Supplementary data

Supplementary Statistical Report

Methods

Statistical analysis

A segmented regression design for controlled interrupted time series analysis was used for the evaluation of changes in total antibiotic use after two changes in national policies that came into effect in 2000 and 2002.\textsuperscript{1-3} We used data from Belgium and England as control groups for the devolution of health administration in Northern Ireland, Scotland and Wales in 2000. Data from Scotland, Northern Ireland, England and Belgium were used as control groups to evaluate changes after the age of prescription exemption in Wales in 2002. We had no data on prescriptions (PID) from Northern Ireland before 2002 so were unable to include Northern Ireland in either of the interrupted time series analyses of prescription data. The Republic of Ireland was excluded from longitudinal analysis as we had only 2005 data.

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.\textsuperscript{4} We then applied Durbin-Watson and Breusch-Godfrey statistics to test for presence of autocorrelation. We used two tests for these analyses as each test has limitations. As data exhibited seasonal effects at lag 4, we removed the seasonality and used seasonally adjusted series for segmented regression.\textsuperscript{1-3} Then we applied segmented regression analysis. For outcomes measurements we considered the change in trend and the trend without the intervention and then compared the study and control groups.\textsuperscript{5, 6} We did not present change in mean level or intercept after the intervention in the BMJ manuscript.
because seasonal adjustment obscured these changes. STATA version 9 was used for statistical analysis.

We ran all analyses with the complete data and with data from 1999 onwards because we only had data from Wales from 1999 onwards. In the BMJ paper we have used the analysis from 1999 onwards as explained in the interpretation of results below.
Results

Analyses of all data from 1997-2005 are presented in Tables 1-6.

Analyses of data from 1999-2005 are presented in Tables 7-12.

The results can be summarized in two simple tables:

With all data (from 1997 to 2005 for all countries except Wales, Wales data start in 1999)

<table>
<thead>
<tr>
<th></th>
<th>Linear trend without intervention 1997-2005</th>
<th>Interrupted Time Series Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DID</td>
<td>PID</td>
</tr>
<tr>
<td>Bel</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>Eng</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Nlr</td>
<td>NS</td>
<td>---</td>
</tr>
<tr>
<td>Sco</td>
<td>NS</td>
<td>---</td>
</tr>
<tr>
<td>Wal</td>
<td>+++</td>
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</tr>
</tbody>
</table>

With data from 1999 to 2005

<table>
<thead>
<tr>
<th></th>
<th>Linear trend without intervention 1999-2005</th>
<th>Interrupted Time Series Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DID</td>
<td>PID</td>
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<tr>
<td>Bel</td>
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</tr>
<tr>
<td>Eng</td>
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</tr>
<tr>
<td>Nlr</td>
<td>++</td>
<td>---</td>
</tr>
<tr>
<td>Sco</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Wal</td>
<td>+++</td>
<td>---</td>
</tr>
</tbody>
</table>

Key
- or + p<0.1
-- or ++ p<0.01
--- or +++ p<0.001

Interpretation

For most analyses there are marked differences in the results using 1997-2005 data compared with 1999-2005. Therefore if we want to compare Wales with the other countries the analysis should be restricted to 1999-2005, when data were available for all five countries.
The likely explanation for the marked difference between analyses with 1997-2005 data versus 1999-2005 data is that there was a steep reduction in DID and PID between 1997 and 1999 in all of the countries for which we have complete data.

Visual inspection of the time series from 1997 or from 1999 shows that there are some non-linear trends so it is not helpful to present the analysis of linear trend without intervention in the main paper.

The interpretation of the analyses of data from 1999-2005 is given in the main paper.
Table 1- Stationary tests on time series of total outpatient antibiotic use in four UK nations and Belgium measured in DDD per 1000 inhabitants. 1997-2005

