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European Surveillance of Antimicrobial Consumption (ESAC): systemic antiviral use in Europe

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Objectives: To assess the total systemic antiviral use in Europe and to identify the antiviral substances most commonly used.

Methods: Within the European Surveillance of Antimicrobial Consumption (ESAC; www.esac.ua.ac.be), using the anatomical therapeutic chemical (ATC) classification and defined daily dose (DDD) measurement unit, data on total (out- and inpatient) systemic antiviral use (ATC J05), aggregated at the level of the active substance, were collected for 2008, and use was expressed in DDD (WHO ATC/DDD, version 2010) per 1000 inhabitants per day (DID). Antiviral substances were grouped according to their main indication.

Results: In Europe, 12 countries (Belgium, Croatia, Denmark, Estonia, Finland, France, Hungary, Italy, Luxembourg, Russia, Slovenia and Sweden) provided total (out- and inpatient) data and 4 countries (Austria, the Netherlands, Portugal and Norway) provided outpatient data only. Total systemic antiviral use varied by a factor of 10.95 between the country with the highest (3.53 DID in France) and the country with the lowest (0.32 DID in Croatia) use. HIV/AIDS antivirals represented more than 50% of the total antiviral use in most countries. The amount and spectrum of antivirals used varied greatly between countries.

Conclusions: Our study demonstrated a wide variation of total systemic antiviral use in several European countries, as striking as that of outpatient systemic antibiotic, antimycotic and antifungal use. The variation is mainly determined by the use of HIV/AIDS antivirals. These observations should stimulate further analysis to understand the variation of specific antiviral substances. The ESAC data facilitate auditing of antiviral prescriptions and evaluation of the implementation of guidelines and public health policies.

Keywords: antiviral agents, drug consumption, pharmacoepidemiology

Introduction

Comparisons of antibiotic, antifungal and antimycotic use in different European countries have been reported extensively by the European Surveillance of Antimicrobial Consumption (ESAC) project.[1–6] However, data on the use of antivirals are scarce. Published information on antiviral use is mainly limited to single countries and single drugs, and is based on market or sales data using different denominators to express the use.[7–10] In 2005, data on the consumption of antivirals were collected for the first time within the ESAC project, which was funded at that time by a grant from DG SANCO of the European Commission and is currently funded by the European Centre for Disease Prevention and Control (ECDC). ESAC is an international network of surveillance systems aiming to collect comparable and reliable data on antimicrobial use in Europe.[11] This article presents the first total (out- and inpatient) systemic antiviral use data from 16 European countries in 2008. With regard to antiviral use for the prevention and/or treatment of influenza, these data could serve as a historical reference before the outbreak of the A/H1N1 pandemic.

Methods

In 2008, 36 countries participated in the ESAC project, including all 27 European Union (EU) member states, 4 applicant countries (Bulgaria, Croatia, Romania and Turkey), 3 of the 4 members of the European Free Trade Association (Iceland, Norway and Switzerland), Israel and Russia. ESAC collects data on antimicrobial use aggregated at the level of the active substance and according to the anatomical therapeutic chemical (ATC) classification and the defined daily dose (DDD) measurement unit (WHO, version 2010).[12] The ATC J05 class, dedicated to antivirals for systemic use, includes 57 unique substances (Table 1). For four substances (J05AC02, J05AG02, J05AR05 and J05AX05), no DDD has been assigned by WHO, but to allow valid and comparable measurement of their use, an estimated theoretical daily dose was adopted during the ESAC annual meeting, held in June 2010 in Stockholm, Sweden, and included in Table S1 (available as Supplementary data at *JAC* Online). After this meeting, an extra validation for these four substances and also for antiviral combinations for the treatment of HIV infections (ATC J05AR) was requested. Only countries with validated data will be presented in this analysis.

