

Measuring trends of outpatient antibiotic use in Europe: jointly modelling longitudinal data in defined daily doses and packages

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Objectives: To complement analyses of the linear trend and seasonal fluctuation of European outpatient antibiotic use expressed in defined daily doses (DDD) by analyses of data in packages, to assess the agreement between both measures and to study changes in the number of DDD per package over time.

Methods: Data on outpatient antibiotic use, aggregated at the level of the active substance (WHO version 2011) were collected from 2000 to 2007 for 31 countries and expressed in DDD and packages per 1000 inhabitants per day (DID and PID, respectively). Data expressed in DID and PID were analysed separately using non-linear mixed models while the agreement between these measurements was analysed through a joint non-linear mixed model. The change in DDD per package over time was studied with a linear mixed model.

Results: Total outpatient antibiotic and penicillin use in Europe and their seasonal fluctuation significantly increased in DID, but not in PID. The use of combinations of penicillins significantly increased in DID and in PID. Broad-spectrum penicillin use did not increase significantly in DID and decreased significantly in PID. For all but one subgroup, country-specific deviations moved in the same direction whether measured in DID or PID. The correlations are not perfect. The DDD per package increased significantly over time for all but one subgroup.

Conclusions: Outpatient antibiotic use in Europe shows contrasting trends, depending on whether DID or PID is used as the measure. The increase of the DDD per package corroborates the recommendation to adopt PID to monitor outpatient antibiotic use in Europe.

Keywords: antibiotic consumption, ambulatory care, dose change, non-linear mixed model

Introduction

A link between antibiotic use and antimicrobial resistance has been demonstrated both in ecological studies and in randomized controlled trials in individual patients.^{1–3} Resistance is a major public health problem because it is related to treatment failure, prolonged hospitalization, increased costs of care and increased mortality.⁴ One part of the solution is to gather trustworthy information on the consumption of antibiotics.⁵

In Europe, the European Surveillance of Antimicrobial Consumption (ESAC) project—currently ESAC-Net, coordinated by the European Centre for Disease Prevention and Control (ECDC; www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net)—consists of a network of surveillance systems that enables the collection of data on European antibiotic consumption. The ESAC

project 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 (between 1997 and 2009), while showing a significant seasonal fluctuation with a high winter peak, which decreased over time.⁶ More detailed analyses of major antibiotic subgroups have been described in separate papers.^{7–12}

The ESAC project group also proposed an additional outcome measure, i.e. the number of packages per 1000 inhabitants per day (PID), because expressing outpatient antibiotic use in DID is not always optimal.⁶ This is the case when the number of DDD per package (or prescription or treatment or person) differs substantially between the elements of a comparison, e.g. when comparing between different countries or within a country over time. More recently, a comparison of different measures showed that

the number of packages is indeed a good proxy for the number of treatments, and a more appropriate measure than the number of DDD when assessing outpatient antibiotic use over time, especially when the number of DDD per package differs over time.¹³ Therefore, in this paper we aim to complement the analyses of the linear trend and seasonal fluctuation in European outpatient antibiotic use expressed in DID by analyses of data in PID, to assess the agreement between both measures and to study changes in DDD per package over time.

Methods

Data

Data on outpatient antibiotic use expressed in DID and PID between 2000 and 2007 were available within ESAC through IMS Health (www.imshealth.com). This private company provided comparable quarterly data on national sales of antibiotics from 2000 until 2007 for 31 countries, encompassing 26 EU member states (all but Cyprus and Malta), 1 candidate country (Turkey), 2 founding members of the European Free Trade Association (Norway and Switzerland) and 2 other countries (Israel and the Russian Federation), gathered from different sources including manufacturers, wholesalers, pharmacies, prescribing doctors and hospitals. The data were aggregated at the level of the active substance in accordance with the Anatomical Therapeutic Chemical (ATC) classification and the DDD measurement unit (WHO version 2011).¹⁴

For most countries, information was given on ambulatory care, while for some only information on total care was available (Denmark, the Netherlands, the Russian Federation, Sweden and Slovenia). Data on total care were also used as ambulatory care represents over 90% of total care. In this article, information on consumption of antibacterials for systemic use (J01) was used. This group is further divided into eight pharmacological subgroups: 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 and chemical substances. For this article, data on all pharmacological subgroups and two chemical subgroups were used, the latter being penicillins with extended spectrum (J01CA) and combinations of penicillins (J01CR). Consumption data were expressed in DID and PID. The DDD per package was calculated by dividing DID by PID per quarter for each country at the substance level.

