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) consumption of combinations of penicillins expressed in PID.

The estimates for the variance components are:

$$D = \begin{pmatrix} 0.0887 & -0.00016 & 0.0186 \\ & 0.00009 & 0.00019 \\ & & 0.0049 \end{pmatrix} \text{ and } \sigma^2 = 0.0045.$$

This covariance structure implies that the correlation between the random effects equals -0.0566 (between random intercept and random slope), 0.8922 (between random intercept and random amplitude) and 0.2861 (between random slope and random amplitude).

A joint model was fit to the data by using the rescaled outcomes (DID and 10*PID). The correlations between matching random effects are 0.9205 (between random intercepts), 0.7898 (between random slopes) and 0.9899 (between random amplitudes). Only the correlation between the random amplitudes appeared not to be significantly different from 1 (corrected p-value = 0.2946).

3.5 Macrolides (J01F)

The consumption of macrolides ranges from 0.17 to 18.42 DID. The most complex starting model that could be fit to the data was a model with fixed and random intercepts, slopes and amplitudes and a fixed change in amplitude. Likelihood ratio tests indicated that none of the random effects could be removed. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

The residuals plot (appendix Figure 7 (left)) shows that there is no clear structure in the residuals. Parameter estimates are given in Table 9 and the good model fit is shown in Figure 13.

Table 9. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for macrolides consumption measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01F	2.1834 (0.2589)**	0.0270 (0.0107)*	0.5906 (0.1185)**	0.0114 (0.0021)**

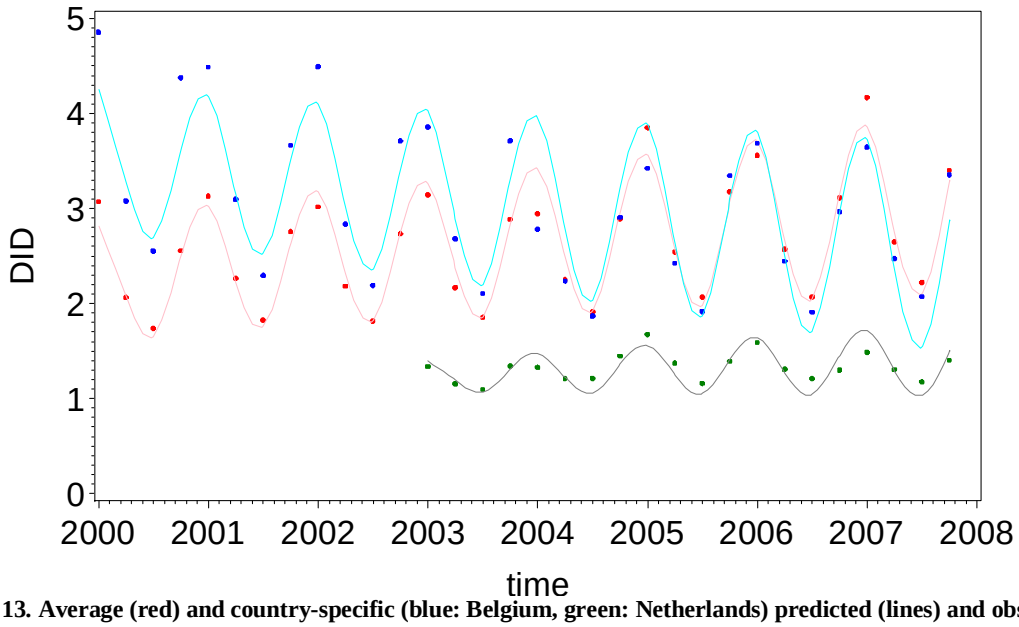

Figure 13. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) macrolides consumption expressed in DID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 2.0361 & -0.0053 & 0.7048 \\ & 0.0035 & 0.0190 \\ & & 0.3844 \end{pmatrix} \text{ and } \sigma^2 = 0.1821.$$

This covariance structure implies that the correlation between the random effects equals -0.0628 (between random intercept and random slope), 0.7967 (between random intercept and random amplitude) and 0.5180 (between random slope and random amplitude).

Macrolides consumption ranges from 0.09 to 1.80 PID. The most complex starting model that could be fitted to these data was a model containing random and fixed intercepts, slopes and amplitudes and a fixed but no random change in amplitude. A Likelihood ratio test indicated that the fixed change in amplitude could be removed from the model. None of the random effects could be removed. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.

There is no clear structure in the residuals, as can be seen on the residuals plot (appendix Figure 7 (right)). Parameter estimates are shown in Table 10 and the good model fit is illustrated on Figure 14.

Table 10. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for macrolides consumption measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001).**

	β_0	β_1	β_2
J01F	0.4543 (0.0494)**	0.0006 (0.0012)	0.1334 (0.0158)**

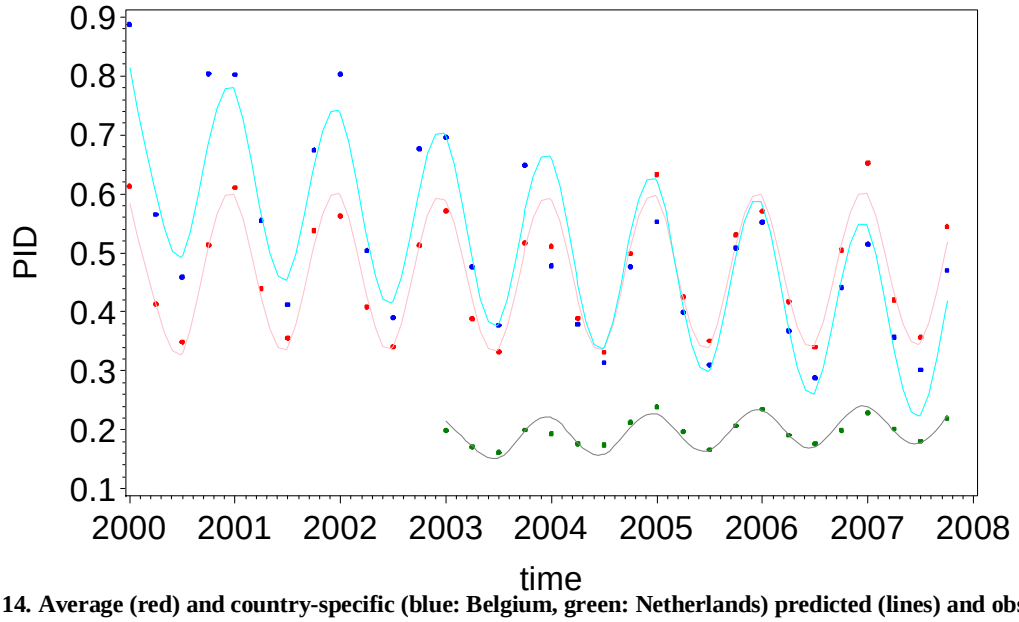

Figure 14. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) macrolides consumption expressed in PID.

The estimates for the variance components are:

$$D = \begin{pmatrix} 0.0748 & -0.0007 & 0.0217 \\ & 0.00004 & -0.00004 \\ & & 0.0074 \end{pmatrix} \text{ and } \sigma^2 = 0.0046.$$

This covariance structure implies that the correlation between the random effects equals -0.4047 (between random intercept and random slope), 0.9223 (between random intercept and random amplitude) and -0.074 (between random slope and random amplitude).

A joint model was fit to the data by using the rescaled outcomes (DID and 10*PID). The correlations between matching random effects are 0.9443 (between random intercepts), 0.7946 (between random slopes) and 0.9924 (between random amplitudes). Only the correlation between random amplitudes appeared to not be significantly different from 1 (corrected p-value = 0.2743).

3.6 Quinolones (J01M)

Consumption of quinolones ranges from 0.20 to 5.15 DID. A likelihood ratio test indicated that the random change in amplitude could be removed from the model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

A plot of the residuals (appendix Figure 8 (left)) shows that there is no clear structure in the residuals. Parameter estimates for the final model are shown in Table 11. The model appeared to fit the data well as is shown in Figure 15.

Table 11. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for quinolones consumption measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01M	1.1847 (0.1403)**	0.0178 (0.0044)*	0.0858 (0.0238)*	0.0021 (0.0009)*

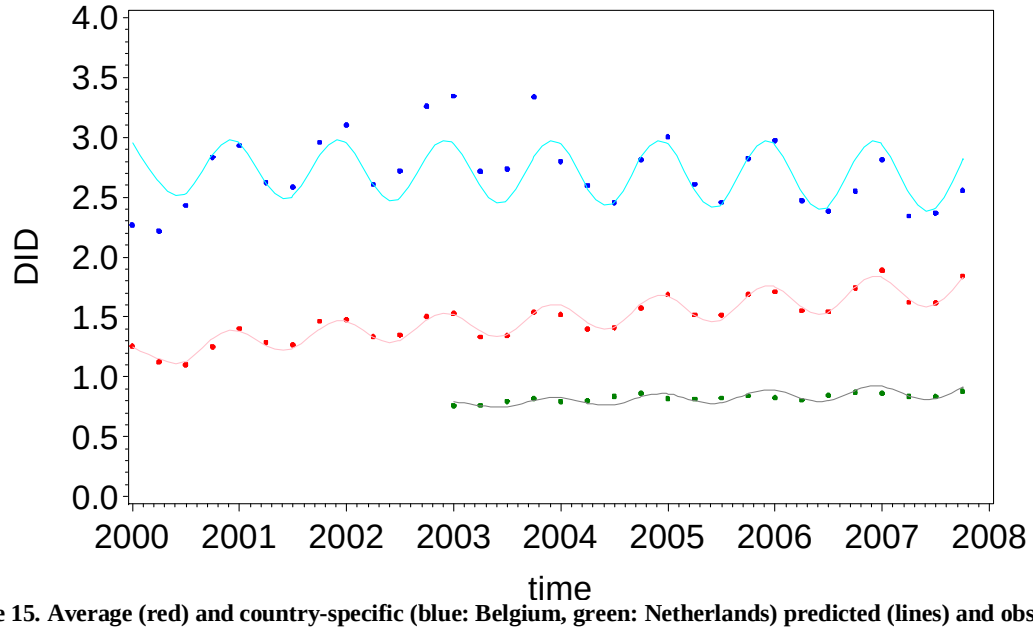

Figure 15. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) quinolones consumption expressed in DID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.6026 & -0.0041 & 0.0643 \\ & 0.0006 & -0.0003 \\ & & 0.0089 \end{pmatrix} \text{ and } \sigma^2 = 0.0305.$$

This covariance structure implies that the correlation between the random effects equals -0.2156 (between random intercept and random slope), 0.8780 (between random intercept and random amplitude) and -0.1298 (between random slope and random amplitude).

Quinolones consumption lies between 0.03 and 0.88 PID. Likelihood ratio tests indicated that the random change in amplitude could be removed from the model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

There is no clear structure in the residuals, as is illustrated on the residuals plot (appendix Figure 8 (right)). Parameter estimates are given in Table 12 and the good model fit is shown in Figure 16.

