

## Exploring the association between resistance and outpatient antibiotic use expressed as DDDs or packages

Robin Bruyndonckx<sup>1\*</sup>, Niel Hens<sup>1,2</sup>, Marc Aerts<sup>1</sup>, Herman Goossens<sup>3</sup>, José Cortiñas Abrahantes<sup>4</sup> and Samuel Coenen<sup>3,5</sup>

<sup>1</sup>Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-BIOSTAT), Hasselt University, Hasselt, Belgium; <sup>2</sup>Centre for Health Economic Research and Modelling Infectious Diseases (CHERMID), Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium; <sup>3</sup>Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium; <sup>4</sup>European Food Safety Authority, Parma, Italy; <sup>5</sup>Centre for General Practice, Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium

\*Corresponding author. Tel: +32-11-268246; Fax: +32-11-268299; E-mail: robin.bruyndonckx@uhasselt.be

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**Objectives:** The objective of this study was to explore the association between resistance and outpatient antibiotic use, expressed as either DDDs per 1000 inhabitants per day (DID) or packages per 1000 inhabitants per day (PID).

**Methods:** IMS Health data on outpatient penicillin and cephalosporin ( $\beta$ -lactam) and tetracycline, macrolide, lincosamide and streptogramin (TMLS) use, aggregated at the level of the active substance (WHO version 2011) expressed as DID and PID (2000–07) were linked to European Antimicrobial Resistance Surveillance System (EARSS) data on proportions of penicillin-non-susceptible *Streptococcus pneumoniae* (PNSP) and erythromycin-non-susceptible *S. pneumoniae* (ENSP) (2000–09). Combined data for 27 European countries were analysed with a generalized linear mixed model. Model fit for use in DID, PID or both and 0, 1 or 2 year time lags between use and resistance was assessed and predictions of resistance were made for decreasing use expressed as DID, PID or both.

**Results:** When exploring the association between  $\beta$ -lactam use and PNSP, the best model fit was obtained for use in PID without time lag. For the association between TMLS use and ENSP, the best model fit was obtained for use in both PID and DID with a 1 year time lag. PNSP and ENSP are predicted to decrease when use decreases in PID, but not when use decreases in DID.

**Conclusions:** Associations between outpatient antibiotic use and resistance and predictions of resistance were inconsistent whether expressing antibiotic use as DID or PID. We recommend that data on antibiotic use be expressed as PID and that time lags between use and resistance be considered when exploring these associations.

**Keywords:** antibiotic resistance, generalized linear mixed model, predictions of resistance

### Introduction

Antibiotic resistance is a major public health problem because it is related to treatment failure, increased mortality and increased costs of care.<sup>1</sup> One of the main drivers of resistance is antibiotic use.<sup>2–4</sup> Total outpatient antibiotic use can be expressed as the number of DDDs per 1000 inhabitants per day (DID) or the number of packages per 1000 inhabitants per day (PID).<sup>5</sup> When monitoring outpatient antibiotic use in Europe, these two measurement units should be presented simultaneously as it has been demonstrated that outpatient antibiotic use in Europe shows contrasting trends depending on whether DID or PID is

used.<sup>6</sup> This is explained by changes over time in the number of DDDs per package.<sup>6,7</sup>

To date, it is not clear what measurement unit should be used when analysing antibiotic resistance in Europe. DID is most often used, but a study in Belgium that assessed the association between proportions of erythromycin-resistant *Streptococcus pyogenes* and the use of tetracycline, macrolide, lincosamide and streptogramin (TMLS) found that expressing use as PID and including a time lag between use and resistance provided the best-fitting model.<sup>8</sup> Therefore, in this study we set out to explore the association between resistance and antibiotic use, expressed as either DID or PID, using outpatient use data from 27 European countries.