Analysis of DID and PID separately

Because measurements were taken quarterly for each country, the data are correlated and hence mixed-effects models are an adequate tool to study the trends in the data. Mixed-effects models describe an outcome in terms of fixed effects, which here reflect the average trend in Europe based on the countries in the sample, and random effects, which here represent the deviation of individual countries from this average trend.^{15,16} The seasonal fluctuation in the data can be modelled using a non-linear mixed model.¹⁶

As a starting model, the non-linear mixed model previously applied in the analysis of the ESAC data was used.¹⁷ In this model, the intercept reflects the antibiotic consumption at baseline (first quarter of 2000) and the slope reflects the change in antibiotic consumption over time (per quarter); the amplitude for the sine function is split into two parts, with a time-independent part reflecting the amplitude of the upward winter and downward summer peak and a time-dependent part reflecting the change of the amplitude over time. From this starting model the final model was obtained by means of maximum likelihood. A more elaborate description of this procedure and the motivation for the use of maximum likelihood rather than restricted maximum likelihood can be found in the

Technical Notes (available as Supplementary data at JAC Online). The overall fit of the model was evaluated by plotting the observed and predicted values over time for all countries. To present a clear illustrative figure, the fit was plotted for the European average as well as for two neighbouring member states with contrasting outpatient antibiotic use (Belgium and the Netherlands).

Analysis of DID and PID jointly

To see whether the models for DID and PID were in agreement, a joint non-linear mixed model was constructed. The correlations between the country-specific effects in DID and PID were estimated and 95% CI were constructed.

Analysis of the change in DDD per package

As before, a mixed-effects model was used to study the trend in DDD per package over time. As both DID and PID measure the same seasonal fluctuation, dividing DID by PID cancelled out most of the seasonality. For this reason, a linear mixed model was sufficient for modelling the DDD per package data.

Results

A detailed description of the results for the group of antibacterials for systemic use (J01) will be given. Results for other major subgroups will be shown in tables, but their full description can be consulted elsewhere.¹⁸

Analysis of DID and PID separately

Analysis of DID

Antibacterial consumption ranged from 3.24 to 48.06 DID. In DID there was a significant increase in total antibiotic consumption over time in Europe, with a significant seasonal fluctuation that increased significantly over time (Table 1). The model seemed to fit the data well, given that both the average and country-specific lines approximated the observed data (Figure 1). Furthermore, the longitudinal analysis showed a high positive correlation between the volume of use and the seasonal fluctuation (see the Technical Notes). This means that, in terms of absolute amounts in DID, high-consumption countries at baseline tended to have higher seasonal fluctuation and vice versa.

Analysis of PID

Antibacterial consumption varied from 1.024 to 9.899 PID. In PID there was a non-significant decrease in total antibiotic consumption in Europe over time, with a significant seasonal fluctuation that did not significantly change over time (Table 1). The model appears to fit the data well (Figure 2). Also in the PID model, the longitudinal analysis showed a high positive correlation between the volume of use and the seasonal fluctuation (see the Technical Notes), meaning that in terms of absolute amounts in PID, high-consumption countries at baseline tended to have higher seasonal fluctuation and vice versa.

Parameter estimates in DID and PID separately are also shown in Table 1 for the major antibiotic subgroups. Both in DID and in PID, the use and seasonal fluctuation of combinations of

Table 1. Estimated linear trend and seasonal variation in outpatient antibiotic use in Europe expressed in DID and PID based on available quarterly data for 2000–07

ATC classification	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*

J01, antibacterials for systemic use; J01C, penicillins; J01CA, penicillins with extended spectrum; J01CR, combinations of penicillins; J01F, macrolides; J01M, quinolones; J01D, cephalosporins; J01A, tetracyclines; J01E, sulphonamides; J01X, urinary antiseptics; J01BGR, other antibiotics [concatenation of amphenicols (J01B), aminoglycosides (J01G) and combinations of antibacterials (J01R)].

β_0 (fixed intercept), predicted average outpatient use in the first quarter of 2000; β_1 (fixed slope), predicted average increase (if positive)/decrease (if negative) in use per quarter; β_2 (fixed seasonal variation), predicted average amplitude of the upward winter and downward summer peak in use; β_3 (fixed damping effect), predicted average increase (if positive)/decrease (if negative) of the amplitude of the upward winter and downward summer peak in use per quarter.

* $P < 0.05$.