Table 12. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for quinolones consumption measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01M	0.2012 (0.0239)**	0.0026 (0.0006)*	0.0153 (0.0043)*	0.0003 (0.0001)*

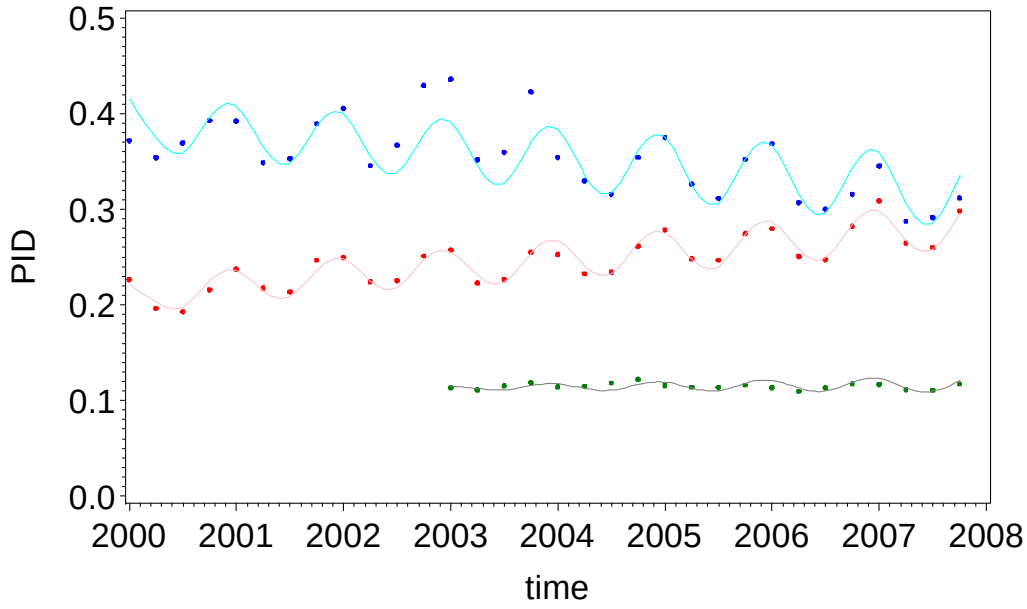

Figure 16. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) quinolones consumption expressed in PID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.0175 & -0.00004 & 0.0022 \\ & 0.00001 & 0.000003 \\ & & 0.0004 \end{pmatrix} \text{ and } \sigma^2 = 0.0007.$$

This covariance structure implies that the correlation between the random effects equals -0.0956 (between random intercept and random slope), 0.8315 (between random intercept and random amplitude) and 0.015 (between random slope and random amplitude).

A joint model was fit to the data by using the rescaled outcomes (DID and 10*PID). In order to reach convergence the covariance between the random amplitudes for DID and 10*PID was set equal to zero. The correlations between the other matching random effects are 0.9013 (between random intercepts) and 0.8913 (between random slopes). Both correlations were significantly different from 1.

3.7 Cephalosporin (J01D)

The consumption of cephalosporins ranges from 0.04 to 11.94 DID. Likelihood ratio tests showed that none of the random effects could be removed from the model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + (\beta_3 + b_{3i})*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

There is no systematic structure in the residuals, as can be seen on the residuals plot (appendix Figure 9 (left)). Parameter estimates are shown in Table 13 and the good model fit is illustrated in Figure 17.

Table 13. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for cephalosporin consumption measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001).**

	β_0	β_1	β_2	β_3
J01D	1.8794 (0.3042)**	0.0125 (0.0094)	0.5247 (0.0997)**	0.0007 (0.0022)

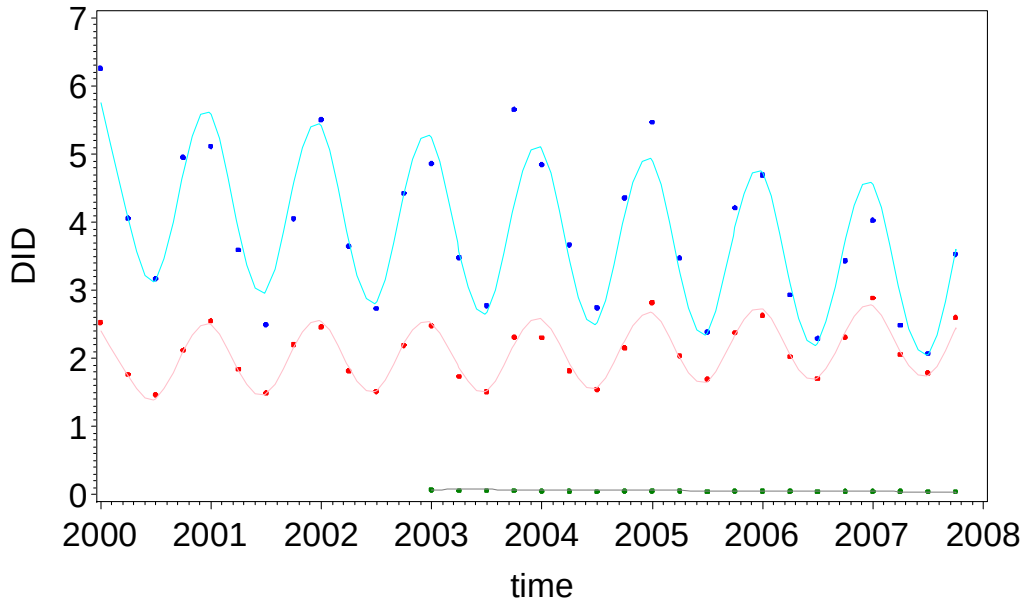

Figure 17. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) cephalosporin consumption expressed in DID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 2.8399 & -0.0146 & 0.8278 & 0 \\ & 0.0027 & -0.0023 & 0 \\ & & 0.2745 & 0 \\ & & & 0.00005 \end{pmatrix} \text{ and } \sigma^2 = 0.1173.$$

This covariance structure implies that the correlation between the random effects equals -0.1667 (between random intercept and random slope), 0.9376 (between random intercept and random amplitude) and -0.0845 (between random slope and random amplitude).

Cephalosporin consumption ranges between 0.008 and 3.54 PID. According to the likelihood ratio tests, none of the random effects could be removed from the starting model. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + (\beta_3 + b_{3i})*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.

The residuals plot (appendix Figure 9 (right)) shows that there is no clear structure in the residuals. Parameter estimates for the final model are shown in Table 14. The model appears to fit the data well, as is shown in Figure 18.

Table 14. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for cephalosporin consumption measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001).**

	β_0	β_1	β_2	β_3
J01D	0.5268 (0.0908)**	0.000014 (0.0026)	0.1446 (0.0301)**	-0.0009 (0.021)

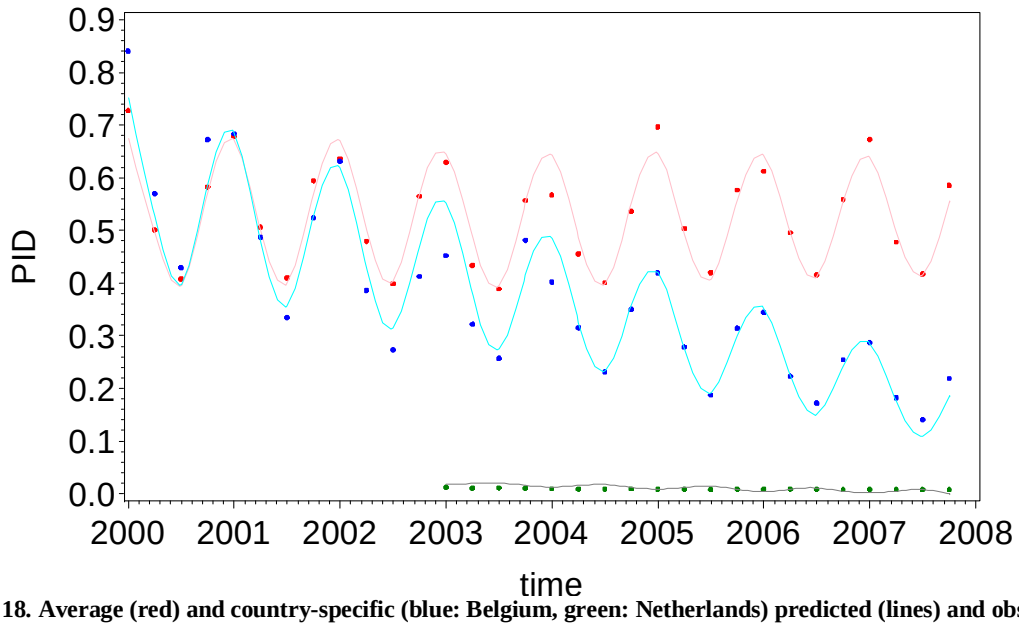

Figure 18. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) cephalosporin consumption expressed in PID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.2536 & -0.0018 & 0.0789 & 0 \\ & 0.0002 & -0.0008 & 0 \\ & & 0.0257 & 0 \\ & & & 0.000008 \end{pmatrix} \text{ and } \sigma^2 = 0.0079.$$

This covariance structure implies that the correlation between the random effects equals -0.2527 (between random intercept and random slope), 0.9773 (between random intercept and random amplitude) and -0.3529 (between random slope and random amplitude).

A joint model was fit to the data by using the rescaled outcomes (DID and 10*PID). The correlations between matching random effects are 0.7679 (between random intercepts), 0.8214 (between random slopes) and 0.7774 (between random amplitudes). All correlations were significantly different from 1.

3.8 Tetracyclines (J01A)

Consumption of tetracyclines ranges from 0.06 to 5.83 DID. Likelihood ratio tests showed that none of the random effects could be removed from the model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + (\beta_3 + b_{3i})*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

The residuals plot (appendix Figure 10 (left)) shows that there is no systematic structure in the residuals. Parameter estimates are given in Table 15 and the good model fit is illustrated in Figure 19.

Table 15. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for tetracycline consumption measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01A	1.8911 (0.2041)**	-0.0106 (0.0047)*	0.3660 (0.052)**	-0.0047 (0.0014)*

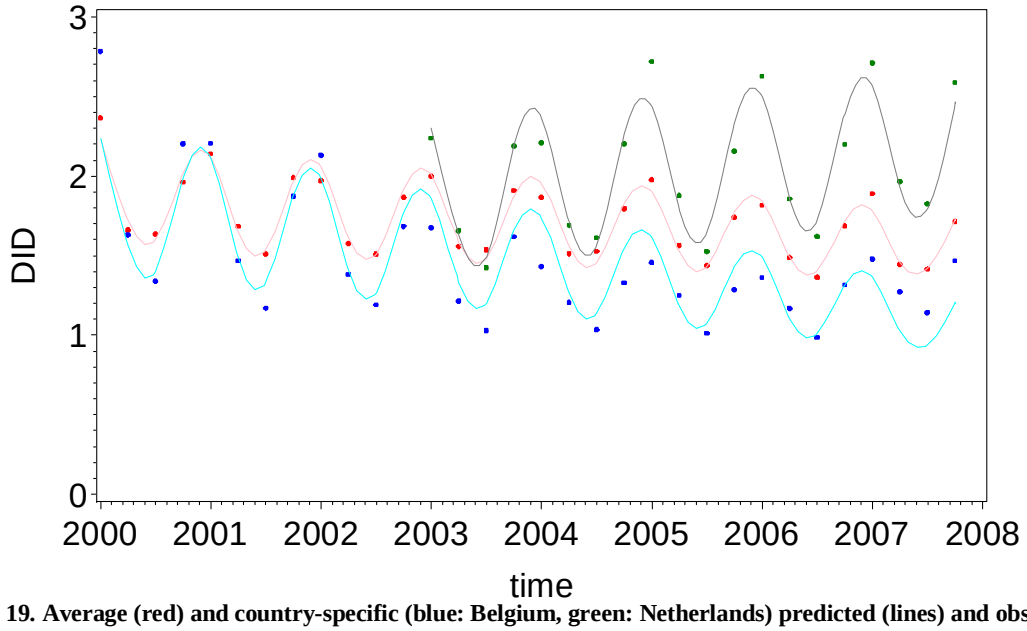

Figure 19. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) tetracycline consumption expressed in DID.

