Systemic antimycotic and antifungal use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe

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The participating country representatives constructed an exhaustive valid national antimicrobial drug register and use file, including detailed information (unit strength, pack size, galenic form and route of administration) for all antimycotic and antifungal products and the number of corresponding packages available on the market (ambulatory and hospital care). As in the previously published data collected within the ESAC project, each medicinal product was classified according to the WHO Anatomical Therapeutic Chemical (ATC) coding system, i.e. antimycotics (ATC J02) and antifungals (ATC D01BA) for systemic use. The denominator data used were the total number of inhabitants per year of a country (mid-year population). The J02 and D01BA data expressed in DID per 1000 inhabitants per day (DID) were compared with published ESAC-Net data from 2011, and the data expressed in packages per 1000 inhabitants per day (PID) were compared with published ESAC data from 2009.

A more detailed overview of the network, data availability, data suppliers, coverage, denominator data, data collection, validation and reporting is described elsewhere.

Table 1 presents reliable total antimycotic and antifungal use data in DID for 12 countries, states or areas not belonging to ESAC-Net, i.e. 4 south-eastern European (SEE) countries (Bosnia and Herzegovina, Montenegro, Serbia and Turkey), 7 newly independent states (NIS) (Armenia, Azerbaijan, Republic of Belarus, Georgia, Kyrgyzstan, Republic of Moldova and Tajikistan) and Kosovo. Total antimycotic and antifungal use was low in DID in most countries and areas and ranged from 0.08 DID for Bosnia and Herzegovina and Kosovo to 2.33 DID for Turkey; proportional use differed widely between countries, states and areas. Terbinafine, overall the most frequently used antifungal in DID in ESAC-Net, was the most used substance in Turkey only. In Serbia, ketoconazole was the most used antifungal substance, while in the other nine countries and Kosovo fluconazole was mainly used.

Superficial mycotic skin infections represent the most frequent form of fungal infections with a prevalence of 20%–25% of the entire world population and are caused mainly by dermatophytes. According to most publications and treatment guidelines, the drug of choice for treating these infections is terbinafine. Furthermore, terbinafine is more cost-effective against dermatophytes compared with other antifungal agents. Whether the lower

**Keywords:** antimycotic use, antifungal agents, drug consumption, pharmacoepidemiology

Sir,

The WHO Regional Office for Europe and the Laboratory of Medical Microbiology of the University of Antwerp, Belgium, established a sustainable surveillance network to collect valid, representative and comparable antimicrobial consumption data in non-EU countries of the WHO European Region and Kosovo. Recently, the first results of this project discussing systemic antibiotic use were published.

In this letter, we aim to report a cross-national comparison of the antimycotic and antifungal use rates in 2011 of 11 non-EU European countries and Kosovo and to compare these results with the EU countries involved in European Surveillance of Antimicrobial Consumption (ESAC, since 2011 ESAC-Net). All references, including those in the reference list, to ‘Kosovo’ mean ‘Kosovo [in accordance with UN Security Council resolution 1244 (1999)].’


Table 1. Total systemic antimycotic and antifungal use in 2011, expressed in DID, in 11 non-EU European countries and Kosovo (total use) and 12 ESAC-Net countries (outpatient use only)