** $P < 0.0001$.

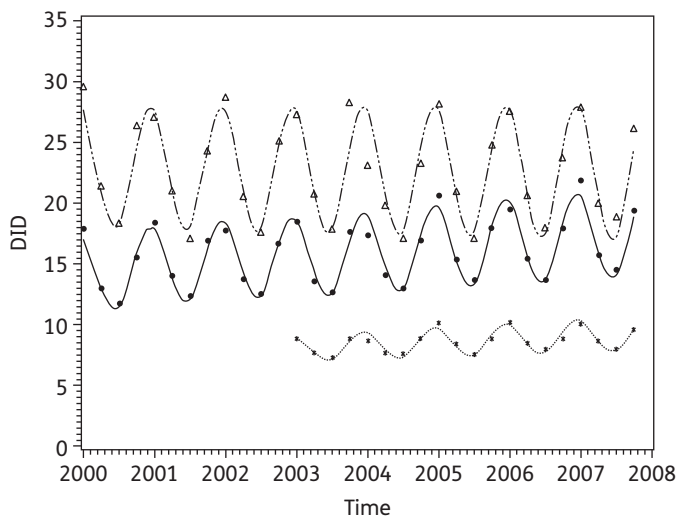


Figure 1. Total outpatient antibiotic use expressed in DID. Predicted average (solid line), predicted country-specific [Belgium (dashed line) and the Netherlands (dotted line)] and observed (circles, triangles and stars, respectively).

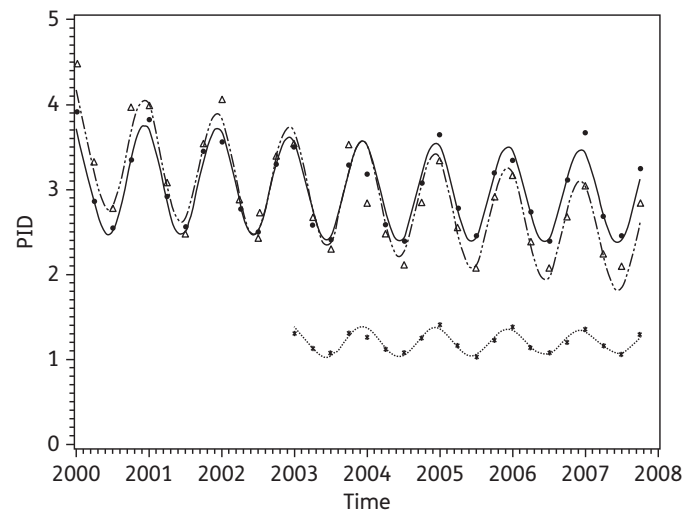


Figure 2. Total outpatient antibiotic use expressed in PID. Predicted average (solid line), predicted country-specific [Belgium (dotted line) and the Netherlands (dashed line)] and observed (circles, triangles and stars, respectively).

penicillins (J01CR) and quinolones (J01M) increased in Europe, and that of tetracyclines (J01A) and trimethoprim (J01E) decreased significantly over time. Penicillin (J01C) use and seasonal fluctuation significantly increased in DID and not in PID. Broad-spectrum penicillin (J01CA) use did not increase significantly in

DID and decreased significantly in PID, as did its seasonal fluctuation. For cephalosporins (J01D), no significant changes over time were observed. For all but one subgroup (J01X) the seasonal fluctuation with an upward winter peak was significant whether expressing the consumption in DID or PID.