<table>
<thead>
<tr>
<th>DID</th>
<th>Number of data points</th>
<th>T statistics and MacKinnon approximate (p-value)</th>
<th>5% Critical value</th>
<th>10% Critical value</th>
<th>T statistics and MacKinnon approximate (p-value)</th>
<th>5% Critical value</th>
<th>10% Critical value</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>1(12-24) 2(20-16)</td>
<td>-3.35 (0.01)</td>
<td>-2.98</td>
<td>-2.62</td>
<td>-5.2 (&lt;0.0001)</td>
<td>-2.97</td>
<td>-2.62</td>
</tr>
<tr>
<td>Belgium</td>
<td>1(12-24) 2(20-16)</td>
<td>-3.35 (0.01)</td>
<td>-2.98</td>
<td>-2.62</td>
<td>-6.45 (&lt;0.0001)</td>
<td>-2.972</td>
<td>-2.62</td>
</tr>
<tr>
<td>Scotland</td>
<td>1(12-24) 2(20-16)</td>
<td>-2.249 (0.2)</td>
<td>-2.98</td>
<td>-2.62</td>
<td>-5.57 (&lt;0.0001)</td>
<td>-2.972</td>
<td>-2.62</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1(10-24) 2(18-16)</td>
<td>-1.53 (0.5)</td>
<td>-2.9</td>
<td>-2.6</td>
<td>-4.49 (&lt;0.001)</td>
<td>-2.98</td>
<td>-2.62</td>
</tr>
<tr>
<td>Wales</td>
<td>1(4-24) 2(12-16)</td>
<td>-1.41 (0.6)</td>
<td>-3.00</td>
<td>-2.63</td>
<td>-0.441 (&lt;0.001)</td>
<td>-2.99</td>
<td>-2.62</td>
</tr>
</tbody>
</table>

Table 2- Testing for autocorrelation on time series of total outpatient antibiotic use in four UK nations and Belgium measured in DDD per 1000 inhabitants. 1997-2005

<table>
<thead>
<tr>
<th>DID</th>
<th>Test for autocorrelation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Durbin-Watson test d-statistics</td>
</tr>
<tr>
<td>England</td>
<td>1.46</td>
</tr>
<tr>
<td>Belgium</td>
<td>1.93</td>
</tr>
<tr>
<td>Scotland</td>
<td>1.44</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1.61</td>
</tr>
<tr>
<td>Wales</td>
<td>1.92</td>
</tr>
</tbody>
</table>
Table 3- Segmented regression analysis on seasonally adjusted time series data of total outpatient antibiotic use in four UK nations and Belgium measured in DDD per 1000 inhabitants (DID). 1997-2005

<table>
<thead>
<tr>
<th>DID</th>
<th>Interrupted time series regression analysis of antibiotic use, adjusted for seasonality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Devolution of health administration in Northern Ireland, Scotland and Wales</td>
</tr>
<tr>
<td></td>
<td>Change in trend after the intervention (p-value)</td>
</tr>
<tr>
<td>England</td>
<td>0.36 (&lt;0.0001)</td>
</tr>
<tr>
<td>Belgium</td>
<td>-0.11 (0.3)</td>
</tr>
<tr>
<td>Scotland</td>
<td>0.38 (&lt;0.0001)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>0.45 (&lt;0.0001)</td>
</tr>
<tr>
<td>Wales</td>
<td>-0.68 (0.004)</td>
</tr>
</tbody>
</table>

Table 4- Stationary tests on time series of total outpatient antibiotic use in four UK nations and Belgium measured in prescriptions per 1000 inhabitants per day (PID). 1997-2005

<table>
<thead>
<tr>
<th>PID</th>
<th>Unit root test to establish whether the series is trend or difference stationary in nature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of data points</td>
</tr>
<tr>
<td></td>
<td>1 (Pre-post intervention 1) 2 (Pre-Post intervention 2)</td>
</tr>
<tr>
<td>England</td>
<td>1(12-24) 2(20-16)</td>
</tr>
<tr>
<td>Belgium</td>
<td>1(12-24) 2(20-16)</td>
</tr>
<tr>
<td>Scotland</td>
<td>1(12-24) 2(20-16)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1(0-16) 2(0-16)</td>
</tr>
<tr>
<td>Wales</td>
<td>1(4-24) 2(12-16)</td>
</tr>
</tbody>
</table>
Table 5- Testing for autocorrelation on time series of total outpatient antibiotic use in four UK nations and Belgium measured in prescriptions per 1000 inhabitants per day (PID). 1997-2005

<table>
<thead>
<tr>
<th>PID</th>
<th>Test for autocorrelation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Durbin-Watson test</td>
<td>Breusch-Godfrey test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>d-statistics</td>
<td>Chi2 (P value)</td>
<td></td>
</tr>
<tr>
<td>England</td>
<td>1.61</td>
<td>22.988 (0.0001)</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>1.987</td>
<td>28.46 (&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>1.574</td>
<td>20.583 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>1.99</td>
<td>21.376 (&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