Estimate for the variance components are:

$$D = \begin{pmatrix} 1.2791 & -0.0182 & 0.2352 & 0 \\ & 0.00066 & -0.0019 & 0 \\ & & 0.0706 & 0 \\ & & & 0.00002 \end{pmatrix} \text{ and } \sigma^2 = 0.0464.$$

This covariance structure implies that the correlation between the random effects equals -0.6264 (between random intercept and random slope), 0.7827 (between random intercept and random amplitude) and -0.2783 (between random slope and random amplitude).

Tetracycline consumption ranges between 0.0002 and 1.23 PID. According to the likelihood ratio tests, the random change in amplitude could be dropped from the model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

No systematic structure is detected on the residuals plot (appendix Figure 10 (right)). Parameter estimates are given in Table 16 and the good fit of the model is shown in Figure 20.

Table 16. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for tetracycline consumption measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01A	0.2371 (0.0316)**	-0.0026 (0.0010)*	0.0442 (0.0050)**	-0.0008 (0.0001)**

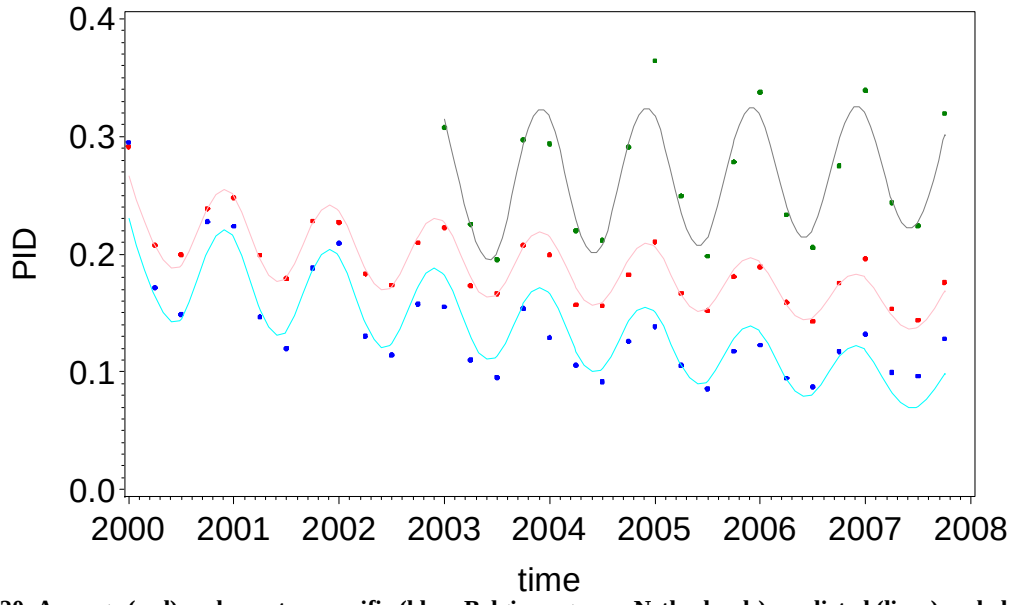

Figure 20. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) tetracycline consumption expressed in PID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.0308 & -0.0008 & 0.0026 \\ & 0.00003 & -0.00004 \\ & & 0.0005 \end{pmatrix} \text{ and } \sigma^2 = 0.0008.$$

This covariance structure implies that the correlation between the random effects equals -0.8323 (between random intercept and random slope), 0.6625 (between random intercept and random amplitude) and -0.3266 (between random slope and random amplitude).

A joint model was fit to the data by using the rescaled outcomes (DID and 10*PID). Correlations between the matching random effects are 0.7513 (between random intercepts), 0.9042 (between random slopes) and 0.8591 (between random amplitudes). All correlations were significantly different from 1.

3.9 Sulphonamides (J01E)

Consumption of sulphonamides ranges between 0.13 and 2.58 DID. A likelihood ratio test showed that the random change in amplitude could be removed from the model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

The residuals plot (appendix Figure 11 (left)) shows that there is no systematic structure in the residuals. Parameter estimates are given in Table 17 and the good model fit is shown in Figure 21.

Table 17. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for sulphonamides consumption measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1	β_2	β_3
J01E	0.9900 (0.0803)**	-0.0089 (0.0021)*	0.1560 (0.0263)**	-0.0024 (0.0006)*

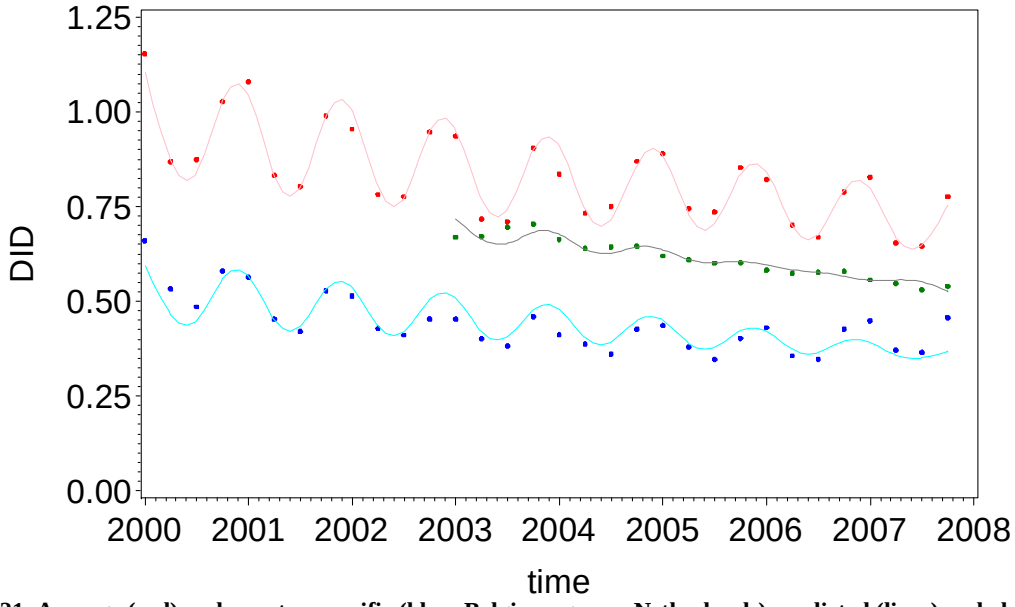

Figure 21. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) sulphonamide consumption expressed in DID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.1902 & -0.0029 & 0.0379 \\ & 0.0001 & -0.0004 \\ & & 0.0172 \end{pmatrix} \text{ and } \sigma^2 = 0.0121.$$

This covariance structure implies that the correlation between the random effects equals -0.6649 (between random intercept and random slope), 0.6626 (between random intercept and random amplitude) and -0.3049 (between random slope and random amplitude).

Sulphonamide consumption ranges from 0.026 to 0.56 PID. A Likelihood ratio test showed that the random change in amplitude could be removed from the model. The final model is defined as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3*t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}.$$

The residuals plot (appendix Figure 11 (right)) shows that there is no clear structure in the residuals. Parameter estimates are given in Table 18 and the good mode fit is shown in Figure 22.

Table 18. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for sulphonamides consumption measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.0001).**

	β_0	β_1	β_2	β_3
J01E	0.1876 (0.019)**	-0.0021 (0.0004)**	0.0331 (0.0052)**	-0.0006 (0.0001)**

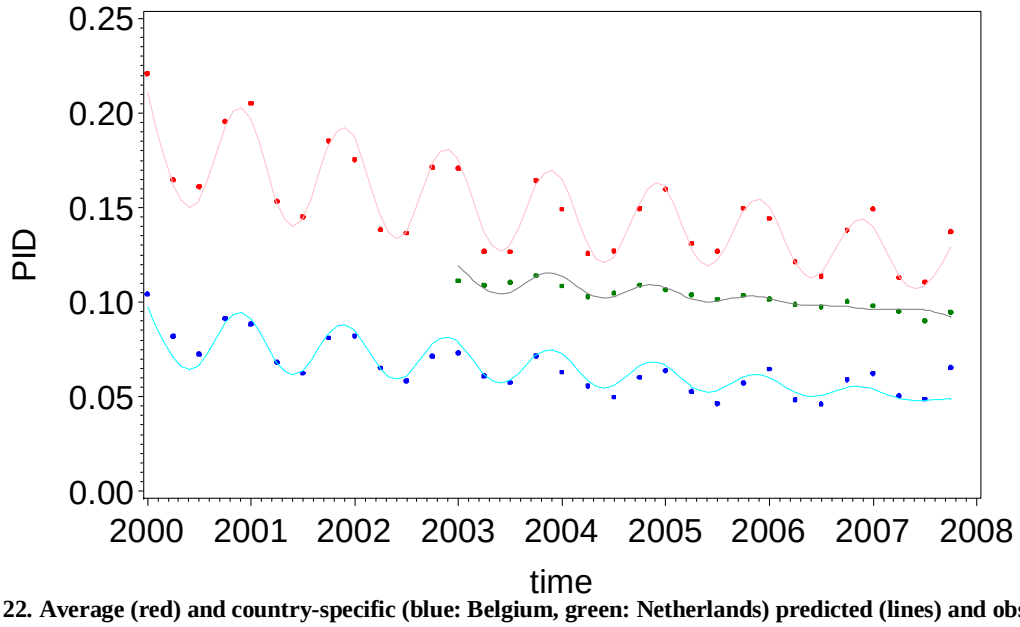

Figure 22. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) sulphonamide consumption expressed in PID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.0107 & -0.00016 & 0.0022 \\ & 0.0000044 & -0.00003 \\ & & 0.0007 \end{pmatrix} \text{ and } \sigma^2 = 0.0004.$$

This covariance structure implies that the correlation between the random effects equals -0.7374 (between random intercept and random slope), 0.8039 (between random intercept and random amplitude) and -0.5406 (between random slope and random amplitude).