## Methods

### Data

Data on outpatient antibiotic use expressed as DID and PID between 2000 and 2007 were available within the European Surveillance of Antimicrobial Consumption (ESAC) project, currently ESAC-Net, coordinated by ECDC ([www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net](http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net)) through IMS Health ([www.imshealth.com](http://www.imshealth.com)), as described earlier.<sup>6</sup> 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).<sup>9</sup>  $\beta$ -Lactam (penicillins and cephalosporins) and TMLS use was expressed as DID and PID. Data on proportions of penicillin-non-susceptible *Streptococcus pneumoniae* (PNSP) and erythromycin-non-susceptible *S. pneumoniae* isolates (ENSP) between 2000 and 2009 were available through the European Antimicrobial Resistance Surveillance System (EARSS) project, currently EARS-Net, also coordinated by ECDC (<http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx>). Three datasets were created by combining use data with resistance data for the same year (time lag=0), resistance data for 1 year later (time lag=1) and resistance data for 2 years later (time lag=2). Each combined dataset contained data from 27 countries, encompassing 25 EU member states (all but Cyprus, Malta and Greece) and 2 founding members of the European Free Trade Association (Norway and Switzerland).

### Analysis of the association between antibiotic use and resistance

Because country-specific information on resistance is gathered annually, the data are correlated and hence a mixed-effects model is a suitable tool to study the trends in the data. A mixed-effects model consists of a fixed component, which represents the average time trend, and a random component, which represents the country-specific deviation from this average trend.<sup>10,11</sup> As resistance is a binomial response, a generalized linear mixed model employing a logit link was used.<sup>10</sup> This model can be presented as follows:

$$\log\left(\frac{\pi_{ij}}{1 - \pi_{ij}}\right) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}) t_{ij} + \beta_2 X_{ij}^{DID} + \beta_3 X_{ij}^{PID}$$

where  $\pi_{ij}$  is the proportion of PNSP or ENSP in country  $i$  at timepoint  $t_{ij}$  ( $j=1, \dots, n_i$ ),  $n_i$  is the number of observations from the  $i$ th country,  $t_{ij}=1$  corresponds to the start of the study (year 2000),  $\beta_0$  is the global intercept,  $\beta_1$  is the global slope,  $\beta_2$  and  $\beta_3$  represent the effects of DID and PID in country  $i$  at timepoint  $t_{ij}$  and  $\mathbf{b}_i = (b_{0i}, b_{1i})$  is a vector of country-specific random effects (for intercept and slope) for which we assume  $\mathbf{b}_i \sim (\mathbf{0}, \mathbf{D})$ . The matrix  $\mathbf{D}$  is an unstructured covariance matrix with  $d_{11}$  the variance of the random intercept  $b_{0i}$ ,  $d_{22}$  the variance of the random slope  $b_{1i}$ , and  $d_{12}$  the covariance between the random intercept and the random slope.

We assessed the need for inclusion of a time lag by comparing goodness-of-fit statistics for the model fitted to the common part of the three datasets (time lag=0, 1 or 2). The fit statistic that was used was the Akaike information criterion (AIC).<sup>12</sup>

The same statistics were used in comparing a model containing both DID and PID, only DID and only PID.

### Predictions of antibiotic resistance

Using the full model, we predicted the proportion of PNSP and ENSP if  $\beta$ -lactam or TMLS use expressed as DID, PID or both were to be 5% lower than the value reported for the last observed year (2007 for time lag=0, 2008 for time lag=1 and 2009 for time lag=2).

## Results

### $\beta$ -Lactam use and PNSP

When exploring the association between PNSP and  $\beta$ -lactam use, the best model fit was found for a model including  $\beta$ -lactam use in PID without time lag. A full mathematical description of this model is available in the technical note (available as Supplementary data at JAC Online). From this model, we conclude that the odds of PNSP increased significantly with increasing  $\beta$ -lactam use expressed as PID [OR (95% CI) 1.96 (1.57–2.44)] and did not change significantly over time [1.00 (0.97–1.03)].

### TMLS use and ENSP

When exploring the association between ENSP and TMLS use, the best model fit was found for a model including TMLS use in PID and DID with a 1 year time lag. A full mathematical description of this model is available in the technical note. From this model, we conclude that the odds of ENSP increased significantly with increasing TMLS use in PID [3.68 (1.27–10.72)] and with decreasing TMLS use in DID [0.78 (0.65–0.93)], while it did not change significantly over time [1.01 (0.97–1.04)].