Use was expressed in DDD per 1000 inhabitants per day (DID). The number of inhabitants in the participating countries was based on the midyear population in the country.[13]

All antiviral substances were grouped according to their main indication into seven categories (Table S1), including: 'Influenza antivirals' (i.e. substances used for the treatment of influenza, ATC J05AC02 and J05AH); 'Hepatitis C antivirals' (i.e. substances used for the treatment of hepatitis C, ATC J05AB04); 'Herpes antivirals' (i.e. substances used for the treatment of herpetic infection, ATC J05AC03, J05AD01 and J05AB except J05AB04); 'HIV/AIDS antivirals' (i.e. substances used for the treatment of HIV/AIDS, ATC J05AE, J05AF01–04, J05AF06, J05AG, J05AR and J05AX07–09); and 'Hepatitis B antivirals' (i.e. substances used for the treatment of hepatitis B, ATC J05AF08 and J05AF10–12). Lamivudine (ATC J05AF05), tenofovir (ATC J05AF07) and emtricitabine (ATC J05AF09), used for both HIV and hepatitis B treatment, were labelled as 'HIV/hepatitis B antivirals' and grouped as a separate category to allow assessment of their relative contribution in each country when considered as part of HIV treatment or hepatitis B treatment. The remaining antivirals (ATC J05AA, J05AD02, J05AX01, J05AX02, J05AX05 and J05AX06) were labelled as 'Others'.

The correlation between substances used for the treatment of HIV/AIDS patients (i.e. 'HIV/AIDS antivirals' and 'HIV/hepatitis B antivirals') and the number of HIV/AIDS patients was assessed using Spearman's coefficient for non-parametric correlation. For an estimation of the number of HIV/AIDS patients the cumulative total reported in the HIV/AIDS surveillance report was used.[14] All *P* values were based on two-tailed tests of significance. A *P* value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software, version 15.0 for Windows (SPSS, Inc., Chicago, IL, USA). Data sources, validity of the data collection and details of the methodology used, as well as the associated problems, have been described and discussed in detail previously.[4,11]

Results

Total antiviral use data, i.e. out- and inpatient use, were collected from 12 countries (Belgium, Croatia, Denmark, Estonia, Finland, France, Hungary, Italy, Luxembourg, Russia, Slovenia and Sweden). In these countries the outpatient use ranged from 9.7% (Italy) to 98.3% (Sweden) of the total antiviral use. Antiviral use data were derived from reimbursement data in Austria, Belgium, Italy and Luxembourg and from distribution or sales data in the other countries (Table S2, available as Supplementary

Table 1. Classification of antivirals according to WHO ATC codes

Thiosemicarbazones
J05AA01 metisazone[a]
Nucleosides and nucleotides excl. reverse transcriptase inhibitors
J05AB01 aciclovir
J05AB02 idoxuridine[a]
J05AB03 vidarabine[a]
J05AB04 ribavirin
J05AB06 ganciclovir
J05AB09 famciclovir
J05AB11 valaciclovir
J05AB12 cidofovir
J05AB13 penciclovir[a]
J05AB14 valganciclovir
J05AB15 brivudine
Cyclic amines
J05AC02 rimantadine
J05AC03 tromantadine[a]
Phosphonic acid derivatives
J05AD01 foscarnet
J05AD02 fosfonet[a]
Protease inhibitors
J05AE01 saquinavir
J05AE02 indinavir
J05AE03 ritonavir
J05AE04 nelfinavir
J05AE05 amprenavir
J05AE06 lopinavir
J05AE07 fosamprenavir
J05AE08 atazanavir
J05AE09 tipranavir
J05AE10 darunavir
Nucleoside and nucleotide reverse transcriptase inhibitors
J05AF01 zidovudine
J05AF02 didanosine
J05AF03 zalcitabine
J05AF04 stavudine
J05AF05 lamivudine
J05AF06 abacavir
J05AF07 tenofovir disoproxil
J05AF08 adefovir dipivoxil
J05AF09 emtricitabine
J05AF10 entecavir
J05AF11 telbivudine
J05AF12 clevudine[a]
Non-nucleoside reverse transcriptase inhibitors
J05AG01 nevirapine
J05AG02 delavirdine[a]
J05AG03 efavirenz
J05AG04 etravirine
Neuraminidase inhibitors
J05AH01 zanamivir
J05AH02 oseltamivir