Table 6- Segmented regression analysis on seasonally adjusted time series data of total outpatient antibiotic use in four UK nations and Belgium measured in prescriptions per 1000 inhabitants per day (PID). 1997-2005

<table>
<thead>
<tr>
<th>PID</th>
<th>Interrupted time series regression analysis of antibiotic use, adjusted for seasonality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Devolution of health administration in Northern Ireland, Scotland and Wales</td>
</tr>
<tr>
<td></td>
<td>Increase in the age of prescription exemption in Wales</td>
</tr>
<tr>
<td></td>
<td>布伦布-威森特 test</td>
</tr>
<tr>
<td></td>
<td>Breusch-Godfrey test</td>
</tr>
<tr>
<td></td>
<td>Ch2 (P value)</td>
</tr>
<tr>
<td></td>
<td>Change in trend after the intervention (p-value)</td>
</tr>
<tr>
<td></td>
<td>Change in mean level or intercept after the intervention (p-value)</td>
</tr>
<tr>
<td></td>
<td>Trend without intervention (p-value)</td>
</tr>
<tr>
<td></td>
<td>Change in trend after the intervention (p-value)</td>
</tr>
<tr>
<td></td>
<td>Change in mean level or intercept after the intervention (p-value)</td>
</tr>
<tr>
<td></td>
<td>Trend without intervention (p-value)</td>
</tr>
<tr>
<td>England</td>
<td>0.05 (&lt;0.0001)</td>
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<tr>
<td></td>
<td>0.01 (0.7)</td>
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<tr>
<td></td>
<td>-0.02 (&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>0.03 (&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>0.12 (0.04)</td>
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<tr>
<td></td>
<td>-0.02 (&lt;0.0001)</td>
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<tr>
<td>Belgium</td>
<td>-0.031 (0.03)</td>
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<tr>
<td></td>
<td>-0.08 (0.5)</td>
</tr>
<tr>
<td></td>
<td>-0.05 (&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>-0.01 (0.6)</td>
</tr>
<tr>
<td></td>
<td>-0.12 (0.3)</td>
</tr>
<tr>
<td></td>
<td>-0.05 (&lt;0.0001)</td>
</tr>
<tr>
<td>Scotland</td>
<td>0.05 (&lt;0.0001)</td>
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<tr>
<td></td>
<td>0.01 (0.8)</td>
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<tr>
<td></td>
<td>-0.02 (&lt;0.001)</td>
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<tr>
<td></td>
<td>0.03 (&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>0.01 (0.08)</td>
</tr>
<tr>
<td></td>
<td>-0.02 (&lt;0.001)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>-</td>
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<tr>
<td></td>
<td>-</td>
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<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Wales</td>
<td>0.031 (0.3)</td>
</tr>
<tr>
<td></td>
<td>-0.06 (0.4)</td>
</tr>
<tr>
<td></td>
<td>-0.01 (&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>0.01 (0.06)</td>
</tr>
<tr>
<td></td>
<td>-0.01 (0.9)</td>
</tr>
<tr>
<td></td>
<td>-0.01 (&lt;0.0001)</td>
</tr>
</tbody>
</table>
Table 7- Stationary tests on time series of total outpatient antibiotic use in four UK nations and Belgium measured in DDD per 1000 inhabitants. 1999-2005

<table>
<thead>
<tr>
<th>DID</th>
<th>Number of data points</th>
<th>Augmented Dickey-Fuller</th>
<th>Phillips-Perron test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T statistics</td>
<td>5% Critical value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and MacKinnon</td>
<td>value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>approximate</td>
<td>(p-value)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>England</td>
<td>1(4-24) 2(12-16)</td>
<td>-0.36 (1)</td>
<td>-3.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>1(4-24) 2(12-16)</td>
<td>-1.96 (0.3)</td>
<td>-3.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>1(4-24) 2(12-16)</td>
<td>0.4 (1)</td>
<td>-3.00</td>
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</tr>
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<td>Northern Ireland</td>
<td>1(4-24) 2(12-16)</td>
<td>-0.56 (0.9)</td>
<td>-3.00</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>1(4-24) 2(12-16)</td>
<td>-1.41 (0.6)</td>
<td>-3.00</td>
</tr>
</tbody>
</table>