A joint model was fit to the data by using the rescaled outcomes (DID and 10*PID). In order to reach convergence the covariance between the random amplitudes was set equal to zero. The correlations between the other matching random effects are 0.9235 (between random intercepts) and 0.84 (between random slopes). Both correlations were significantly different from 1.

3.10 Urinary antiseptics (J01X)

The consumption of urinary antiseptics ranges from 0.000037 to 0.77 DID. In order to reach convergence, all covariances had to be set equal to zero. Likelihood ratio tests indicated that the random change in amplitude, as well as the fixed change in amplitude could be removed from the model. In this reduced model the covariances had to be kept at zero in order to maintain convergence. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.
The residuals plot (appendix Figure 12 (left)) shows that there is no clear structure. Parameter estimates for this final model are shown in Table 19. The good model fit is illustrated in Figure 23.

Table 19. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for the consumption of urinary antiseptics measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope and β_2 the fixed amplitude for the sine wave (*: p-value < 0.05).

	β_0	β_1	β_2
J01X	0.0357 (0.0209)	0.0018 (0.0006)*	-0.0029 (0.0015)

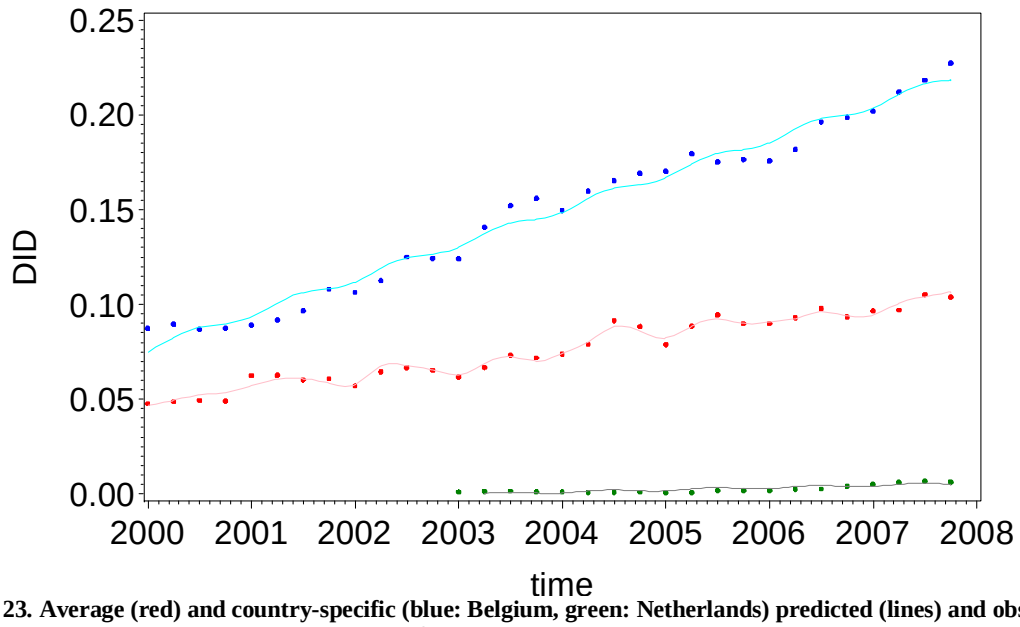

Figure 23. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) consumption of urinary antiseptics expressed in DID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.0101 & 0 & 0 \\ & 0.000008 & 0 \\ & & 0.000044 \end{pmatrix} \text{ and } \sigma^2 = 0.000095.$$

Consumption of urinary antiseptics ranges between 0.000016 and 0.216 PID. In order to reach convergence in the starting model, all covariances were set equal to zero. Likelihood ratio tests indicated that both fixed and random change in amplitude could be removed from the model. In this reduced model covariances could be specified while maintaining convergence. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.

There is no clear structure in the residuals, as can be seen on the residuals plot (appendix Figure 12 (right)). Parameter estimates are given in Table 20. The model fitted well for the majority of the countries with the exception being the Netherlands where a big change is observed around 2004. For these data the model fits the data well before this change and afterwards (Figure 24).

Table 20. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for the consumption of urinary antiseptics measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope and β_2 the fixed amplitude for the sine wave (*: p-value < 0.05).

	β_0	β_1	β_2
J01X	0.0187 (0.0055)*	0.00056 (0.00019)*	-0.00054 (0.00033)

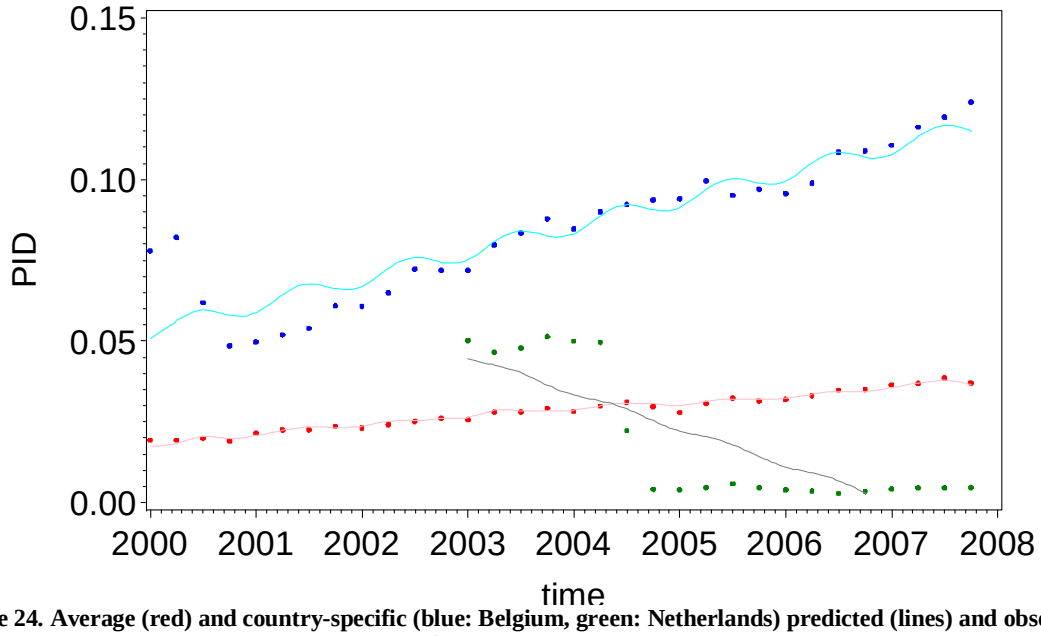

Figure 24. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) consumption of urinary antiseptics expressed in PID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.00094 & 0.0000077 & -0.00004 \\ & 0.0000012 & -0.000001 \\ & & 0.0000022 \end{pmatrix} \text{ and } \sigma^2 = 0.000019.$$

This covariance structure implies that the correlation between the random effects equals 0.2337 (between random intercept and random slope), -0.8827 (between random intercept and random amplitude) and -0.6285 (between random slope and random amplitude).

A joint model was fitted to the data by using the rescaled outcomes (DID and 10*PID). The correlations between the random effects are 0.8563 (between random intercepts) and 0.8224 (between random slopes). All correlations were significantly different from 1.

3.11 Other antibiotics (concatenation of J01B, J01G and J01R)

The consumption of other antibiotics ranges between 0.00021 and 0.86 DID. Likelihood ratio tests show that the random and fixed change in amplitude can be removed from the model. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.

On the residuals plot (appendix Figure 13 (left)), no clear structure is detected. Parameter estimates for the final model are shown in Table 21 and the good fit of the model is illustrated in Figure 25.

Table 21. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for the consumption of other antibiotics measured in DID with β_0 representing the fixed intercept, β_1 the fixed slope and β_2 the fixed amplitude for the sine wave (*: p-value < 0.05).

	β_0	β_1	β_2
J01BGR	0.1179 (0.0348)*	-0.0017 (0.0010)	0.0072 (0.0033)*

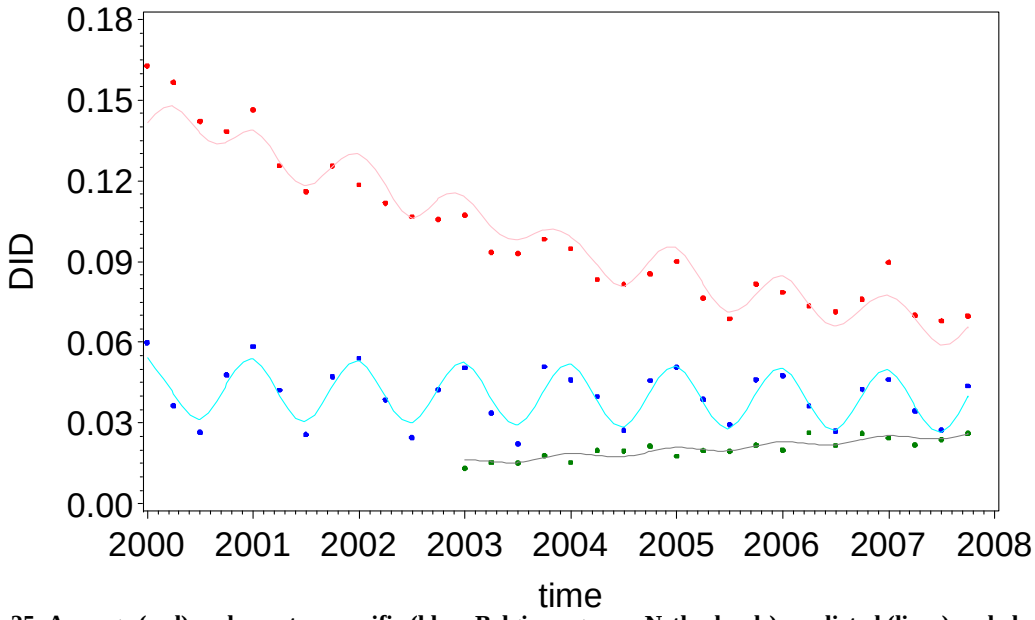

Figure 25. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) consumption of other antibiotics expressed in DID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.0349 & -0.0008 & 0.0010 \\ & 0.00003 & -0.00004 \\ & & 0.00026 \end{pmatrix} \text{ and } \sigma^2 = 0.0008.$$

This covariance structure implies that the correlation between the random effects equals -0.2472 (between random intercept and random slope), 0.3320 (between random intercept and random amplitude) and -0.4529 (between random slope and random amplitude).

The consumption of other antibiotics ranges from 0.0000033 to 1.26 PID. Likelihood ratio tests indicated that only the random change in amplitude could be removed from the model. The final model is defined as: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*t_{ij} + (\beta_2 + b_{2i} + \beta_3 *t_{ij})*\sin(\omega*t_{ij} + \delta) + \varepsilon_{ij}$.

The residuals plot shows that there is no clear structure in the residuals (appendix Figure 13 (right)). Parameter estimates are given in Table 22 and the good model fit can be seen in Figure 26.

Table 22. Parameter estimates (standard errors) for the fixed effects in the nonlinear mixed model for the consumption of other antibiotics measured in PID with β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (*: p-value < 0.05).

