The More Antibacterial Trade Names, The More Consumption of Antibacterial Agents: A European Study

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Recent studies have shown large differences in the use of antibacterial agents among European countries. We found a relationship between community consumption and the number of trade names of oral antibacterial agents. This relationship was observed in countries in which consumption was high, as well as in countries in which it was low, and in markets that were opened or were not opened to the sale of copies of original agents.

Until recently, data on the consumption of antibacterial agents in Europe were not available to the public. The publication by Cars et al. [1] in 2001, followed in the same year by the implementation of the European Surveillance of Antimicrobial Consumption (ESAC) project [2] suddenly shed light on the large differences in the consumption of antibacterial agents among European countries. Many reasons have been proposed to explain these differences, including cultural and social determinants and differences in health care systems and regulatory practices [3–5]. However, it seems obvious that the characteristics of antibiotic markets represent another important factor. For example, we noticed that, in 1997, the Danish drug compendium (Lægemiddelkataloget) listed <100 antibacterial trade names, whereas the Spanish drug compendium (Vademecum Internacional) listed >200 trade names, which coincided with a much lower rate of consumption of antibacterial agents in Denmark than in Spain [1, 2]. This prompted us to study the relationship between the number of antibacterial trade names and community consumption of antibacterial agents in European countries.

Methods. From the ESAC database [6], we extracted data on community consumption in 1998 (and, in Italy, in 1999) for 8 major antibacterial classes for systemic use (table 1). These data were obtained for the 15 countries that were members of the European Union in 1998 and were expressed as a number of defined daily doses per 1000 inhabitants per day [7]. Because the data reported to ESAC by Spain did not include over-the-counter sales without a prescription, Spanish data were corrected using a multiplicative factor corresponding, for each class, to the difference observed in 1997 between IMS Health data as reported by Cars et al. [1] and ESAC data for the same year.

Data on the number of trade names of oral antibacterial agents registered in each country in 1998 were extracted from the Eudract pharmaceutical prices database [8]. In the present study, the generic copies of an agent that were marketed by different companies were each considered to represent a trade name. However, packages of tablets of various dosages sharing the same commercial name and marketed by the same company in the same country were considered to represent a single trade name. As a surrogate for defining a market opened to copies of original antibacterial agents, whether generic or branded copies, we used the ratio of the number of trade names to the number of active substances. For each combination of country and antibacterial class, we considered an open market to be one in which this ratio was >2—in other words, when there were >2 times as many trade names as there were active substances.

Because some countries may represent a more attractive or a less attractive market for antibacterial agents, we studied the relationship between community consumption and the number of trade names for oral antibacterial agents separately for the 5 countries that had the highest rate of consumption of antibacterial agents (and were thus considered to be attractive markets for these drugs) and for the 5 countries that had the lowest rates of consumption (and were thus considered to be poorly attractive markets) (table 1). Germany, which has a low rate of consumption of antibacterial drugs, was analyzed separately because of the very high number of trade names in this country.

For assessing correlations between the number of trade names and community consumption, we used the 2-tailed Spearman coefficient ($r$) for nonparametric correlations. The analysis was performed using SPSS software, version 12.0 for Windows (SPSS), and GraphPad Prism, version 3.02 for Windows (GraphPad Software).

Results. Correlations between community use and the...
number of trade names for oral antibacterial agents are presented in Table 1 and Figure 1. Because they showed no correlation, first- and second-generation cephalosporins were excluded from additional analyses.

**Discussion.** The results we report are consistent with our hypothesis that a quantitative relationship exists between the number of marketed products for oral use in an antibacterial class, represented here by the number of trade names, and consumption of this class of antibacterial agents in the community. This relationship was observed for most antibacterial classes and for countries with a high rate of consumption of antibacterial agents as well as countries with a low rate of consumption. In Germany, the relationship was different than that in the rest of the European Union. The German pharmaceutical market is largely opened to generic agents and, in each studied class (with the exception of fluoroquinolones and combinations of penicillins with β-lactamase inhibitors), included a much larger number of antibacterial trade names than did other European countries [8]. However, for an equivalent number of trade names, the rate of consumption was lower in Germany than in other European Union member states. The most probable explanation is the existence of prescribing budgets, leading to collective sanctions for German doctors and the pharmaceutical industry in the case of overspending [9].

Our results, however, do not prove a causal relationship between the number of marketed products for oral use in an antibacterial class and use of this class of antibacterial agents in the community. For example, some countries may represent more attractive markets for antibacterial agents than do other countries, and the number of trade names may simply reflect the fact that a market exists in these countries. This is certainly true for older antibacterial agents, such as β-lactamase–sensitive penicillins, which are still extensively used in Denmark and Sweden but not in other countries. Inversely, countries with a high level of regulation and a stringent national antibiotic policy represent poorly attractive markets for new antibacterial agents.

However, other data suggest that the relationship works in the other direction—in other words, that an increase in the number of trade names within one antibacterial class increases market competition in this class and results in an increase in consumption. First, in the present study, the relationship was the same in the 5 European countries with the highest overall rates of consumption of antibacterial agents, thus considered to be attractive markets for these drugs, and in the 5 countries with the lowest rates of consumption of these drugs—this despite European countries having very different health care systems, reimbursement rules, and prices for pharmaceuticals [8–10]. Second, our recent experience in Denmark—a country with a conservative national policy regarding the use of fluoroquinolones and antibacterial agents in general—shows that the opening of the market to generic ciprofloxacin led to a major price decrease immediately followed by an increase in ciprofloxacin consumption [11].

