Outpatient antibiotic use in the four administrations of the UK: cross-sectional and longitudinal analysis

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Objectives: We compared community antibiotic use in the four administrations of the UK with that in other European countries.

Patients and methods: A cross-sectional analysis of 24 European countries and UK administrations in 2005 with longitudinal analysis of data from Belgium and UK from 1997 was performed. Antibiotic use was measured as defined daily doses per 1000 inhabitants per day (DID) or as prescriptions or packages per 1000 inhabitants per day (PID) with aggregate data from patients who received antibiotics in the primary care or outpatient setting.

Results: In 2005, there were marked differences in antibiotic prescriptions between the four UK administrations, for example, in descending order of DIDs, Northern Ireland and England ranked 8th and 24th, respectively, out of the 28 countries. DIDs for Northern Ireland were 37% greater than that for England. Longitudinal analysis showed that differences were present before devolution in 1999. Increase in the age of exemption from prescription charges in Wales in 2002 was not associated with significant change in use in comparison with the other UK countries. There were discrepancies between changes in DID and changes in PID, particularly in Belgium. This suggests that some changes in DID were due to changes in dosing or duration of the treatment rather than in the number of people treated and shows the importance of using both measures.

Conclusions: The European Surveillance of Antimicrobial Consumption project has for the first time made data about antibiotic use in the four UK administrations publicly available. This reveals important practice variations that should stimulate research to explain differences and assess their consequences.

Keywords: pharmacoepidemiology, practice variation, primary care, DDDs (defined daily doses)

Introduction

Antibiotic resistance is a major European and global public health problem and international efforts are needed to counteract the emergence of resistance. Antibiotic use is increasingly recognized as the main driver for resistance and differential selection pressure of antibiotic agents may be responsible for some of the observed differences.1 European Surveillance of Antimicrobial Consumption (ESAC) (www.esac.ua.ac.be) is an international network of surveillance systems. The aim is to collect and make publicly available comparable and reliable data on antibiotic use in Europe in order to inform efforts to improve prescribing and reduce antimicrobial resistance.

The United Kingdom of Great Britain and Northern Ireland (UK) is composed of four administrations: England, Northern Ireland, Scotland and Wales. Since 1999, Health Administration has been devolved in Scotland to its parliament and in Northern Ireland and Wales to their national assemblies.2,3 Initial predictions were that devolution would have little impact on health policy but that opinion has changed radically, prompting the British Medical Association to write a policy paper explaining the key differences with a commitment to annual review of the
impact of the different political contexts in which their members work.5

Devolution has created a natural experiment in which systematic changes in healthcare policy have been made in four regions that remain united within an overall system and culture that retains more similarities than differences. The Editor of the BMJ recently stated ‘We could all do more to celebrate these differences and learn from them’.6 Discussion about the impact of devolution on prescribing has focused on the differences in advice on use of new treatments.5 A negative consequence of devolution is that there is no longer a common source for information across the four administrations of the UK.6 The ESAC project provided us with an opportunity to investigate the availability of data about antibiotic use in the UK and compare changes over time in the context of changes in other European nations. Our second objective was to analyse the impact of two changes in policy: the devolution of the Health Administration during 1999 and the raising of the exemption age for prescription charges in Wales in 2001.7

Methods

Quarterly data on outpatient antibiotic use for the period 1997–2005 were collected from the Prescription Pricing Authority in England, the Information Services Division of National Services in Scotland, Health Solutions in Wales and the Central Services Agency in Northern Ireland. The data from the Republic of Ireland were obtained from IMS (Intercontinental Medical Statistics, http://imshealth.com/ims/portal/pages/homeFlash/europe/0,2768,6025,00.html). The drugs were classified according to the ATC coding system with the 2006 version. Quantities of antibiotics were expressed in defined daily doses (DDDs) per 1000 inhabitants per day (DID)8 or in prescriptions per 1000 inhabitants per day (PID).

Data for 2005 were compared with data from 24 other European countries. We did not include data from Greece or Italy because we did not have reliable data for 2005.