	β_0	β_1	β_2	β_3
J01BGR	0.1302 (0.0342)*	-0.0018 (0.0005)*	0.0179 (0.0057)*	-0.0005 (0.0001)*

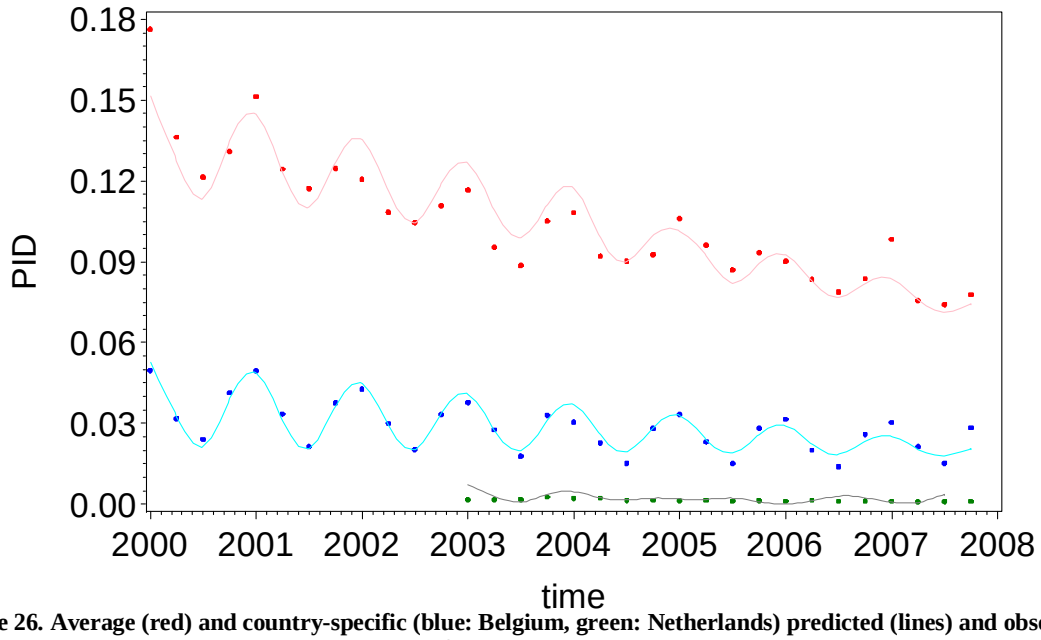

Figure 26. Average (red) and country-specific (blue: Belgium, green: Netherlands) predicted (lines) and observed (dots) consumption of other antibiotics expressed in PID.

Estimates for the variance components are:

$$D = \begin{pmatrix} 0.0361 & -0.0003 & 0.0036 \\ & 0.000007 & -0.00001 \\ & & 0.00079 \end{pmatrix} \text{ and } \sigma^2 = 0.0008.$$

This covariance structure implies that the correlation between the random effects equals -0.5968 (between random intercept and random slope), 0.6741 (between random intercept and random amplitude) and -0.1345 (between random slope and random amplitude).

A joint model was fitted to the data by using the rescaled outcomes (DID and 10*PID). Correlations between matching random effects are 0.2090 (between random intercepts), 0.2763 (between random slopes) and -0.6684 (between random amplitudes). All correlations were significantly different from 1. The correlation between the random amplitudes was however not significantly different from -1 (corrected p-value = 0.1112).

3.12 Comparison IMS Health – ESAC

The final models, that were built for the IMS Health data, were fitted to the IMS Health and the ESAC data. Both datasets were adjusted prior to this analysis by only keeping common countries and timepoints. The resulting parameter estimates are shown in Table 23. We can see that, although the absolute values of the estimates change, the sign remains the same and hence the conclusions based on the estimates for both datasets are similar. However, also the significance of the estimates changes from one dataset to the other.

Table 23. Comparison of the parameter estimates for the final nonlinear models, built for the IMS Health data, fitted to both the adjusted IMS Health and the adjusted ESAC data. Parameters are β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave (: p-value < 0.01 and *: p-value < 0.05).**

	IMS (DID)				ESAC			
	β_0	β_1	β_2	β_3	β_0	β_1	β_2	β_3
JO1	14.2954**	0.0769*	2.9010**	0.0248*	17.6246**	0.0594	3.6124**	0.0109
JO1A	1.8903**	-0.0105	0.3699**	-0.0048**	2.3730**	-0.0107*	0.4851**	-0.0050**
JO1C	6.0360**	0.0435**	1.2788**	0.0125*	7.7536**	0.0408	1.7626**	0.0037
JO1F	2.0851**	0.0330*	0.5643**	0.0132**	2.0509**	0.0340*	0.6562**	0.0107**
JO1M	1.2358**	0.0119**	0.0650*	0.0032**	1.1618**	0.0144**	0.0829*	0.0021
JO1D	1.8979**	0.0095	0.5078**	0.0012	1.8782**	0.0061	0.4960**	-0.0014
JO1E	0.9985**	-0.0096**	0.1084**	-0.0005	0.9984**	-0.0145*	0.1176**	-0.0011
JO1X	0.0415	0.0015*	-0.0032	-	0.6076**	0.0057	0.01767	-

3.13 Change in DDD per package over time

The defined daily dose per package (DP) was calculated as DID divided by PID, providing a link between both measurements. In order to study the variability within one country and between different countries, individual profiles of DP were constructed. The profiles for the J01 subgroup are shown in Figure 27, profiles for all other subgroups studied are shown in the appendix (appendix Figure 14).

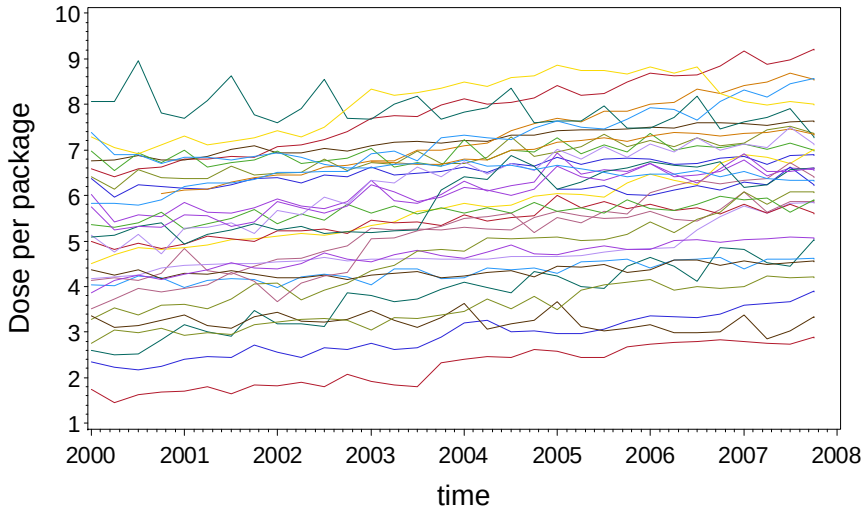

Figure 27. Observed country-specific changes in quarterly DP (for the J01 subgroup) in 31 European countries.

The individual profiles demonstrate the need for random intercepts and slopes to account for the heterogeneity across countries. It can also be seen on the profiles that the seasonal fluctuations, which were observed in the antibiotics consumption for all studied subgroups in DID and PID, have indeed disappeared in DP. For the linear mixed model, containing both fixed and random intercepts and slopes, likelihood ratio tests indicated that none of the random effects could be removed. In one subgroup (i.e. J01X) the likelihood ratio tests indicated that both random intercepts and slopes could be removed. The final model for J01X thus only contains a fixed intercept and slope. The need for random effects in all but one subgroup suggests that the average DDD per package in 2000 and the

change in DP over time differ substantially between the countries. The correlation between the random effects is rather low, indicating that there is no clear connection between the random intercept and the random slope. Estimates for the fixed effects in models for all subgroups are shown in Table 24.

Table 24. Parameter estimates (standard errors) for the fixed effects in the linear mixed model for DDD per package with β_0 representing the fixed intercept and β_1 the fixed slope (: p-value < 0.0001 and *: p-value < 0.05).**

	β_0	β_1
J01	4.9149 (0.2891)**	0.0436 (0.0059)**
J01C	4.8265 (0.3798)**	0.0617 (0.0087)**
J01CA	6.6670 (0.4998)**	0.0573 (0.0106)**
J01CR	5.8891 (0.3731)**	0.0693 (0.0099)**
J01F	4.9924 (0.3571)**	0.0390 (0.0079)**
J01M	6.1181 (0.2671)**	0.0105 (0.0075)
J01D	3.9906 (0.3487)**	0.0428 (0.0115)*
J01A	9.2237 (0.9723)**	0.0433 (0.0146)*
J01E	5.2627 (0.2154)**	0.0083 (0.0034)*
J01X	1.0179 (0.2254)*	0.0086 (0.0037)*
J01BGR	1.1447 (0.3420)*	0.0778 (0.0367)*

In Table 24 we can see that, obviously, the estimates for the intercept are significantly different from zero as there always is a non-zero DDD per package. The estimates range from 1.02 to 9.22 indicating that the average dose per package in 2000 for different subgroups of antibiotics was varying between 1 (for urinary antiseptics) and 9 (for tetracyclines) defined daily doses (DDD).

We also see that the slope for the linear mixed model ranges between 0.0105 and 0.0778, reflecting a quarterly increase of the dose per package between 0.01 and 0.08 DDD. This translates to a yearly increase between 0.04 and 0.31 defined daily doses per package. For all but one subgroups (i.e. J01M) the quarterly increase over time was significantly different from zero.

4 Discussion

4.1 Longitudinal data analysis under REML or ML

Estimates for mixed models are usually based on maximum likelihood (ML) estimation where the likelihood is maximized jointly for fixed effects and variance components. However, the ML estimators can be biased downwards and for this reason restricted maximum likelihood (REML) estimates are often preferred. Rather than maximizing the joint likelihood, REML maximizes the likelihood of a set of error contrasts U=A'Y where A is any (n x (n – p)) full-rank matrix with columns orthogonal to the columns of the X matrix. The vector of error contrasts follows a normal distribution with mean zero and covariance matrix A'V(α)A, which is not dependent on the fixed effects any longer and where α represents the vector of all variance and covariance parameters.

Also likelihood ratio tests can be REML or ML-based when checking whether random effects can be left out of the model. When checking whether all fixed effects are required in the model, the likelihood ratio test should however always be ML based. In those circumstances REML is no longer valid as a different mean structure goes together with different error contrasts.

To determine whether it was required to use REML rather than ML, the same model was fitted under REML and under ML. Under both conditions a likelihood ratio test was conducted to test whether the random amplitudes (b_{2i}) could be left out of the fitted model. Parameter estimates and likelihood ratio tests obtained from both models were compared.