In the present study, the differences in the number of trade names of macrolides, fluoroquinolones, penicillins with extended spectrum, and combinations of penicillins with β-lactamase inhibitors were mainly a result of the fact that the market was opened or was not opened to copies of the original drug. In most countries, these copies were generic agents; however, in Spain, Portugal, and Italy, these copies often were branded because, until recently, patents protected the fabrication processes and not the active substances in these countries. The only advantage of a copy over the original drug is its price [12]. More generally, when a product that has very few advantages over existing products is introduced into a market, it is usually priced slightly less than similar competing products. The addition of many other similar products increases com-

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**Table 1. Correlations between community consumption and the number of trade names for oral agents for 8 antibacterial classes in European countries.**

<table>
<thead>
<tr>
<th>Level of analysis</th>
<th>( r^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>By antibacterial class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillins with extended spectrum (J01CA)(^b)</td>
<td>0.62</td>
<td>.01</td>
</tr>
<tr>
<td>β-Lactamase–sensitive penicillins (J01CE)(^c)</td>
<td>0.59</td>
<td>.02</td>
</tr>
<tr>
<td>Combinations of penicillins with β-lactamase inhibitors (J01CR)(^d)</td>
<td>0.65</td>
<td>.009</td>
</tr>
<tr>
<td>Cephalosporins First-generation (J01DB)</td>
<td>0.26</td>
<td>.358</td>
</tr>
<tr>
<td>Second-generation (J01DC)</td>
<td>0.24</td>
<td>.395</td>
</tr>
<tr>
<td>Third-generation (J01DD)</td>
<td>0.70</td>
<td>.004</td>
</tr>
<tr>
<td>Macrolides (J01FA)</td>
<td>0.65</td>
<td>.008</td>
</tr>
<tr>
<td>Fluoroquinolones (J01MA)</td>
<td>0.76</td>
<td>.001</td>
</tr>
<tr>
<td>Market opened to copies of original agents(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes(^f)</td>
<td>0.33</td>
<td>.04</td>
</tr>
<tr>
<td>No</td>
<td>0.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>By country(^g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 countries with highest consumption(^h)</td>
<td>0.69</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5 countries with lowest consumption(^i)</td>
<td>0.63</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Germany(^j)</td>
<td>0.99</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**NOTE.** Codes in parentheses are Anatomical Therapeutical Chemical codes, shown with examples when relevant.

\( ^a \) Two-tailed Spearman coefficient for nonparametric correlations.

\( ^b \) e.g., Amoxicillin.

\( ^c \) e.g., Phenoxymethylpenicillin.

\( ^d \) e.g., Amoxicillin–clavulanic acid.

\( ^e \) First- and second-generation cephalosporins, which did not show a correlation, were excluded.

\( ^f \) This result was largely influenced by Germany (see footnotes below and Discussion section). When Germany was excluded from the analysis, the following results were obtained: \( r = 0.46; P = .006 \).

\( ^g \) Belgium, France, Italy, Luxembourg, and Spain.

\( ^h \) Austria, Denmark, Netherlands, Sweden, and United Kingdom. Germany was excluded.

\( ^i \) Germany is presented separately because, despite having a low consumption of antibacterial drugs, it showed a very different relationship than that shown in other countries.

\( ^j \) Germany is presented separately because, despite having a low consumption of antibacterial drugs, it showed a very different relationship than that shown in other countries.
petition and forces prices down, thus making these products affordable for a larger proportion of the population and leading to increased consumption [13]. In addition, aggressive marketing practices, such as large discounts offered to pharmacists by pharmaceutical companies that manufacture generic agents, have been reported in, for example, France [14].

The results of our study suggest that a competition among agents within one antibacterial class exists not only between copies of original antibacterial agents, but also between branded agents with a similar mechanism of action, before the market is opened to the sale of copies. The number of trade names may represent a useful surrogate for promotional activity of antibacterial agents. A new agent in an existing antibacterial class often differentiates itself by its pharmacokinetic-pharmacodynamic properties, tolerability, and effectiveness, and these are used for promoting the use of this new agent. Despite these improvements, the new agent, however, generally has a mechanism of action and indications similar to that of other agents in the class and is, therefore, competing with these agents for use determined by these indications. Even when the new agent has a broader spectrum of activity and new indications, its use will not totally replace that of existing agents in the class. For example, the introduction of levofloxacin in Belgium resulted in an increase in the overall use of fluoroquinolones [2].

Antibacterials already represent a crowded market with numerous agents in most classes. Our study showed a relationship between the number of antibacterial trade names and rates of consumption of antibacterial drugs. This suggests that approval of more agents with a mechanism of action similar to that of existing agents, as well as the opening of the market to copies of original agents, would result in increases in consumption. This would, in turn, lead to increasing resistance, as is suggested by the growing number of reports on an ecological relationship between the consumption of antibacterial agents in the community and resistance in major pathogens isolated from clinical samples from outpatients [2, 11, 15–20]. The present study, however, should be seen to be a hypothesis-generating study, and future studies should include time series of consumption data to study (1) the influence of the loss of patents and the introduction of generic antibacterial agents and (2) the influence of the opening of a market to additional agents with the same mechanism of action within an existing antibacterial class, as well as time series of resistance data to study the effect of these changes on resistance.

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