Continued

Table 1. *Continued*

Antivirals for treatment of HIV infections, combinations
J05AR01 zidovudine and lamivudine
J05AR02 lamivudine and abacavir
J05AR03 tenofovir disoproxil and emtricitabine
J05AR04 zidovudine, lamivudine and abacavir
J05AR05 zidovudine, lamivudine and nevirapine[a]
J05AR06 emtricitabine, tenofovir disoproxil and efavirenz
Other antivirals
J05AX01 moroxydine[a]
J05AX02 lysozyme[a]
J05AX05 inosine pranobex
J05AX06 pleconaril[a]
J05AX07 enfuvirtide
J05AX08 raltegravir
J05AX09 maraviroc

Bold font means that the use represented more than 1% of the total outpatient antiviral use in Europe in 2008.
[a]No use of this antiviral in Europe was reported in 2008.

data at *JAC* Online). Belgium was not able to provide total J05 data for 2008, therefore the total J05 data for 2007 are presented.

Four countries (Austria, the Netherlands, Norway and Portugal) could only provide outpatient data. The use of these countries is presented separately in tables and figures, as well as in the text, if relevant. Nevertheless, the antiviral use pattern of Austria, the Netherlands and Norway is similar to the countries providing total use data. In contrast, in Portugal, no use was reported of ribavirin, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, neuraminidase inhibitors, antiviral combinations for treatment of HIV infections and other antivirals.

For only 20 of the 57 substances assigned an ATC code, the use in 2008 represented more than 1% of the total antiviral use, while no use was recorded for 12 substances, including 2 substances with an estimated theoretical daily dose (Table 1).

Table 2 shows total systemic antiviral use in 2008 expressed in DID according to the fourth level of chemical subgroup (ATC 4-level), ranging from the country with the highest to the lowest systemic antiviral use. Total systemic antiviral use varied by a factor of 10.95 between the country with the highest (3.53 DID in France) and lowest (0.32 DID in Croatia) use. Outpatient use only was highest in the Netherlands (1.62 DID), among the countries reporting only outpatient use, and even higher than most countries reporting total use.

Figure 1(a) shows the total systemic antiviral use in 2008 grouped into categories and Figure 1(b) shows the proportional use.

Total use of 'HIV/AIDS antivirals' represented 60.13% of the total antiviral use and varied by a factor of 162.11 between the country with the highest (2.43 DID in France) and the country with the lowest (0.02 DID in Russia) use. In all countries these substances represented more than 50% except in Finland (49.45%), Slovenia (40.49%), Hungary (14.58%) and Russia (2.55%).

Total use of 'HIV/hepatitis B antivirals' (lamivudine, tenofovir and emtricitabine) represented 12.39% of the total antiviral use and varied by a factor of 136.81 between the country with

Table 2. Total systemic antiviral use in 16 European countries in 2008; use according to the fourth level of chemical subgroup (ATC 4-level) in DDD per 1000 inhabitants per day

Country	J05AB	J05AC	J05AD	J05AE	J05AF	J05AG	J05AH	J05AR	J05AX	Grand total
France	0.67	—	0.00	0.83	0.60	0.45	0.02	0.96	0.00	3.53
Italy	0.47	—	0.00	0.53	0.60	0.29	0.00	1.19	0.03	3.11
Luxembourg	0.35	—	0.00	0.32	0.62	0.27	0.00	0.39	0.01	1.95
Denmark	0.38	—	—	0.25	0.14	0.32	0.01	0.50	0.01	1.61
Belgium[a]	0.11	—	0.00	0.24	0.51	0.23	—	0.24	0.01	1.33
Estonia	0.20	0.00	—	0.04	0.45	0.28	0.00	0.29	—	1.27
Sweden	0.37	—	0.00	0.21	0.14	0.13	0.00	0.31	0.01	1.18
Finland	0.29	—	—	0.07	0.08	0.09	0.03	0.17	0.01	0.73
Russia	0.12	0.41	—	0.00	0.01	0.00	0.00	0.01	0.03	0.59
Slovenia	0.21	—	0.00	0.06	0.06	0.03	0.00	0.08	0.00	0.44
Hungary	0.19	—	0.00	0.02	0.04	0.02	0.00	0.02	0.14	0.43
Croatia	0.07	—	—	0.04	0.10	0.06	0.00	0.04	—	0.32
Netherlands[b]	0.20	—	0.00	0.24	0.38	0.35	0.00	0.44	0.01	1.62
Austria[b]	0.48	—	—	0.17	0.22	0.11	0.03	0.22	0.01	1.25
Norway[b]	0.19	—	0.00	0.20	0.09	0.12	0.00	0.29	0.01	0.90
Portugal[b]	0.17	—	—	—	0.01	—	—	—	—	0.18