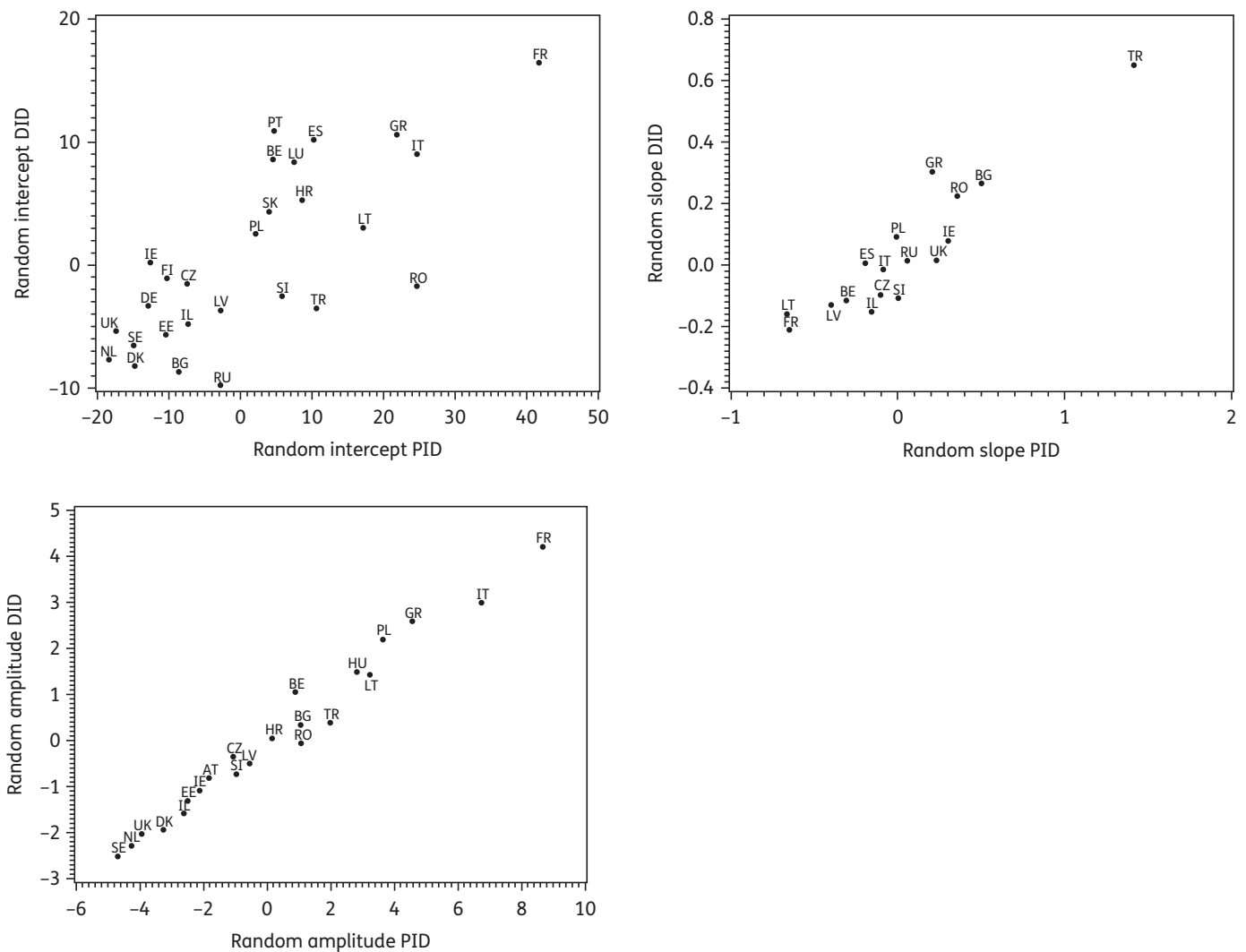


Figure 3. Correlation between matching random effects from the joint model of total outpatient antibiotic use in DID and PID: intercepts (top left), slopes (top right) and amplitudes (bottom). Note: that the intercepts combination for CH is close to UK, for NO it is close to NL, for AT to DE, and for HU to PL; that the slopes combination for HR is close to BE, for EE, HU and PT it is close to CZ, for FI to SI, for SK to IT, for NL, CH, DE, SE, NO and AT to RU, and for LU to ES; and that the amplitudes combination for NO is close to NL, for RU it is close to DK, for DE, CH and FI to UK, for PT and ES to BE, and for SK and LU to PL. These countries are omitted from the figures for clarity. Random intercept: predicted country-specific antibiotic use at baseline (first quarter of 2000). Slope: predicted country-specific change in antibiotic use over time. Amplitude: predicted country-specific amplitude of the upward winter peaks and downward summer troughs in antibiotic use. AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IL, Israel; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; NL, Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RU, Russian Federation; SE, Sweden; SI, Slovenia; SK, Slovakia; TR, Turkey; UK, United Kingdom.

Joint analysis of DID and PID

A joint model was constructed based on the final models for DID and PID. The estimated correlations between matching random effects in DID and PID were 0.77 (95% CI: 0.63, 0.92; between random intercepts), 0.86 (95% CI: 0.75, 0.97; between random slopes) and 0.96 (95% CI: 0.89, 1.02; between random amplitudes; Figure 3). All correlations were high and positive, indicating that there is an agreement in the random effects. This means that when the random term in DID is above average it will generally be above average in PID as well, and vice versa. Only the correlation between the random amplitudes seemed perfect.

For the major antibiotic subgroups the same procedure was followed, which also resulted in a joint model for DID and PID and correlations between matching random effects. Both the correlation between random intercepts in DID and PID and the correlation between random slopes in DID and PID were positive for all subgroups, but none seemed perfect. The correlation between the amplitudes in DID and PID was positive for all but one subgroup (other antibiotics, concatenation of J01B, J01G and J01R). It seemed perfect for combinations of penicillins [J01CR; 0.90 (95% CI: 0.95, 1.03)], macrolides [J01F; 0.99 (95% CI: 0.97, 1.02)] and the subgroup of other antibiotics [concatenation of J01B, J01G and J01R; -0.67 (95% CI: -1.20, -0.13)].