<table>
<thead>
<tr>
<th>Country</th>
<th>Griseofulvin</th>
<th>Terbinafine</th>
<th>Amphotericin B</th>
<th>Ketoconazole</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>0</td>
<td>1.82</td>
<td>0</td>
<td>0.07</td>
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<td>0.68</td>
<td>0.01</td>
<td></td>
<td>3.31</td>
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<td>1.64</td>
<td>0</td>
<td>0.08</td>
<td>0.31</td>
<td>0.42</td>
<td>0</td>
<td>0</td>
<td>2.46</td>
</tr>
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<td>1.89</td>
<td>&lt;0.01</td>
<td>0.02</td>
<td>0.35</td>
<td>0.16</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>2.42</td>
</tr>
<tr>
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<td>&lt;0.01</td>
<td>0.04</td>
<td>0.16</td>
<td>0.37</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>2.33</td>
</tr>
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<td>1.53</td>
<td>&lt;0.01</td>
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<td>0.26</td>
<td>0.10</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>1.93</td>
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<td>0.44</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>1.82</td>
</tr>
<tr>
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<td>1.17</td>
<td>&lt;0.01</td>
<td>0.02</td>
<td>0.11</td>
<td>0.32</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>1.64</td>
</tr>
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<td>1.00</td>
<td>0</td>
<td>0.10</td>
<td>0.11</td>
<td>0.11</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>1.33</td>
</tr>
<tr>
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<td>0</td>
<td>0.99</td>
<td>0</td>
<td>0</td>
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<td>0.01</td>
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<td>1.29</td>
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<td>0.05</td>
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<td>0.01</td>
<td>0</td>
<td>&lt;0.01</td>
<td>1.03</td>
</tr>
<tr>
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<td>0</td>
<td>0.64</td>
<td>&lt;0.01</td>
<td>0</td>
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<td>0.17</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.90</td>
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<td>&lt;0.01</td>
<td></td>
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<td>0</td>
<td>0.27</td>
<td>0.25</td>
<td>0.03</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.79</td>
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<td>&lt;0.01</td>
<td>0.53</td>
<td>&lt;0.01</td>
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<td>0.02</td>
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<td>Republic of Belarus</td>
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<td>&lt;0.01</td>
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<td>0.33</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<td>0</td>
<td>0.08</td>
<td>0.11</td>
<td>0.04</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.64</td>
</tr>
<tr>
<td>Tajikistan</td>
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<td>&lt;0.01</td>
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<td>0.63</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.63</td>
</tr>
<tr>
<td>Azerbaijan</td>
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<td>—</td>
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<td>—</td>
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<td>0.38</td>
</tr>
<tr>
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<td>0.06</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.38</td>
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<td>0.01</td>
<td>—</td>
<td>&lt;0.01</td>
<td>0.26</td>
</tr>
<tr>
<td>Georgia</td>
<td>—</td>
<td>0.07</td>
<td>—</td>
<td>0.03</td>
<td>0.10</td>
<td>&lt;0.01</td>
<td>0</td>
<td>&lt;0.01</td>
<td>0.20</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>—</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>0.06</td>
<td>0</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Kosovo</td>
<td>—</td>
<td>0.03</td>
<td>&lt;0.01</td>
<td>0.04</td>
<td>—</td>
<td>—</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.08</td>
</tr>
</tbody>
</table>

—, no use reported.  
Shaded grey, non-EU European countries and Kosovo.  

aTurkey and Georgia reported outpatient antimycotic and antifungal use only.  
bLithuania reported total use.

The proportional use of terbinafine in DID in most non-EU European countries and Kosovo compared with ESAC-Net countries and Turkey is due to sociocultural differences, differences in education, healthcare organization, resources and utilization, pharmaceutical market and regulatory practices needs further investigation.

The high proportional use of systemic ketoconazole in Serbia is of concern due to its severe side effects. The world’s leading regulatory agencies, such as US FDA and EMA, have issued warnings that taking ketoconazole orally can cause severe liver injuries and antiandrogenic and antiglucocorticoid side effects. In Serbia, it is only indicated in patients who are hypersensitive to fluconazole, terbinafine and itraconazole, and who cannot be treated locally with antimycotics due to location, lesion size or depth of skin infection (according to the Serbian summary of product characteristics) (Vesela Radonjic, Medicines and Medical Devices Agency of Serbia, Belgrade, Serbia, personal communication). Possible reasons for the high use of ketoconazole could be its low cost, as it is an older substance and its cost is entirely reimbursed, or promotional activities by the local pharmaceutical industry.

When the DDD per package differs between regions, the DDD as a single outcome measure is not sufficient for a valid assessment of antimicrobial use. In this case, the number of packages could be a more appropriate measure, i.e. a better proxy for the number of treatments, assuming that for an acute infection doctors usually prescribe one package containing sufficient medication to treat the infection. Therefore, we also expressed total antimycotic and antifungal use in PID and compared the data with the results of 13 ESAC countries (Figure S1, available as Supplementary data at JAC Online). Use in PID ranged from 0.02 PID in Kosovo to 0.54 PID in Republic of Moldova. In contrast to the results in DID, Republic of Moldova, Azerbaijan, Republic of Belarus and Kyrgyzstan could be considered among the high users expressed PID in DID compared with the rest of Europe. As in the ESAC results, in most countries and areas, proportional use of fluconazole in PID was the highest. In general, azoles have been shown to be the most selective antifungal agents in developing resistance. With their high affinity for drug interactions and their natural poor absorption, azoles are more prone to resistance development, in contrast to terbinafine, which has a low rate of drug interactions and a low rate of exhibiting resistance.

In conclusion, our study demonstrates, for the first time, wide variation in systemic antimycotic and antifungal use in four SEE countries, seven NIS and Kosovo. In all countries and areas except Serbia (ketoconazole) and Turkey (terbinafine), proportional use of fluconazole is the highest. Compared with the rest of Europe, systemic antimycotic and antifungal use is low expressed in DID, but
Acknowledgements

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Funding

The Ministry of Health, Welfare and Sport of the Netherlands has provided funding in support of a partnership programme between the Netherlands and WHO. Part of this funding enabled this work. The work carried out by the Kosovo team has been supported from the European Union grant ‘Research Capacity Development in Kosovo’.

The funders had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication, following agreement from all authors.

Supplementary data

Figure S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References