It appeared that estimates and standard errors for fixed effects were the same for both models while estimates for the variance components varied slightly. It was noted that ML estimates were smaller than REML estimates hence confirming the downwards bias. However we concluded that the size of the bias was so small that it was not necessary to use REML rather than ML. The likelihood ratio tests under REML and ML resulted in the same conclusions and the test statistics themselves were very close together. For these reasons all models considered were fitted under ML and in SAS where proc nlmixed does not contain the option to specify REML,

4.2 Nonlinear mixed models

In this study nonlinear mixed models were fitted to antibiotics consumption data, expressed in DID or PID, in order to analyze the overall trend in antibiotic consumption over time. Parameter estimates for both models fitted in all studied subgroups are shown in Table 25. The estimates for β_0, the intercept, and for β_2, the amplitude of the sine wave, are not too different between DID and PID. Although they obviously differ in absolute value, as DID and PID are taken on a different scale, the significance of the estimates remains the same (with β_0 in the J01X data as an exception) and conclusions based on these estimates are similar. Interesting differences lie in the estimates for β_1, the slope, and for β_3, the change in the amplitude of the sine wave. Regarding the slope, there are two kinds of differences observed. One difference is seen in subgroups J01, J01C and J01F. In these subgroups antibiotics

consumption is significantly increasing over time when expressed in DID, but when expressed in PID there is no significant change over time (insignificant decrease over time). The other difference is seen in subgroups J01CA and J01BGR. There the antibiotic consumption is not significantly changing over time when expressing it in DID (insignificant increase over time), but it is significantly decreasing over time when expressing antibiotic consumption in PID. Difference in the change in amplitude of the sine wave (β_3) are situated in the J01 and J01C subgroups. When expressing antibiotics consumption in DID, the amplitude of the sine wave is increasing over time. Opposite to that, when we express antibiotics consumption in PID, there is no significant change in amplitude over time (insignificant decrease over time). This means that when we look at DID, the seasonal fluctuation is getting bigger, while for PID it is remaining constant. For the other subgroups conclusions related to the change in amplitude for the sine wave are similar for DID and PID.

Table 25. Summary of the parameter estimates for the nonlinear models fitted to the antibiotic consumption data, expressed in DID or PID. Parameters are β_0 representing the fixed intercept, β_1 the fixed slope, β_2 the fixed amplitude for the sine wave and β_3 the fixed change in the amplitude for the sine wave.
(: p-value < 0.0001 and *: p-value < 0.05)**

	DID				PID			
	β_0	β_1	β_2	β_3	β_0	β_1	β_2	β_3
J01	14.2404**	**0.1037****	3.0858**	**0.0187***	3.1006**	-0.0061	0.6608**	-0.0033
J01C	5.9694**	**0.0649****	1.3531**	**0.0116***	1.3529**	-0.0037	0.2866**	-0.0016
J01CA	3.6967**	0.0113	0.9633**	-	0.6533**	**-0.0040***	0.1645**	-0.0015*
J01CR	2.0284**	0.0506**	0.4515**	0.0098**	0.3486**	0.0037*	0.0797**	0.0007*
J01F	2.1834**	**0.0270***	0.5906**	0.0114**	0.4543**	0.0006	0.1334**	-
J01M	1.1847**	0.0178*	0.0858*	0.0021*	0.2012**	0.0026*	0.0153*	0.0003*
J01D	1.8794**	0.0125	0.5247**	0.0007	0.5268**	0.000014	0.1446**	-0.0009
J01A	1.8911**	-0.0106*	0.3660**	-0.0047*	0.2371**	-0.0026*	0.0442**	-0.0008**
J01E	0.9900**	-0.0089*	0.1560**	-0.0024*	0.1876**	-0.0021**	0.0331**	-0.0006**
J01X	0.0357	0.0018*	-0.0029	-	0.0187*	0.00056*	-0.00054	-
J01BGR	0.1179*	-0.0017	0.0072*	-	0.1302*	**-0.0018***	0.0179*	-0.0005*

When looking at the correlations between the random effects in both models we see that they are rather similar. Correlation between random intercept and random slope is in general rather low (below 0.5). The correlation between random intercept and random amplitude does not differ too much either and is in general rather high (around 0.85). An exception here is J01BGR which has a rather low correlation. The correlation between random slope and random amplitude does not differ too much either and is in general rather low.

An interesting aspect is the high correlation between the random intercept and the random amplitude. This confirms that countries with a high antibiotic intake at baseline tend to have a higher amplitude, and hence a stronger seasonal fluctuation in absolute terms.

In order to see whether the models for DID and PID were in agreement, a joint nonlinear mixed model was constructed. The correlation between the intercepts was positive for all subgroups. Some subgroups had a high (> 0.8) correlation (i.e. J01CR, J01F, J01M and J01X) but all were significantly different from 1. Also the correlation between the slopes was positive for all subgroups. Some had a high correlation (i.e. J01, J01M, J01D, J01A, J01E, J01X) but all correlations were significantly different from 1. The correlation between the amplitudes was positive for all but one subgroup (i.e. J01BGR). This negative correlation was not significantly different from -1. The positive correlation was high for some subgroups (i.e. J01, J01C, J01CA, J01CR, J01F and J01A). In some cases it was even not significantly different from 1 (i.e. J01, J01CR and J01F).

The positive correlations that were observed imply that when the random effect in the model for DID is above average, it will also be above average in the model for PID. They also imply that for all but one subgroup (i.e. J01BGR) the models for DID and PID are in agreement.

4.3 General conclusions

In this study we looked at the antibiotic consumption in 31 countries, expressed in DID and PID. We found that conclusions based on the nonlinear models for DID and PID sometimes are contradictory. We have also seen that the random intercept is highly correlated with the random amplitude, indicating that a country with a high antibiotic intake in the first quarter of 2000 will in general have a stronger seasonal effect in absolute terms.

In the joint model for DID and PID we have seen that there was a positive correlation between the random effects, indicating that when the random effect is above average for DID it will also be above average for PID and vice versa.

When looking at the DDD per package, we learned that the average DP in the first quarter of 2000 and the change of DP over time differs substantially among the studied countries as random effects are required in the linear mixed model. We have also seen that the average DDD per package in the first quarter of 2000 and the change of DP over time differs among the antibiotic subgroups and that the DDD per package is increasing in all but one subgroup. In the J01M subgroup the DP is staying constant over time as the quarterly increase is not significantly different from zero.

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APPENDIX

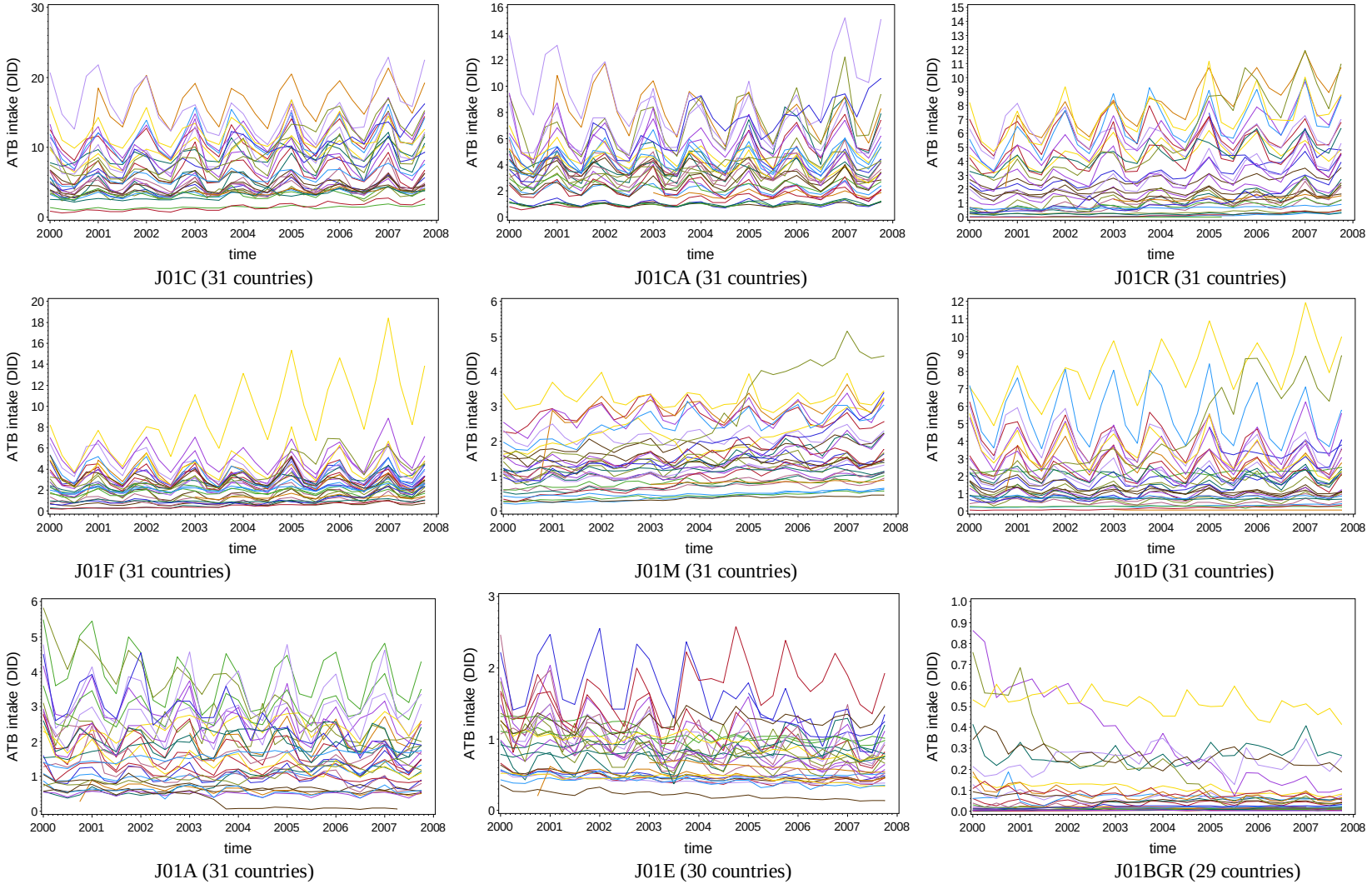

Figure 28. Observed country-specific changes in quarterly antibiotics use expressed in DID for penicillins (J01C), penicillins with extended spectrum (J01CA), combinations of penicillins (J01CR), macrolides (J01F), quinolones (J01M), cephalosporins (J01D), tetracyclines (J01A), sulphonamides (J01E) and other antibiotics (J01BGR).