Table 8- Testing for autocorrelation on time series of total outpatient antibiotic use in four UK nations and Belgium measured in DDD per 1000 inhabitants. 1999-2005

<table>
<thead>
<tr>
<th>DID</th>
<th>Test for autocorrelation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Durbin-Watson test d-statistics</td>
</tr>
<tr>
<td>England</td>
<td>1.99</td>
</tr>
<tr>
<td>Belgium</td>
<td>1.99</td>
</tr>
<tr>
<td>Scotland</td>
<td>2.02</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1.78</td>
</tr>
<tr>
<td>Wales</td>
<td>1.92</td>
</tr>
</tbody>
</table>
Table 9- Segmented regression analysis on seasonally adjusted time series data of total outpatient antibiotic use in four UK nations and Belgium measured in DDD per 1000 inhabitants (DID). 1999-2005

<table>
<thead>
<tr>
<th>DID</th>
<th>Interrupted time series regression analysis of antibiotic use, adjusted for seasonality</th>
<th>Increase in the age of prescription exemption in Wales</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Devolution of health administration in Northern Ireland, Scotland and Wales</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change in trend after the intervention (p-value)</td>
<td>Change in mean level or intercept after the intervention (p-value)</td>
</tr>
<tr>
<td>England</td>
<td>0.11 (0.4)</td>
<td>-0.40 (0.1)</td>
</tr>
<tr>
<td>Belgium</td>
<td>-0.08 (0.01)</td>
<td>-0.12 (0.8)</td>
</tr>
<tr>
<td>Scotland</td>
<td>0.02 (0.9)</td>
<td>-0.41 (0.4)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>0.83 (0.01)</td>
<td>-0.91 (0.16)</td>
</tr>
<tr>
<td>Wales</td>
<td>-0.68 (0.004)</td>
<td>-3.39 (0.4)</td>
</tr>
</tbody>
</table>

Table 10- Stationary tests on time series of total outpatient antibiotic use in four UK nations and Belgium measured in prescriptions per 1000 inhabitants per day (PID). 1999-2005

<table>
<thead>
<tr>
<th>PID</th>
<th>Unit root test to establish whether the series is trend or difference stationary in nature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of data points</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>England</td>
<td>1 (Pre-post intervention 1) 2 (Pre-Post intervention 2)</td>
</tr>
<tr>
<td>Belgium</td>
<td>1 (4-24) 2 (12-16)</td>
</tr>
<tr>
<td>Scotland</td>
<td>1 (4-24) 2 (12-16)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1 (0-16) 2 (0-16)</td>
</tr>
<tr>
<td>Wales</td>
<td>1 (4-24) 2 (12-16)</td>
</tr>
</tbody>
</table>
Table 11- Testing for autocorrelation on time series of total outpatient antibiotic use in four UK nations and Belgium measured in prescriptions per 1000 inhabitants per day (PID). 1999-2005

<table>
<thead>
<tr>
<th>PID</th>
<th>Test for autocorrelation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Durbin-Watson test d-statistics</td>
</tr>
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<td>England</td>
<td>2.03</td>
</tr>
<tr>
<td>Belgium</td>
<td>2.01</td>
</tr>
<tr>
<td>Scotland</td>
<td>2.03</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>-</td>
</tr>
<tr>
<td>Wales</td>
<td>1.99</td>
</tr>
</tbody>
</table>

Table 12- Segmented regression analysis on seasonally adjusted time series data of total outpatient antibiotic use in four UK nations and Belgium measured in prescriptions per 1000 inhabitants per day (PID). 1999-2005

<table>
<thead>
<tr>
<th>PID</th>
<th>Interrupted time series regression analysis of antibiotic use, adjusted for seasonality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Devolution of health administration in Northern Ireland, Scotland and Wales</td>
</tr>
<tr>
<td></td>
<td>Change in trend after the intervention (p-value)</td>
</tr>
<tr>
<td>England</td>
<td>0.08 (0.6)</td>
</tr>
<tr>
<td>Belgium</td>
<td>-0.04 (0.5)</td>
</tr>
<tr>
<td>Scotland</td>
<td>0.004 (0.9)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>-</td>
</tr>
<tr>
<td>Wales</td>
<td>0.031 (0.3)</td>
</tr>
</tbody>
</table>