J05AB, nucleosides and nucleotides excluding reverse transcriptase inhibitors; J05AC, cyclic amines; J05AD, phosphonic acid derivatives; J05AE, protease inhibitors; J05AF, nucleoside and nucleotide reverse transcriptase inhibitors; J05AG, non-nucleoside reverse transcriptase inhibitors; J05AH, neuraminidase inhibitors; J05AR, antiviral combinations for the treatment of HIV infections; J05AX, other antivirals; —, no use reported.
[a]2007 use for Belgium.
[b]Outpatient use only for Austria, the Netherlands, Norway and Portugal.

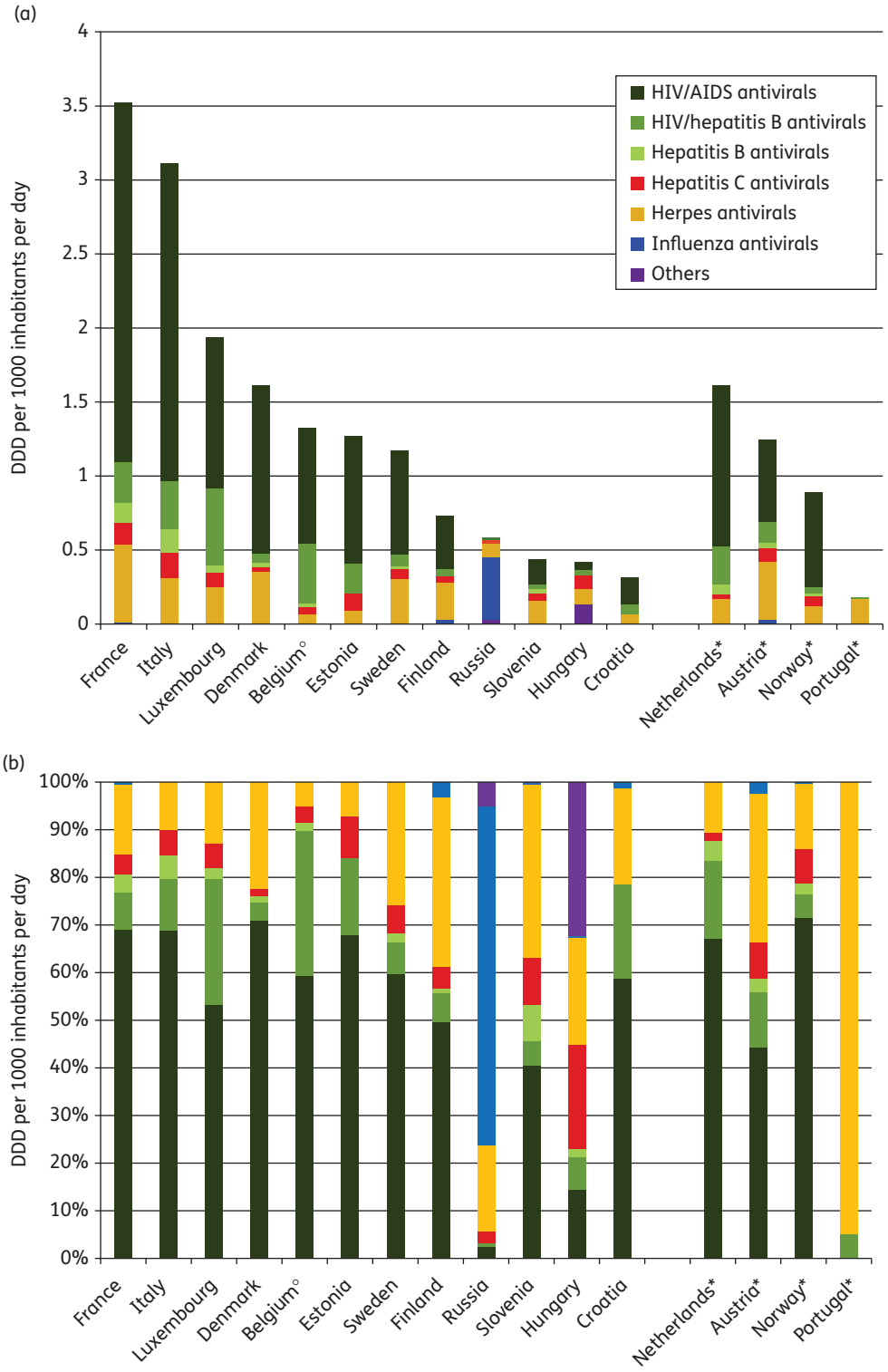

Figure 1. Systemic antiviral use in 16 European countries in 2008; use of the different substances grouped into categories (a) in DDD per 1000 inhabitants per day and (b) as a percentage of the total use. HIV/AIDS antivirals=ATC J05AE, J05AF01–04, J05AF06, J05AG, J05AR and J05AX07–09; HIV/hepatitis B antivirals=ATC J05AF05, J05AF07 and J05AF09; Hepatitis B antivirals=ATC J05AF08 and AF10–12; Hepatitis C antivirals=ATC J05AB04; Herpes antivirals=ATC J05AC03, J05AD01 and J05AB except J05AB04; Influenza antivirals=ATC J05AC02 and J05AH; Others=ATC J05AA, J05AD02, J05AX01, J05AX02, J05AX05 and J05AX06. °2007 use for Belgium. *Outpatient use only for Austria, the Netherlands, Norway and Portugal.

the highest (0.52 DID in Luxembourg) and the country with the lowest (0.004 DID in Russia) use.

Based on total data for 10 countries (no data available for Italy and Russia), a significant correlation was found between use in DDD of antiviral substances used for the treatment of HIV/AIDS and the estimated number of HIV/AIDS patients in each country (Figure 2a; Spearman $\rho=0.96$, $P<0.001$). Excluding France and 'HIV/hepatitis B antivirals' from this analysis did not change the outcome of results (Spearman $\rho=0.95$, $P<0.001$ and Spearman $\rho=0.96$, $P<0.001$, respectively). Including data for the Netherlands and Norway (no data are available for Austria) gave similar results (Spearman $\rho=0.97$, $P<0.001$).

