Surveillance of outpatient antibiotic consumption in Spain according to sales data and reimbursement data

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Objectives: National data on antibiotic consumption are needed in order to interpret trends in antibiotic resistance. We compared antibiotic prescription reimbursement data and sales data in Spain.

Methods: Data covering the years 2002, 2004 and 2005 were examined. Reimbursement data for ambulatory care were provided by the Spanish Agency for Medicines and Healthcare Products and sales data by International Medical Statistics Health. Quantities were standardized using the defined daily dose per 1000 inhabitants per day (DID) in accordance with the anatomical therapeutic classification.

Results: Sales data increased from 26.33 DID in 2002 to 28.12 DID in 2004 and 28.93 DID in 2005. Estimates based on equivalent reimbursement data were ~30% lower and increased from 18.01 DID in 2002 to 18.48 DID in 2004 and 19.29 DID in 2005. The differences were greatest for amoxicillin, amoxicillin/clavulanic acid, clarithromycin and cefuroxime.

Conclusions: Antibiotic consumption as estimated from reimbursement data is substantially less than that from sales data. This finding has major implications for national surveillance of antibiotic consumption.

Keywords: antibiotic resistance, self-antibiotic medication, ESAC, European Surveillance of Antimicrobial Consumption

Introduction

Antibiotic abuse and misuse are recognized as important determinants for the development of antibiotic resistance.¹,² Although frequent calls to stop the excessive use of antibiotics have been made,¹ both consumption and resistance are tending to escalate in some countries.³ To prevent further spread of resistance and to develop effective strategies to foster appropriate antibiotic consumption in all European countries, international cooperation is necessary starting with setting up reliable surveillance systems of both antibiotic resistance and consumption.¹

In 2001, the European Commission (Directorate-General Sanco, Health Monitoring Program) established the European Surveillance of Antimicrobial Consumption (ESAC) project. The aim of the project was to collect data on antibiotic consumption in Europe from publicly available sources and to assess the time trends in human exposure to antibiotics.²,³

Spain shows increased rates of antibiotic resistance in several community pathogens in comparison with other European countries.⁴,⁵ A number of authors and international Health Institutions have identified uncontrolled self-medication and over-the-counter (OTC) consumption of antibiotics as a key health problem for the effective control of antibiotic resistance.⁶ Although community pharmacies in most European Union countries are not legally allowed to dispense antibiotics without a prescription, this is a common practice at least in some of the European countries, and one that can lead to a high OTC consumption.

In Spain (population ~45 million people), important differences in the outpatient consumption of antibiotics have been

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observed depending on the measurement system used. In the study by Cars et al., based on wholesaler sales data provided by International Medical Statistics (IMS) Health, total outpatient antibiotic consumption in Spain was among the highest in Europe, second only to France; however, consumption figures were much lower according to official reimbursement data by the social security system. Nonetheless, these differences have not been studied in detail.

On the other hand, several studies have suggested that Spain may present high rates of self-antibiotic consumption and OTC consumption in comparison with other European countries. However, despite their evident public health interest, rates of OTC antibiotic consumption are not well understood.

In this study, we analysed the community consumption of antibacterials for systemic use in Spain according to sales data (SD) and reimbursement data (RD).

Materials and methods

Use data of systemic antibiotics [anatomical therapeutic chemical (ATC) group J01] for ambulatory care for 2002, 2004 and 2005 aggregated at the level of the active substance were collected, in accordance with the ATC classification and defined daily dose (DDD) measurement unit (WHO, version 2005), and expressed in DDD per 1000 inhabitants per day (DID). Adherence to the ATC/DDD 2005 version was mandatory because of continuous updates, i.e. introduction of new ATC codes and modification of DDD values reflecting real dosage of certain antibiotics in medical practice.

RD for ambulatory care were provided for the study period (2002–05) by the Spanish Agency for Medicines and Healthcare Products (Ministry of Health and Consumer Affairs) and obtained from the ECOM (‘Especialidades Consumo de Medicamentos’) database of retail pharmacy sales of all medicines acquired with National Health System prescriptions, covering nearly 100% of the Spanish population. In addition, wholesaler SD for 2002, 2004 and 2005 were obtained from IMS Health at the level of active substances, expressed in kg or IU, which allowed assignment of the ATC codes and conversion into DDD. The IMS Health information is sourced from a mixed sample of wholesalers and pharmacies which represents ~96.5% of sales to retail pharmacies in Spain, this being projected to a national total.