In the longitudinal analysis, we compared data from 1997 to 2005 from the four administrations of the UK and from Belgium. We included Belgium as a reference country from Europe because data were available about packages as well as DDDs. Packages are the nearest equivalent to scripts (prescriptions) because in most instances one package dispensed indicates one patient treated with antibiotics. The methods of data collection and processing for the ESAC project have been described in detail and are available on the ESAC web site (http://www.esac.ua.ac.be/).9 Prior to the interpretation of the data, the validity of the data provided was evaluated by means of a checklist including possible sources of bias: population coverage, drug coverage and ambulatory/hospital care mix. A complete description of the data providers, details of the methodology used and its associated problems and in-depth discussions of the validity of the collected data have been published in a separate article.9

The use of the ATC/DDD classification is described in detail on the ESAC web site (http://www.esac.ua.ac.be/).9 Prior to the interpretation of the data, the validity of the data provided was evaluated by means of a checklist including possible sources of bias: population coverage, drug coverage and ambulatory/hospital care mix. A complete description of the data providers, details of the methodology used and its associated problems and in-depth discussions of the validity of the collected data have been published in a separate article.9

Information about UK population sizes was obtained from the Office of National Statistics.10 Ethics approval was not required for this study as we used aggregate, national data.

Statistical analysis

We used a segmented regression design11–13 to perform interrupted time-series analysis of total antibiotic use before and after two changes in national policies in 2000 and 2002. In 2000, the health administrations of Northern Ireland, Scotland and Wales were devolved, and in 2002, the Welsh National Assembly introduced an exemption from prescription charging for all people aged from 16 to 25. First we checked whether the time series were stationary or had underlying linear or non-linear time trends using augmented Dickey–Fuller (ADF) and Phillips–Perron tests.14 We then applied Durbin–Watson and Breusch–Godfrey statistics to test for the presence of autocorrelation. We used two tests for these analyses as each test has limitations. The data were quarterly so we used the seasonal decomposition method to minimize the effect of seasonal variation.11–13 We considered the change in trend and the trend without the intervention. STATA version 9 was used for statistical analysis.

Results

Data were available from 1997 to 2005 for Belgium, England and Scotland, whereas data were only available from 1998 for Northern Ireland and from 1999 for Wales. The mid-2003 population (in thousands) for the UK was 59 554. The population for each UK administration was: England 49 856, Northern Ireland 1703, Wales 2938 and Scotland 5057. Data for the whole UK are therefore dominated by England, which has the lowest use of the four UK administrations (Figure 1). Ranking the top consumer (France) as 1st, the rankings for the UK administrations were Northern Ireland 8th, Scotland 16th, Wales 18th and England 24th out of 28 European Countries. Total antibiotic use was 20.4 DID in Northern Ireland, which is 37% higher than that in England (14.9 DID). Total use and the proportions contributed by each class of antibiotics were virtually identical in Northern Ireland and the Republic of Ireland (Figure 1). Crude differences in the use of different classes of antibiotics can be seen in the bar chart (for example, in comparison with England, Wales uses more cephalosporins). These differences are more clearly displayed in a radar chart (Figure 2).

Longitudinal charts of antibiotic use from 1997 show considerable seasonal variation in all countries (Figure 3 and 4). The rank order of prescribing for the four UK administrations has been the same since 1997, so that differences between administrations in 2005 are the result of pre-devolution differences that have persisted after devolution (Figures 3 and 4). The chart of prescriptions and packages (Figure 4) shows that differences between all four UK administrations and Belgium were much less marked for prescriptions (Figure 4) than for DID (Figure 3).

Interrupted time-series analysis

Time-series analysis from 1997 to 2005 showed that our data were stationary with no consistent underlying linear or non-linear time trends (Phillips–Peron and ADF tests) and no serial autocorrelation (Durbin–Watson and Breusch–Godfrey tests). Linear regression analysis over the whole time period showed significant reduction in both DID and PID in Belgium and England (Table 1). In Scotland and Wales, there was a significant reduction in PID but either no change in DID (Scotland) or a significant increase (Wales). There was no significant change in DID for Northern Ireland and no data were available for PID (Table 1).
Interrupted time-series analysis before and after 2000 (the year of devolution of UK administrations) showed significant increases in DID for England, Northern Ireland and Scotland as well as significant increases in PID for England and Scotland (Table 1). No PID data were available before 2002 for Northern Ireland. The increase in DID in Northern Ireland was 20% greater than in England or Scotland (0.45 versus 0.36 and 0.38). In contrast, there were inconsistent results for DID versus PID for Belgium and Wales. In Belgium, there was no significant change in DID after 2000 but a significant decrease in PID.