Within the total of antiviral substances used for the treatment of HIV/AIDS, total protease inhibitors (ATC group J05AE) use represented 21.72% and varied by a factor of 454.03 between the country with the highest (0.83 DID in France) and the country with the lowest (0.001 DID in Russia) use (Figure 2b and c). Russia and Estonia show a relatively low use of protease inhibitors. Total nucleoside and nucleotide reverse transcriptase inhibitors (ATC group J05AF excluding adefovir, entecavir, telbivudine and clevudine) use represented 24.61% and varied by a factor of 85.20 between the country with the highest (0.57 DID in Luxembourg) and the country with the lowest (0.007 DID in Russia) use. Total non-nucleoside reverse transcriptase inhibitors (ATC group J05AG) use represented 18.15% and varied by a factor of 90.59 between the country with the highest (0.45 DID in France) and the country with the lowest (0.005 DID in Russia) use. Overall, the second highest use was reported in the Netherlands (outpatient use only) (0.35 DID). Total antiviral combinations for the treatment of HIV infections (ATC group J05AR) in 2008 represented 34.81% and varied by a factor of 227.00 between the country with the highest (1.19 DID in Italy) and the country with the lowest (0.005 DID in Russia) use. Enfuvirtide, raltegravir and maraviroc (ATC J05AX07–09, respectively) represented 0.71% and varied by a factor of 2311.11 between the country with the highest (0.02 DID in Italy) and the country with the lowest (0.00001 DID in Russia) use. No use was reported in Croatia and Estonia.