### Predictions of antibiotic resistance

The average predicted proportion of isolates that were PNSP associated with  $\beta$ -lactam use was based on all countries that had resistance data in 2007 (all but Slovakia; Figure 1, top). The average predicted proportion of ENSP after TMLS use was based on all countries that had resistance data in 2008 (all but Slovakia and Switzerland; Figure 1, bottom).

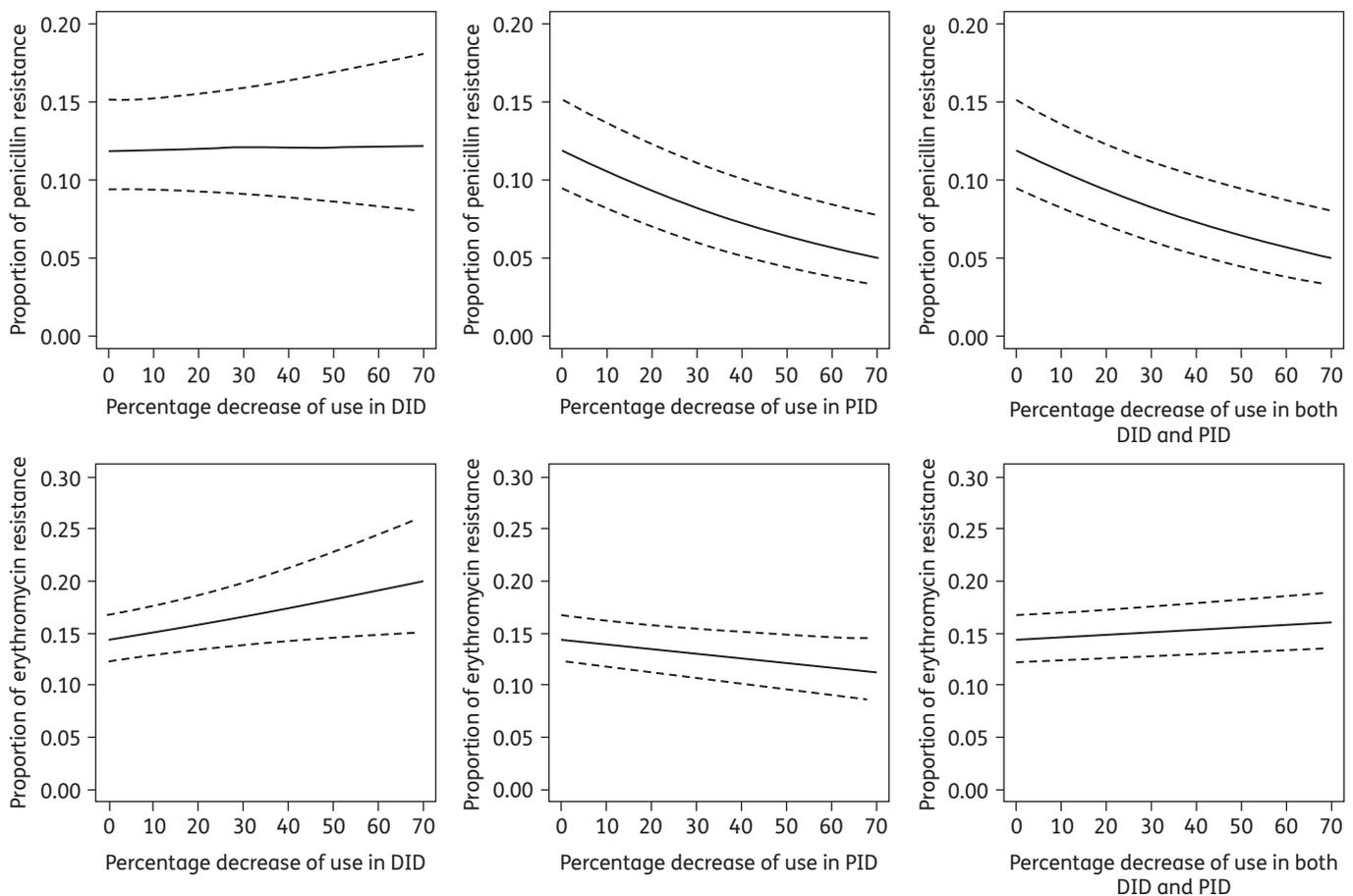
From Figure 1, it can be seen that PNSP proportions are predicted to decrease substantially if  $\beta$ -lactam use expressed as PID alone or as both PID and DID decreases, but are predicted to remain stable with a decrease in  $\beta$ -lactam use expressed as DID.