In Wales, there was a significant decrease in DID but a non-significant increase in PID (Table 1).

Interrupted time-series analysis before and after 2002 (the year of change in the age of prescription exemption in Wales) showed non-significant reduction in DID and non-significant increase in PID for Wales (Table 1). In contrast, for England, Northern Ireland and Scotland, there were significant increases in DID with significant increases in PID for England and Scotland as well. There were no significant changes in DID or PID for Belgium.

We repeated these analyses with data from 1999 to 2005 in order to assess the impact of a shorter time series in Wales. We obtained essentially similar results for the four UK administrations in terms of both direction and significance of change in trend after both interruptions [full data are available in the statistical report which is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].

Figure 1. Comparison of annual use of antibiotics in the four administrations of the UK with 24 other European countries in 2005. *MLS, Macrolides, Lincosamides and Streptogramins.

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Discussion

We found striking differences in 2005 between the four administrations of the UK in their total use of antibiotics (Figure 1) and use of different classes (Figure 2). Longitudinal analysis showed that these differences were present pre-devolution (Figure 3).

Comparison of the four UK administrations with other European countries

In its antibiotic prescribing, Northern Ireland is very similar to the Republic of Ireland and different from the other three UK administrations. This was not what we expected to find because in Northern Ireland, as with the rest of the UK, all health
Figure 3. Longitudinal trends and seasonal variation of total outpatient antibiotic use in four UK administrations and Belgium measured in DDD.

Figure 4. Longitudinal trends and seasonal variation of total outpatient antibiotic use in four UK administrations and Belgium measured in PID.
services are free at the point of delivery. In contrast, the Republic of Ireland has a mixed health economy with 70% of the population covered by a fee for service model private practice. The remaining 30% of the population are eligible for free care at the point of delivery, determined by means testing plus all those over 70 years old.\textsuperscript{15} We had assumed that these free care at the point of delivery, determined by means testing practice. The remaining 30% of the population are eligible for the population covered by a fee for service model private services are free at the point of delivery. In contrast, the Republic of Ireland has a mixed health economy with 70% of the population covered by a fee for service model private practice. The remaining 30% of the population are eligible for free care at the point of delivery, determined by means testing plus all those over 70 years old.\textsuperscript{15} We had assumed that these structural differences in health services between the Republic of Ireland and Northern Ireland would lead to differences in antibiotic use, with use in Northern Ireland being similar to the other UK countries. The data from the Republic of Ireland came from national sales of antibiotics and included drugs dispensed from private prescriptions, so we do not believe that we have underestimated the use generated by private practice in the Republic of Ireland. In addition to structural differences in the medical system, cultural differences can be important determinants of different antibiotic use between countries.\textsuperscript{16} A detailed analysis of communities on either side of the Belgian/Dutch border revealed striking differences in their attitudes to illness and antibiotics. In comparison with people from the Belgian community, people from the Dutch community were less likely to want to see a doctor immediately when they were ill, more likely to self-medicate with analgesics or antipyretics, more likely to want to ‘nurse their own illness’ and more likely to believe that the risks of antibiotics outweighed the benefits.\textsuperscript{17} In the Belgian community, there were much greater concerns about lost working hours or pressure at school, with an underlying belief that it was antisocial not to try to speed up recovery because then you ‘make other people do your work’. The authors concluded that the reflex in Belgium was that ‘illness = seeing a doctor = medicines’. This leads to high consumption of antibiotics and would not be inhibited by the organization of Belgian healthcare, characterized by a high degree of freedom for the physician.\textsuperscript{17} Interestingly, a recent multinational study about national culture and antibiotic use found potentially important differences in culture between Belgium and the Netherlands but not between the Republic of Ireland and the UK. Countries were scored on five dimensions with data from Hofstede’s model of cultural dimensions and these differences were correlated with antibiotic use from ESAC and from the Eurobarometer survey. Two cultural dimensions correlated significantly with antibiotic use from both data sources. Power difference refers to the degree of hierarchy in a country; a lower score indicates a preference for deliberation and mutual dependence between subordinates and their chief. Uncertainty avoidance deals with a society’s tolerance for uncertainty and ambiguity. A higher score indicates that people feel uncomfortable in novel, unknown or surprising situations.\textsuperscript{18} For both of these cultural dimensions, there were significant correlations between high scores and greater antibiotic use. Scores for power distance were very similar in the Netherlands, Republic of Ireland and UK (38, 35, 28) and substantially lower than that for Belgium (61). Similarly, the score for uncertainty avoidance was 97 in Belgium compared with 53 in the Netherlands and 35 in the Republic of Ireland and the UK.\textsuperscript{18} These results may explain why antibiotic use is similar in the Republic of Ireland and Northern Ireland but they do not explain why both countries have higher antibiotic use than England. Research into the structural differences between the Republic of Ireland and Northern Ireland has focused on differences in access to doctors\textsuperscript{15} and on the deterrent effect of consultation charges in the Republic of Ireland.\textsuperscript{19} Qualitative research on attitudes to infection and antibiotics in communities from England, Northern Ireland and the Republic of Ireland may help to explain differences in antibiotic use and to inform interventions to reduce unnecessary antibiotic use.