Total use of 'Hepatitis B antivirals' (i.e. adefovir, entecavir and telbivudine; no use reported for clevudine) in 2008 represented 2.68% of the total antiviral use and varied by a factor of 126.19 between the country with the highest (0.15 DID in Italy) and the country with the lowest (0.001 DID in Russia) use. No use was reported in Croatia.

Total use of 'Hepatitis C antivirals' (i.e. ribavirin) represented 5.10% of the total antiviral use and varied by a factor of 12.63. The use of ribavirin was highest in Italy (0.17 DID) and lowest in Russia (0.01 DID). No use was reported in Croatia (Figure S1, available as Supplementary data at *JAC* Online).

Total use of 'Herpes antivirals' in 2008 represented 15.72% of the total antiviral use and varied by a factor of 7.99 between the country with the highest (0.52 DID in France) and the country with the lowest (0.07 DID in Croatia) use. The proportional use of the substances used for the treatment of herpes infections is shown in Figure S2 (available as Supplementary data at *JAC* Online). Aciclovir and valaciclovir were the most commonly used anti-herpetic drugs in all countries. Brivudine was used considerably in Luxembourg (18.47%), Slovenia (18.02%) and Italy (9.89%). The use of ganciclovir and valganciclovir was lower, ranging from 14.78% in Croatia to 0.25% in Russia.

Total use of 'Influenza antivirals' in 2008 represented 2.91% of the total antiviral use and varied by a factor of 1255.48 between the country with the highest (0.42 DID in Russia) and the country with the lowest (0.0003 DID in Luxembourg) use. Rimantadine represented 86.57% of the use within this category, but is only reported in two countries; Russia (0.41 DID) and Estonia (0.0002 DID). Total neuraminidase inhibitor use represented 13.43% and varied by a factor of 76.44 between the country with the highest (0.025 DID in Finland) and the country with the lowest (0.0003 DID in Luxembourg) use (Figure S3, available as Supplementary data at *JAC* Online). No neuraminidase inhibitor use was reported in Belgium, and overall the highest use was reported in Austria (outpatient use only; 0.033 DID).

The category 'Others' represented 1.07% of the total antiviral use and varied by a factor of 868.77 between the country with the highest (0.14 DID in Hungary) and the country with the lowest (0.0001 DID in Luxembourg) use. Inosine pranobex, mainly used in Hungary, represented 99.16% of the use within this category. No use was reported in Croatia, Denmark, Estonia, Finland, France, Slovenia and Sweden.

Discussion

We observed a striking variation of total systemic antiviral use in Europe. The variation factor between the country with the highest and lowest total antiviral use was more than twice that for systemic outpatient antibiotic use and 1.6 times that for systemic outpatient antimycotic and antifungal use.[5,6]

While for antibiotics, antimycotics and antifungals outpatient use represents at least 90% of the total use, for outpatient antiviral use the proportion ranges from 9.71% in Italy to 98.33% in Sweden. Therefore, we presented total antiviral use in the 12 countries under study separately from outpatient use in Austria, the Netherlands, Norway and Portugal.

The outpatient use pattern of Austria, the Netherlands and Norway is similar compared with the total use patterns, while for Portugal the pattern is completely different. This is probably explained by the exclusive distribution of substances for the treatment of chronic viral-infected patients (like AIDS, HIV and hepatitis B) by hospital pharmacies in Portugal, while for Austria, the Netherlands and Norway these substances are also distributed by public pharmacies.

We used an estimated theoretical daily dose for four substances without an official WHO DDD to allow a valid and comparable measurement of their use in Europe. These substances represented less than 5% of the total antiviral use. Regarding the ATC/DDD methodology, it also has to be taken into account that countries using combination products will have a lower absolute DID than countries using a combination of single substances, e.g. 1 DDD of J05AR02 (DDD=1 tablet containing 600 mg of abacavir and 300 mg of lamivudine) equals 2 DDD of the single substances abacavir (DDD=600 mg) and lamivudine (DDD=300 mg).