In-depth analysis of differences between both data sources was further performed.

Results and discussion

Total outpatient antibiotic consumption in Spain based on RD and SD was 18.01 and 26.33 DID in 2002, respectively; 18.48 and 28.12 DID in 2004 and 19.29 and 28.93 DID in 2005 (Figure 1). The annual differences between RD and SD data were 8.32 (31.6%) DID in 2002, 9.64 (34.3%) DID in 2004 and 9.64 (33.3%) DID in 2005 (mean: 9.20; 95% CI: 7.31–11.09).

Amoxicillin/clavulanic acid and amoxicillin were the most used antibiotics, aggregated consumption of both antibiotics represented 52.4% (2002), 56.8% (2004) and 59.3% (2005) of the overall antibiotic consumption according to RD; and 57% (2001), 57.1% (2004) and 58.8% (2005) according to SD.

Overall antibiotic consumption increased in Spain from 2002 to 2004, 0.47 (2.6%) and 1.79 (6.8%) DID according to RD and SD, respectively; and from 2004 to 2005, 0.81 (4.4%) and 0.81 (2.9%) DID according to RD and SD, respectively (Table 1). This increase was almost exclusively due to amoxicillin/clavulanic acid use with an increase of 2.34 (RD) and 2.46 (SD) DID. The consumption of the majority of the other antibiotics

![Figure 1. Evolution of sales (IMS) and reimbursement (ESAC) data of the five most used antibacterials for systemic use, ATC group J01 (2002, 2004 and 2005).](https://academic.oup.com/jac/article-abstract/60/3/698/735299)
analysed decreased or did not significantly vary between 2002 and 2005 according to both RD and SD data (Table 1). During the study period, the proportion of children aged 0–4 years (believed to be the greatest antibiotic consumers) increased from 4.29% (2002) to 4.74% (2005).

Considerable differences between RD and SD were found for the 20 most used antibiotics, representing over 95% of Spanish outpatient antibiotic use (Table 1). These differences were most marked for amoxicillin (48.2% in 2005), cefpodoxime (49.2%), clindamycin (51.1%), cefaclor (51.9%), fosfomycin (58.6%), erythromycin (72%) and spiramycin (89.6%). However, differences in the use of amoxicillin and amoxicillin/clavulanic acid (3.65 and 1.93 DID, respectively, in 2005) accounted together for 57.9% of the overall difference between RD and SD in 2005. Conversely, the smallest differences were found for fluoroquinolones: moxifloxacin (15.4% in 2005), levofloxacin (14.8%) and ciprofloxacin (13.1%).

During the study period, the proportion of difference between RD and SD remained constant for most antibiotic classes. However, an important increase (>10%) was detected in cefuroxime, 12.3% in 2002 versus 26% in 2005; erythromycin, 50.7% in 2002 versus 72% in 2005; doxycycline, 35.8% in 2002 versus 46.5% in 2005; and spiramycin (3.65 and 1.93 DID, respectively, in 2005) accounted together for 57.9% of the overall difference between RD and SD in 2005. Conversely, the smallest differences were found for fluoroquinolones: moxifloxacin (15.4% in 2005), levofloxacin (14.8%) and ciprofloxacin (13.1%).

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Drug utilization reports can stem either from RD or SD. Both sources have their specific biases: RD exclude the OTC sales, but also the prescriptions made in private practice and within healthcare maintenance organizations for certain civil servants, while SD may include parallel export to other countries and veterinary use. In many European countries, all antibiotics are at least partially reimbursed. However, in some countries, as is the case of some northern European countries, several antibiotics are excluded from the reimbursement list either because they are considered as inappropriate or because their reimbursement is limited to certain diagnoses or population groups. Furthermore in countries with data collection systems based on RD as is the case of Spain, the delivery of antibiotics as OTC medicines may lead to an underestimation of the overall antibiotic consumption.