### Changes following devolution of Northern Ireland, Scotland and Wales in 2000 and changes in prescription policy in Wales in 2002

Devolution in 2000 was not associated with differences in antibiotic use in Northern Ireland or Scotland versus England. Use in Northern Ireland and Scotland was higher than in England. The remaining 30% of the population are eligible for free care at the point of delivery, determined by means testing plus all those over 70 years old.\textsuperscript{15} We had assumed that these free care at the point of delivery, determined by means testing practice. The remaining 30% of the population are eligible for the population covered by a fee for service model private services are free at the point of delivery. In contrast, the Republic of Ireland has a mixed health economy with 70% of the population covered by a fee for service model private practice. The remaining 30% of the population are eligible for free care at the point of delivery, determined by means testing plus all those over 70 years old.\textsuperscript{15} We had assumed that these free care at the point of delivery, determined by means testing practice. The remaining 30% of the population are eligible for the population covered by a fee for service model private

### Table 1. Interrupted time-series analysis of change in slope of DDD or prescriptions of antibiotics after two interventions

<table>
<thead>
<tr>
<th>Country</th>
<th>Defined daily doses per 1000 inhabitants per day</th>
<th>Prescriptions per 1000 inhabitants per day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>trend without intervention ($P$ value)</td>
<td>change in trend after the intervention ($P$ value)</td>
</tr>
<tr>
<td>Belgium</td>
<td>$-0.08$ ($&lt; 0.01$)</td>
<td>$-0.11$ (0.3)</td>
</tr>
<tr>
<td>England</td>
<td>$-0.05$ ($&lt; 0.01$)</td>
<td>$+0.36$ (0.01)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>$-0.004$ (0.8)</td>
<td>$+0.45$ (0.01)</td>
</tr>
<tr>
<td>Scotland</td>
<td>$-0.01$ (0.5)</td>
<td>$+0.38$ (0.01)</td>
</tr>
<tr>
<td>Wales</td>
<td>$+0.06$ (&lt;0.01)</td>
<td>$-0.68$ (0.01)</td>
</tr>
<tr>
<td>Belgium</td>
<td>$-0.08$ (&lt;0.01)</td>
<td>$+0.14$ (0.1)</td>
</tr>
<tr>
<td>England</td>
<td>$-0.05$ (&lt;0.01)</td>
<td>$+0.23$ (0.01)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>$-0.004$ (0.8)</td>
<td>$+0.35$ (0.01)</td>
</tr>
<tr>
<td>Scotland</td>
<td>$-0.01$ (0.5)</td>
<td>$+0.21$ (&lt;0.01)</td>
</tr>
<tr>
<td>Wales</td>
<td>$+0.06$ (&lt;0.01)</td>
<td>$-0.11$ (0.07)</td>
</tr>
</tbody>
</table>

Data were from 1997 to 2005. We had no data about prescriptions for Northern Ireland until 2002.
pre-devolution, and post-devolution, there were significant increases in all three countries, most markedly in Northern Ireland. If anything, devolution seems to have exaggerated pre-existing differences in use between these countries. In contrast, antibiotic use has not increased post-devolution in Wales (Table 1). Further research is required to understand the differences between Wales and England post-devolution. National public information campaigns in Belgium in 2000\textsuperscript{20} may account for the significant reduction in prescriptions associated with interruption of the time series in 2001 (Table 1).