ENSP proportions are predicted to decrease if TMLS use expressed as PID decreases, but are predicted to increase with a decrease in TMLS use expressed as DID alone or both DID and PID.

## Discussion

Exploring the association between outpatient antibiotic use and resistance in Europe revealed that use data expressed as DID alone do not provide the best-fitting models. To assess ENSP proportions, TMLS use expressed both as DID and PID needs to be considered, while for PNSP proportions,  $\beta$ -lactam use expressed as PID is sufficient. Also, predictions of resistance after a decrease in use of TMLS were driven by both DID and PID, while predictions after a decreased  $\beta$ -lactam use were driven by PID alone.

These findings support the recommendation of adopting packages as an additional outcome to better understand outpatient antibiotic use,<sup>6</sup> as well as its relation to resistance. In addition, the differences in time lag between  $\beta$ -lactam use and PNSP proportions and TMLS use and ENSP proportions correspond to the differences in persistence of resistance, which is much longer after exposure to TMLS (clarithromycin or azithromycin)<sup>3</sup> than after exposure to  $\beta$ -lactams (ampicillin).<sup>13</sup>



**Figure 1.** Average predicted proportion of non-susceptible *S. pneumoniae* isolates if outpatient antibiotic use had been lower than reported in 2007 (for  $\beta$ -lactam; top) or 2008 (for TMLS; bottom) due to a decrease in use in DID (left), PID (middle) or both (right).

In Europe, where trends of outpatient antibiotic use over time are contradictory<sup>6,7</sup> and countries rank differently when their use is expressed as DID or PID,<sup>5</sup> the number of packages on average seems to be a better proxy for the number of antibiotic treatments (and the number of individuals treated) than the number of DDDs. Consequently, taking into account use data in PID will provide relevant additional information to comprehend the relationship between outpatient antibiotic use and resistance.

The model for PNSP predicts that PNSP decreases with decreasing  $\beta$ -lactam use expressed as PID (alone or together with a decrease in DID), while it is not altered with decreasing  $\beta$ -lactam use expressed as DID alone. A possible explanation could be that if  $\beta$ -lactam use decreases both in PID and DID, this will probably reflect a decrease in the number of patients exposed to a consistent (and appropriate) antibiotic dose. However, if  $\beta$ -lactam use decreases only in PID (use in DID remaining the same), this would suggest that fewer patients are exposed to antibiotics, but that these patients are receiving a higher dose per treatment (increased grams per pack). In contrast, if  $\beta$ -lactam use decreases only in DID (use in PID remaining the same), this is likely to be due to a decrease in dose per treatment (decreased grams per pack), but the lower dose may remain appropriate to prevent emergence of resistance.

The model for ENSP predicts that ENSP only decreases with decreasing TMLS use expressed as PID alone, while it increases with decreasing TMLS use expressed as DID (alone or together with a decrease in PID). A possible explanation could be that fewer patients are exposed to a higher dose of TMLS treatment when TMLS use is lower only in PID and to the same (inappropriate) dose when it is lower both in PID and DID, while the same number of patients are exposed to lower (even more inappropriate) doses when TMLS use is lower only in DID.

### Conclusions

Associations between outpatient antibiotic use and resistance and predictions of resistance were inconsistent whether expressing antibiotic use as DID or PID, and model fit depended on time lags between use and resistance. We recommend that investigators consider time lags and use data expressed as PID when exploring these associations.

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## Transparency declarations

None to declare.

## Supplementary data

The technical note and raw data are available as Supplementary data at JAC Online (<http://jac.oxfordjournal.org>).

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