This was documented in Spain by in-depth analysis of differences between two parallel data sets based on both RD and SD. These may provide a good estimate of non-reimbursed (principally OTC) sales, although disparity between SD and RD could also be explained in part by additional factors like private health insurance and pet veterinary prescriptions, both not included in RD, and parallel re-exports to other EU countries. Spain, as a country with lower medicine prices within the EU, is considered as a source country for parallel exports to countries with higher price levels.

Dentistry is mostly private in Spain and thus antibiotic prescriptions made by such professionals are largely outside RD, explaining for instance the great difference observed between RD and SD for spiramycin (89.6%), an antibiotic almost exclusively used in this medical field in Spain (combination of spiramycin plus metronidazole).

### Table 1. Comparison of sales (IMS) and reimbursement (ESAC) antibiotic consumption data expressed in DDD per 1000 inhabitants and per day for the 20 most used antibiotics at the substance level in Spain

<table>
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<tbody>
<tr>
<td>Amoxicillin/enzyme inhibitor (J01CR02)</td>
<td>0.19</td>
<td>0.26</td>
<td>−19</td>
<td>0.35</td>
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<td>−8</td>
<td>0.37</td>
<td>0.41</td>
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<td>0.28</td>
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<td>−15</td>
<td>0.40</td>
<td>0.44</td>
<td>−15</td>
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<td>0.41</td>
<td>−21</td>
<td>0.49</td>
<td>0.57</td>
<td>−17</td>
<td>0.50</td>
<td>0.57</td>
<td>−17</td>
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<td>Cefuroxime (J01DD08)</td>
<td>0.57</td>
<td>0.66</td>
<td>−16</td>
<td>0.77</td>
<td>0.86</td>
<td>−12</td>
<td>0.79</td>
<td>0.86</td>
<td>−12</td>
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<td>Ciprofloxacin (J01MA02)</td>
<td>0.35</td>
<td>0.42</td>
<td>−21</td>
<td>0.50</td>
<td>0.57</td>
<td>−15</td>
<td>0.52</td>
<td>0.57</td>
<td>−15</td>
</tr>
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<td>Azithromycin (J01FA10)</td>
<td>0.18</td>
<td>0.23</td>
<td>−27</td>
<td>0.25</td>
<td>0.32</td>
<td>−27</td>
<td>0.27</td>
<td>0.32</td>
<td>−27</td>
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<tr>
<td>Doxycycline (J01AA02)</td>
<td>0.27</td>
<td>0.32</td>
<td>−18</td>
<td>0.35</td>
<td>0.40</td>
<td>−13</td>
<td>0.38</td>
<td>0.40</td>
<td>−13</td>
</tr>
<tr>
<td>Norfloxacin (J01MA06)</td>
<td>0.31</td>
<td>0.37</td>
<td>−20</td>
<td>0.41</td>
<td>0.47</td>
<td>−16</td>
<td>0.44</td>
<td>0.47</td>
<td>−16</td>
</tr>
<tr>
<td>Cefixime (J01DD08)</td>
<td>0.38</td>
<td>0.45</td>
<td>−19</td>
<td>0.48</td>
<td>0.54</td>
<td>−16</td>
<td>0.50</td>
<td>0.54</td>
<td>−16</td>
</tr>
<tr>
<td>Co-trimoxazole (J01EE01)</td>
<td>0.44</td>
<td>0.51</td>
<td>−16</td>
<td>0.53</td>
<td>0.60</td>
<td>−15</td>
<td>0.56</td>
<td>0.60</td>
<td>−15</td>
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<tr>
<td>Moxifloxacin (J01MA14)</td>
<td>0.35</td>
<td>0.42</td>
<td>−20</td>
<td>0.47</td>
<td>0.54</td>
<td>−17</td>
<td>0.50</td>
<td>0.54</td>
<td>−17</td>
</tr>
<tr>
<td>Erythromycin (J01FA01)</td>
<td>0.34</td>
<td>0.40</td>
<td>−18</td>
<td>0.42</td>
<td>0.48</td>
<td>−16</td>
<td>0.45</td>
<td>0.48</td>
<td>−16</td>
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<tr>
<td>Levofloxacin (J01MA12)</td>
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<td>0.42</td>
<td>−17</td>
<td>0.45</td>
<td>0.52</td>
<td>−16</td>
<td>0.47</td>
<td>0.52</td>
<td>−16</td>
</tr>
<tr>
<td>Cloxacin (J01CF02)</td>
<td>0.39</td>
<td>0.45</td>
<td>−16</td>
<td>0.47</td>
<td>0.53</td>
<td>−16</td>
<td>0.50</td>
<td>0.53</td>
<td>−16</td>
</tr>
<tr>
<td>Spiramycin (J01FA02)</td>
<td>0.41</td>
<td>0.48</td>
<td>−17</td>
<td>0.50</td>
<td>0.57</td>
<td>−15</td>
<td>0.53</td>
<td>0.57</td>
<td>−15</td>
</tr>
<tr>
<td>Minocycline (J01AA08)</td>
<td>0.37</td>
<td>0.43</td>
<td>−17</td>
<td>0.45</td>
<td>0.51</td>
<td>−16</td>
<td>0.48</td>
<td>0.51</td>
<td>−16</td>
</tr>
<tr>
<td>Cefaclor (J01DC04)</td>
<td>0.40</td>
<td>0.47</td>
<td>−18</td>
<td>0.50</td>
<td>0.58</td>
<td>−17</td>
<td>0.53</td>
<td>0.58</td>
<td>−17</td>
</tr>
<tr>
<td>Clindamycin (J01FF01)</td>
<td>0.42</td>
<td>0.49</td>
<td>−17</td>
<td>0.51</td>
<td>0.59</td>
<td>−16</td>
<td>0.54</td>
<td>0.59</td>
<td>−16</td>
</tr>
<tr>
<td>Cefpodoxime (J01DD13)</td>
<td>0.43</td>
<td>0.50</td>
<td>−17</td>
<td>0.53</td>
<td>0.60</td>
<td>−16</td>
<td>0.56</td>
<td>0.60</td>
<td>−16</td>
</tr>
<tr>
<td>Telithromycin (J01FA15)</td>
<td>0.44</td>
<td>0.51</td>
<td>−16</td>
<td>0.54</td>
<td>0.61</td>
<td>−16</td>
<td>0.57</td>
<td>0.61</td>
<td>−16</td>
</tr>
<tr>
<td>Total (ATC group J01)</td>
<td>0.27</td>
<td>0.32</td>
<td>−19</td>
<td>0.36</td>
<td>0.42</td>
<td>−18</td>
<td>0.39</td>
<td>0.42</td>
<td>−18</td>
</tr>
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</table>
Outpatient antibiotic consumption in Spain