Devolution did have two major effects on our analysis. First, as others have noted,\textsuperscript{6} we found it time-consuming and difficult to obtain data from the four administrations of the UK. Second, we found that the same data were no longer available from all four administrations as Northern Ireland did not routinely analyse data about the number of prescriptions for part of the study period. This is important evidence to support concerns that devolution will lead to differences in the data that are collected in the four countries, which makes it impossible to analyse the impact of policy changes.\textsuperscript{6} Northern Ireland is now providing the ESAC team with data about prescriptions and these will be included in future analyses.

Our hypothesis was that increasing the age of prescription exemption in Wales in 2002 might increase the antibiotic use because there is some evidence that prescription charges deter medicines’ use. Although exemption charges only apply to 50% of the UK population and only 20% of the prescriptions, they do have a strong influence on patients’ behaviour.\textsuperscript{21} There is already evidence that patients with tuberculosis in London ‘shop around’ to find hospitals that will not charge them a dispensing fee.\textsuperscript{22} However, the increase in exemption age for prescription charges from 16 to 25 in Wales was not associated with significant changes in antibiotic use. Two possible explanations are that this age group only accounts for \~{}10% of all antibiotic use\textsuperscript{23} and in England exemption extends up to the age of 18 for those in full-time education.\textsuperscript{24} However, if Wales does go ahead with complete abolition of prescription charges,\textsuperscript{25} then the effect could be much more marked. Moreover, increases in use in Wales could be artificially inflated by Welsh pharmacies attracting business from England as there is currently no residency qualification to exemptions.\textsuperscript{7} Further investigation of the effects of more recent changes in prescription exemption in Wales (progressive reduction in charges in 2004 and 2006 followed by complete abolition in April 2007) is required.

Possible causes for differences between DID and PID

We found small but potentially important differences between time trends when prescriptions were used as the numerator instead of DDD. There are two likely explanations for this. First, interventions to reduce antibiotic use in primary care have had a relatively greater impact on prescribing to children versus adults.\textsuperscript{26,27} The doses prescribed to children are lower than adult doses but the DDD is based entirely on adult doses. Changes to antibiotic prescribing for children will therefore have a relatively greater impact on measures based on prescriptions versus DDD. Second, changes or differences in the doses prescribed to adults will have a similar impact on the analysis of DDD. This probably accounts for the fact that antibiotic use in Belgium appears to be much higher than in the UK administrations when analysed with DDD, whereas differences are less marked when analysed with prescriptions (Figures 3 and 4). Prescribed doses of co-amoxiclav illustrate the point. In all of the UK administrations in 2005, over 80% of the prescriptions were for a daily dose of 750 mg amoxicillin, whereas in Belgium this accounted for only 20% of the prescriptions; the remainder were for doses of 1–2 g. Prescribed daily doses of all antibiotics tend to be lower in the UK than in other European countries.\textsuperscript{28} Consequently, the position of the UK administrations at the low end of the European distribution of DIDs (Figure 2) is likely to be due at least in part to treating patients with lower daily doses as opposed to treating fewer patients.

Conclusions

The ESAC project has for the first time provided publicly available data about antibiotic use in the four UK administrations. Our analysis reveals important practice variation between the administrations that should be linked to surveillance of resistance and stimulate research to explain differences. Divergence between the UK health systems is likely to increase. In the absence of any effective Federal layer of health administration in the UK, it is up to professional organizations to take a leadership role in their areas of interest, as the British Medical Association is doing for issues such as pensions, law, ethics, employment law and economic incentives.\textsuperscript{3} The natural experiment in health policy that is occurring in the UK provides a rich opportunity for research that will be lost unless UK professional organizations show leadership in collecting and standardizing data. The most important change since devolution is that it has become much more difficult to obtain information for analysis of differences between administrations.

We challenge DID as inadequate as a single measure of antibiotic use. Analysis of PID provides important additional insights.

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Transparency declarations

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Supplementary data

The full statistical report is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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