Table 2. Estimated linear trend in the number of DDD per package for outpatient antibiotic use in Europe based on available quarterly data for 2000–07

ATC classification	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)*

J01, antibacterials for systemic use; J01C, penicillins; J01CA, penicillins with extended spectrum; J01CR, combinations of penicillins; J01F, macrolides; J01M, quinolones; J01D, cephalosporins; J01A, tetracyclines; J01E, sulphonamides; J01X, urinary antiseptics; J01BGR, other antibiotics [concatenation of amphenicols (J01B), aminoglycosides (J01G) and combinations of antibacterials (J01R)].

β_0 (intercept), predicted average (standard errors) DDD per package in the first quarter of 2000; β_1 (slope), predicted average (standard errors) increase (if positive)/decrease (if negative) in DDD per package per quarter. * $P < 0.05$.

** $P < 0.0001$.

Analysis of the change in DDD per package

Parameter estimates for the fixed effects (Europe) are given in Table 2. The average DDD per package in 2000 varied between 1 and 9. There was an increase in DDD per package over time, with the size of the quarterly increase ranging between 0.01 and 0.08 DDD. This translates to a yearly increase of 0.04–0.31 DDD per package. This increase was significant for total antibiotic consumption and in all subgroups except for the quinolones (J01M). The average DDD per package in 2000 and the change in DDD per package over time differed substantially between countries, except for the urinary antiseptics (J01X).

Discussion

Complementing analyses of the trend of outpatient antibiotic use for 31 countries expressed in DID by analyses of PID data shows that using different measures can lead to contradictory conclusions. Total outpatient antibiotic and penicillin use in Europe, as well as their seasonal fluctuation, significantly increased when expressed in DID, but not in PID.

A strong correlation between measurements for DDD and packages at one timepoint (1997) has previously been described by Monnet *et al.*¹⁹ This finding was corroborated here, as for total consumption and consumption of all subgroups, strong correlations between the random intercepts were found. The correlations did not seem perfect, however, implying that when the average antibiotic consumption expressed in DID and PID is known, country-specific information on either measure is not sufficient

to obtain information on the other measure. In addition, this study also found strong correlations between the random changes over time in DID and PID and between the random amplitudes in DID and PID, only the latter seeming perfect for total antibiotic consumption and consumption of combinations of penicillins, macrolides and other antibiotics.

To our knowledge, this is the first longitudinal data analysis of outpatient antibiotic use data in PID. Moreover, we were able to complement analyses of DID data with analyses of PID data from the same source, i.e. IMS Health. The results of the separate DID analyses are comparable to those of the ESAC data, cross-validating both data sources. This is also the first account of the evolution of DDD per package for outpatient antibiotic use in Europe.

Except for the quinolones, the DDD per package increased significantly over time. As DDD per package can change over time, so can the number of packages per treatment in some countries. Therefore, improved fit of pack sizes to treatment regimens might partly explain trends in PID. However, analysis of Belgian national data, also showing increasing DDD per package,⁶ has revealed that this impact is limited and does not alter the conclusion that outpatient antibiotic use in Belgium has been decreasing.¹³

As suggested by ESAC and already adopted by ESAC-Net, ECDC continues collecting both DID and PID data for the surveillance of outpatient antibiotic use in Europe.²⁰ The results of the longitudinal data analyses presented here, e.g. the contrasting trends for Europe and Belgium in DID and PID, respectively, confirm the relevance of adopting packages as an additional outcome to better understand linear trends and seasonal fluctuations in outpatient antibiotic use in Europe, especially in the case of increasing DDD per package and when assessing interventions to reduce antibiotic prescribing.

To study the change in antibiotic consumption over time, it is recommended to collect information on both DID and PID or to be cautious when interpreting results based on DID alone.

Further study could investigate whether the description of outpatient antibiotic use can be improved by including change points in the model, e.g. to assess the impact of the European Antibiotic Awareness Day^{21,22} and what outcome measure correlates best with antimicrobial resistance.

Conclusions

Outpatient antibiotic use in Europe shows contrasting trends depending on whether the internationally accepted DID is used or PID, which is considered a good proxy for treatments. The increase of the DDD per package corroborates the recommendation to adopt PID to survey outpatient antibiotic use in Europe.

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Transparency declarations

None to declare.

Supplementary data

The Technical Notes are available as Supplementary data at JAC Online (<http://jac.oxfordjournal.org>).

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