However, OTC antibiotics do not represent the total rates of self-medication with antibiotics. A recent comparative European study observed a high prevalence of self-medication with antibiotics and storage in Spain suggesting that an important part of the self-medication may be due to the use of antibiotics from leftovers.11 In this study, outpatient antibiotic consumption was relatively high in Spain, according to SD, with a substantial difference in RD – SD information that indirectly could be an indicator of OTC consumption, although prescriptions derived from private practice, civil servants or veterinary use may also have a contribution. The highest deviation between the two sources of information was observed for amoxicillin, fosfomycin and erythromycin, old and inexpensive antibiotics, which suggests that parallel exports may not have played a relevant role in the overall difference RD – SD. Old and inexpensive antibiotics such as amoxicillin, fosfomycin and erythromycin tend to be more frequently purchased OTC than new and expensive ones, such as the new fluoroquinolones.

According to ESAC published data based on RD,2 in 2002 total antibiotic consumption in Spain was close to the average for European countries; however, if the SD for the same year reported in this study were considered, Spain would have been in the five highest antibiotic consumers among European countries, probably a much more realistic position.

Recently, Spain launched a mass media public campaign aimed at promoting a more rational use of antibiotics including the reduction of self-medication and OTC (http://www.antibioticos.msc.es/home.html). The two measurement systems analysed in this study would be useful to measure the campaign impact in general and the reduction in the OTC use in particular.

In summary, in this study we have shown that estimation of the total outpatient antibiotic consumption in Spain strongly varies according to the measurement system. Sales data suggest that ~30% of the total antibiotic consumption was not registered by the reimbursement data of the National Health System. These differences were particularly significant for the most prescribed antibiotics amoxicillin/clavulanic acid, amoxicillin, clarithromycin and cefuroxime. OTC use of antibiotics in this country may account for an important proportion of these differences.

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Transparency declarations

None to declare.

References