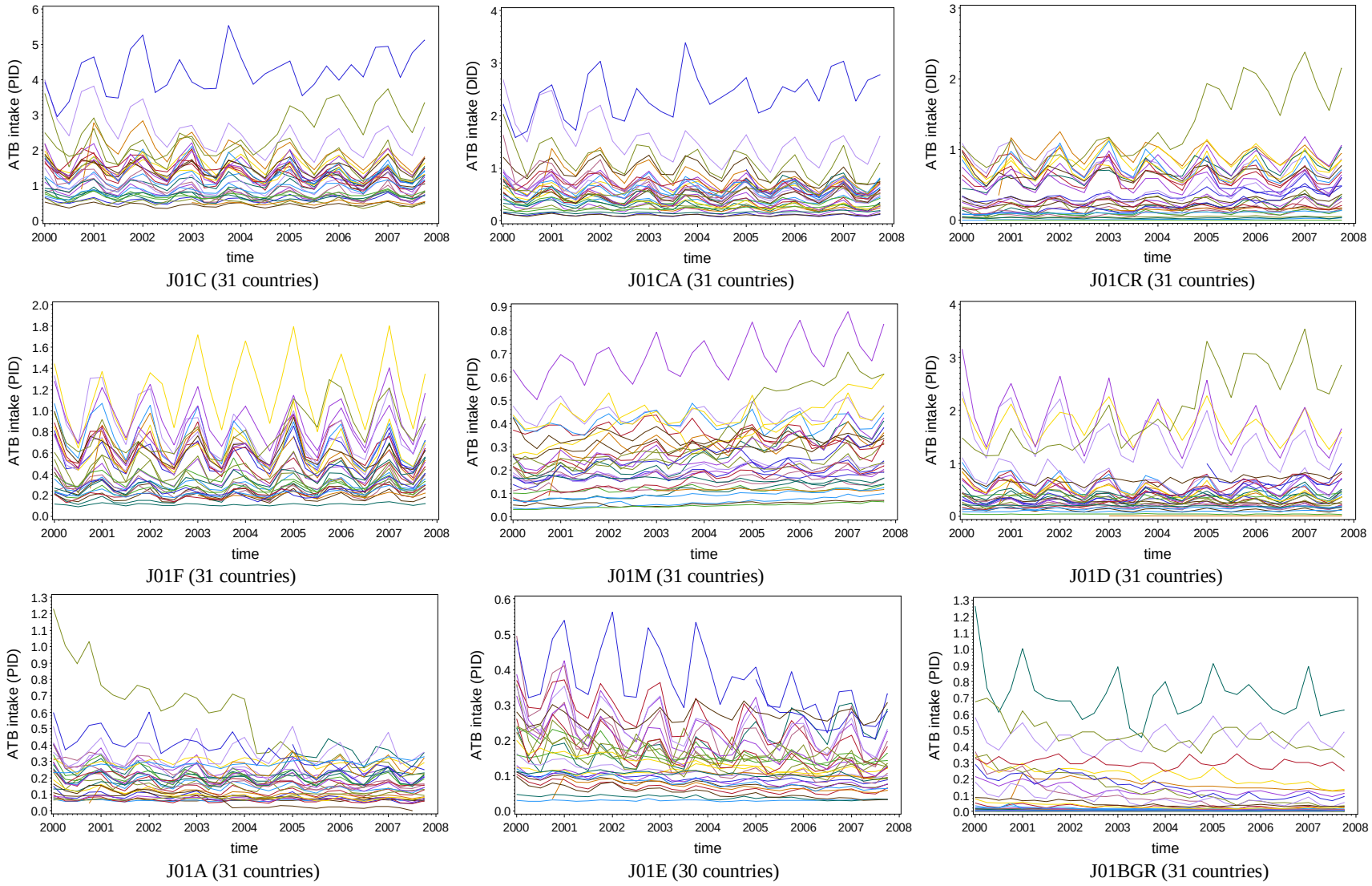

Figure 29. Observed country-specific changes in quarterly antibiotics use expressed in PID for penicillins (J01C), penicillins with extended spectrum (J01CA), combinations of penicillins (J01CR), macrolides (J01F), quinolones (J01M), cephalosporins (J01D), tetracyclines (J01A), sulphonamides (J01E) and other antibiotics (J01BGR).

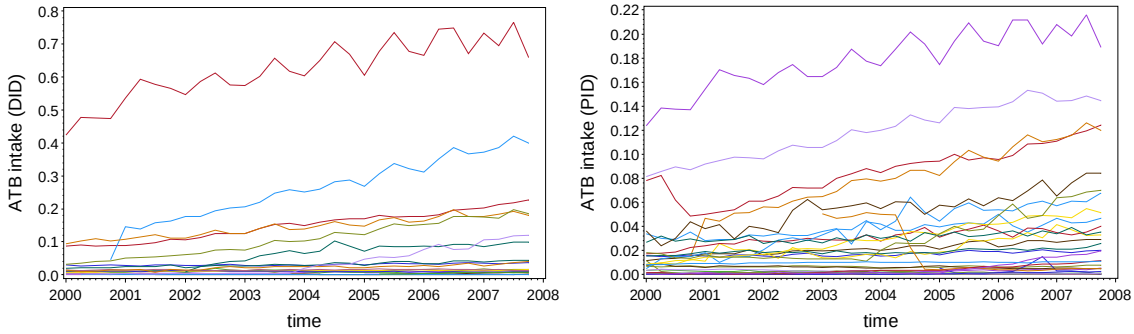

Figure 30. Observed country-specific changes in quarterly urinary antiseptics (J01X) use expressed in DID (left) and PID (right) in respectively 23 and 31 European countries.

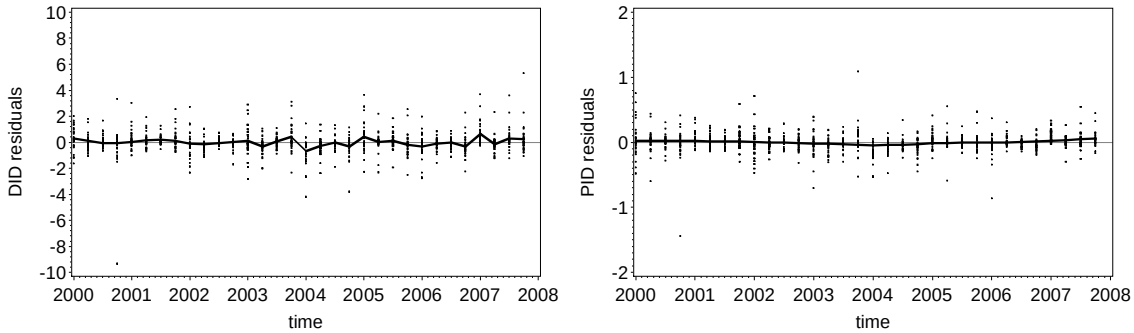

Figure 31. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for penicillin consumption in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

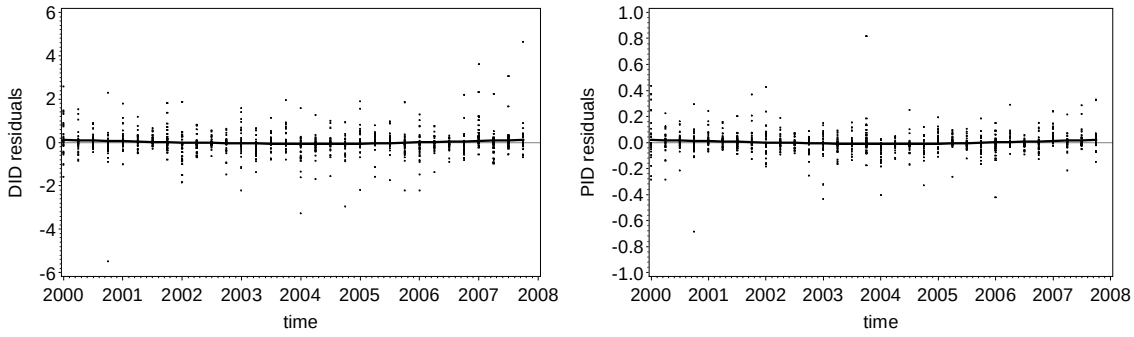

Figure 32. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for penicillins with extended spectrum consumption in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

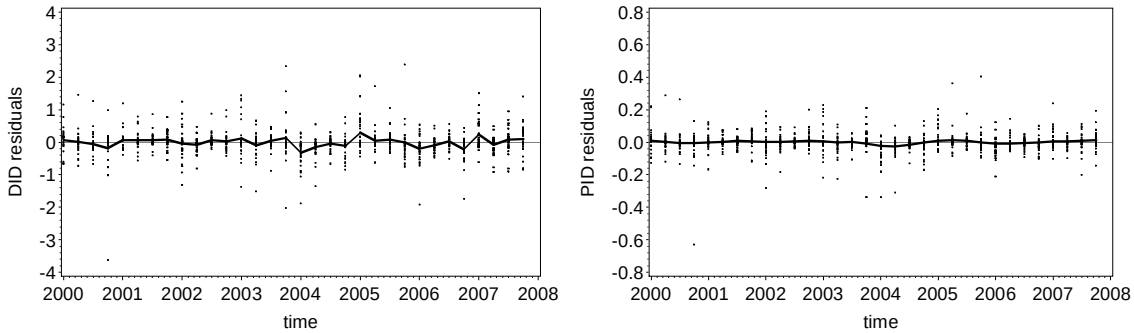

Figure 33. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for consumption of combinations of penicillins in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

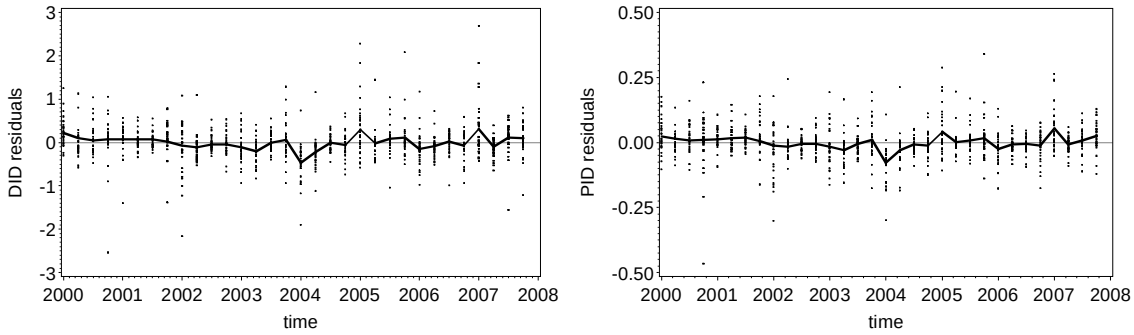

Figure 34. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for macrolides consumption in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

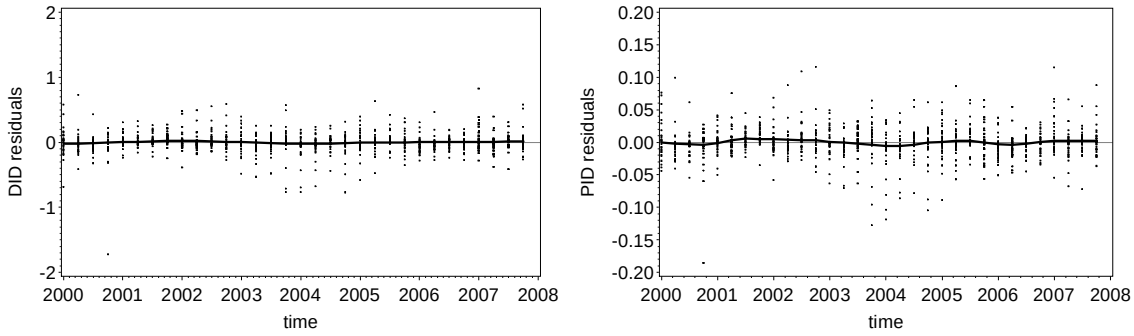

Figure 35. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for quinolones consumption in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

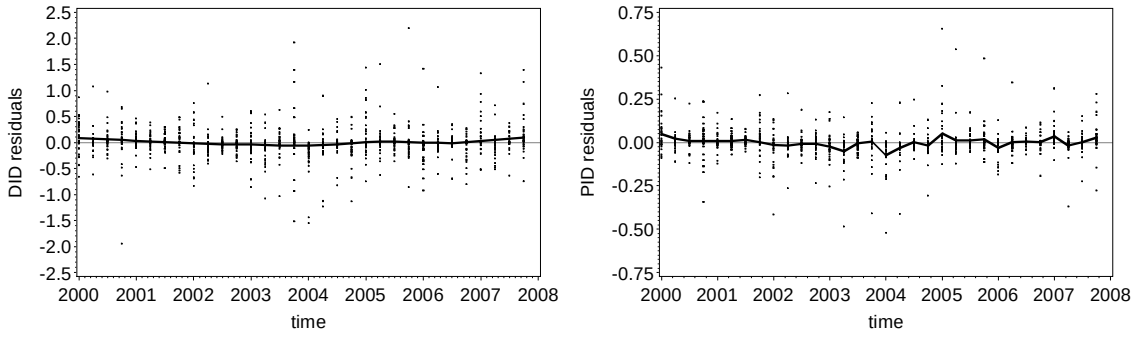

Figure 36. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for cephalosporin consumption in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

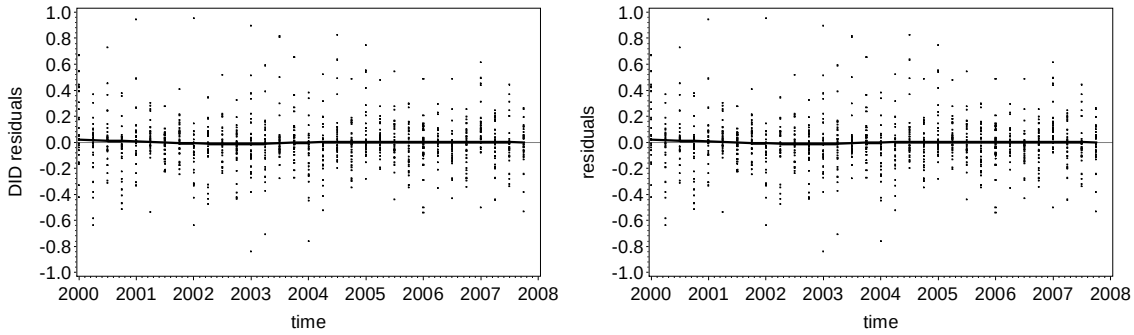

Figure 37. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for tetracycline consumption in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

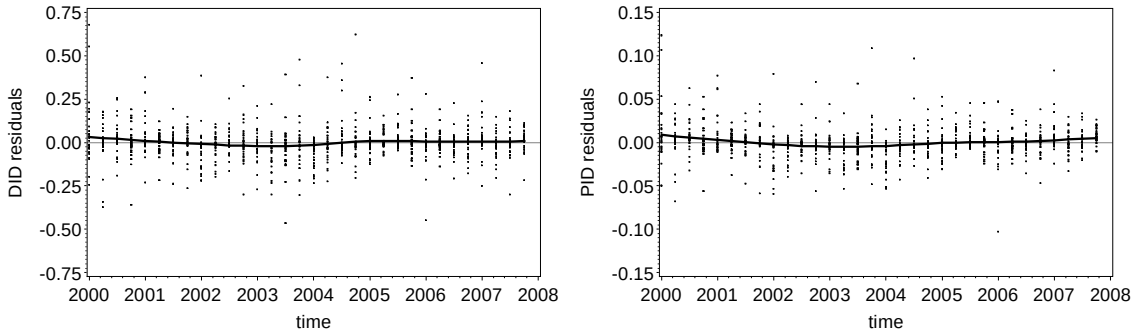

Figure 38. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for sulphonamides consumption in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

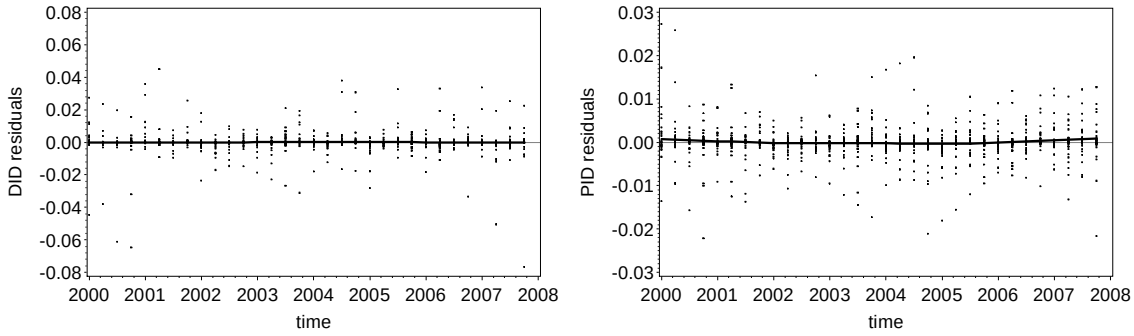

Figure 39. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for consumption of urinary antiseptics in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

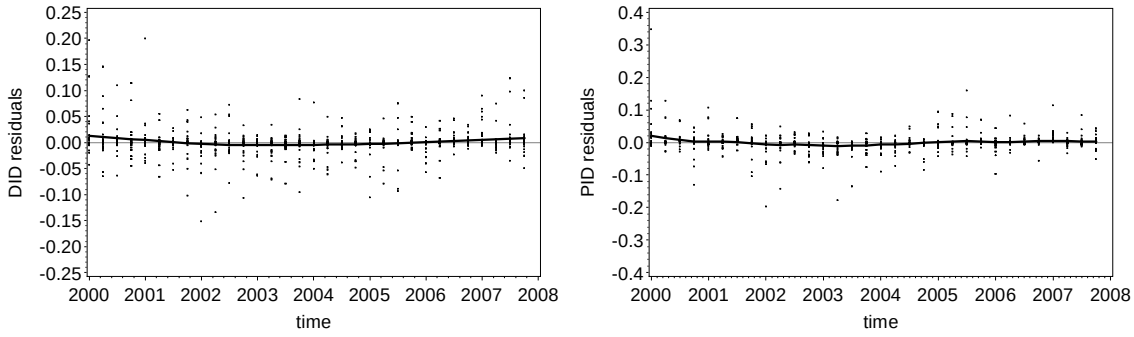

Figure 40. Scatter plot of residuals (dots) from fitting the final nonlinear mixed model for consumption of other antibiotics in DID (left) and PID (right) and the smoothed average trend of the residuals (solid line).

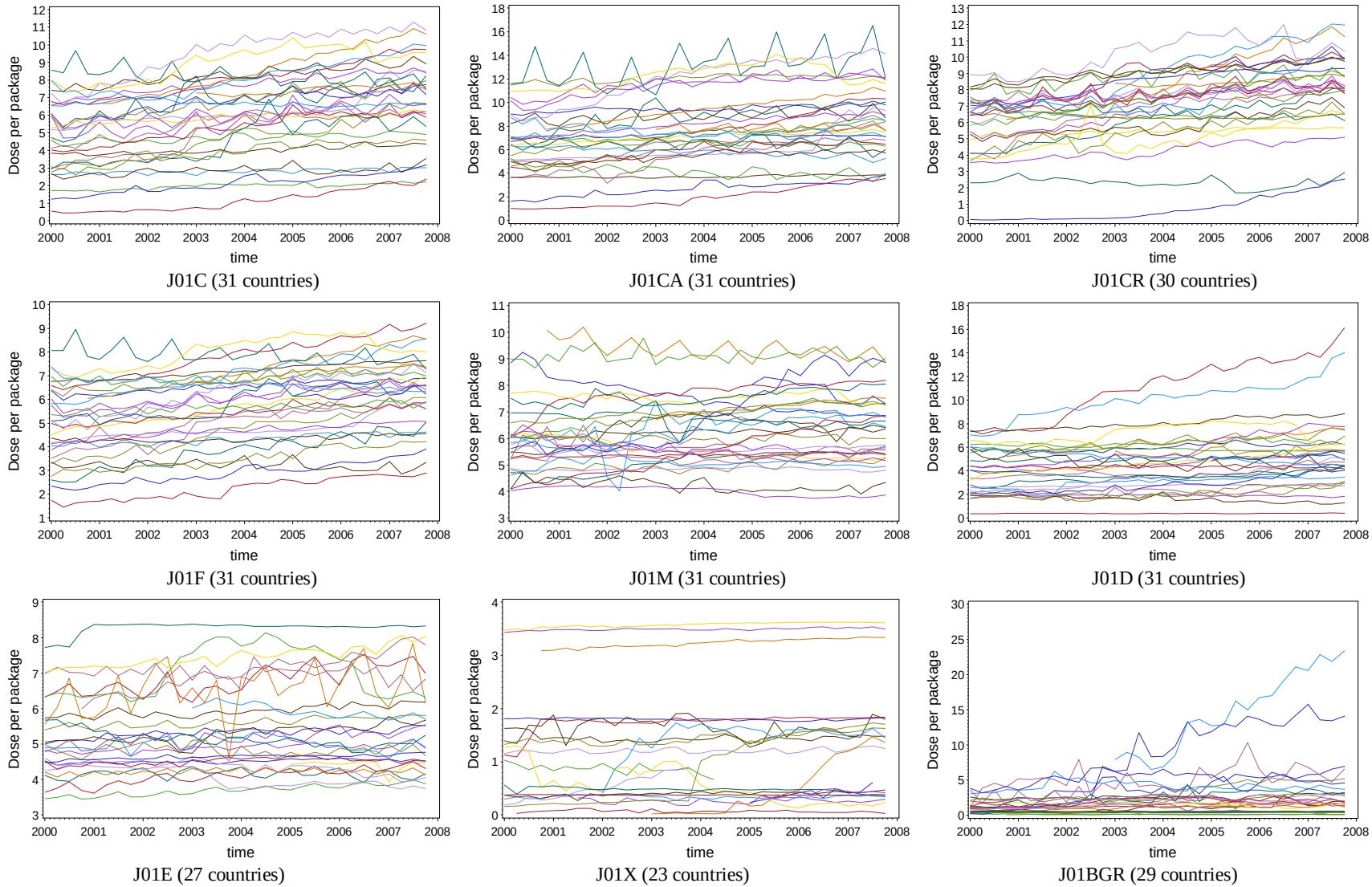

Figure 41. Observed country-specific changes in quarterly DP for penicillins (J01C), penicillins with extended spectrum (J01CA), combinations of penicillins (J01CR), macrolides (J01F), quinolones (J01M), cephalosporins (J01D), tetracyclines (J01A), sulphonamides (J01E), urinary antiseptics (J01X) and other antibiotics (J01BGR).

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Richting: **Master of Statistics-Biostatistics**
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