It is not clear whether large differences in antiviral use among European countries can be explained by similar determinants as for antibiotic, antimycotic and antifungal use (e.g. social-cultural differences, differences in education, healthcare organization, resources and utilization, pharmaceutical market

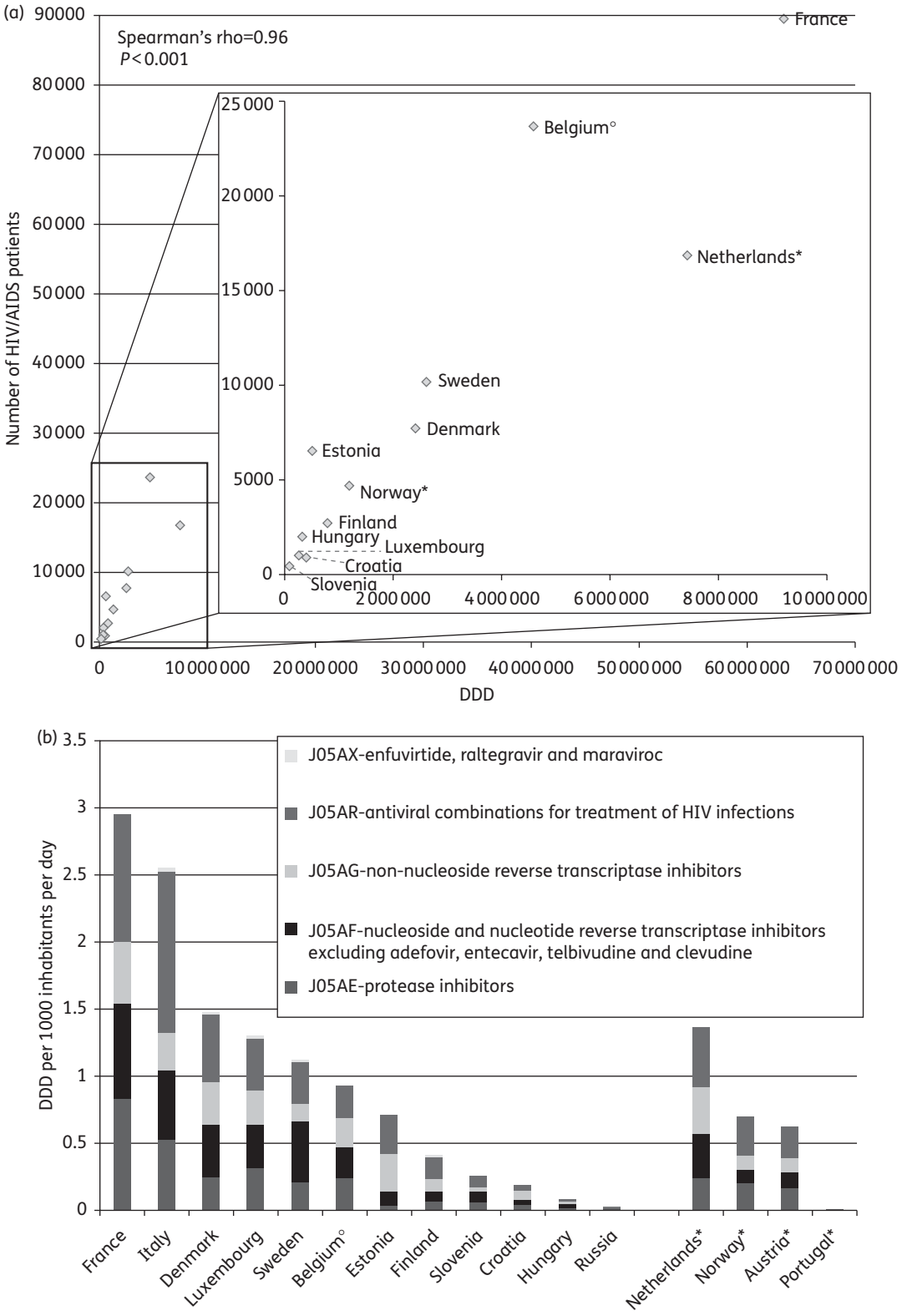

Figure 2. Systemic antiviral use of antiviral classes used for the treatment of HIV/AIDS in 16 European countries in 2008. (a) Correlation between use in DDD (excluding Portugal) on the *x*-axis and estimated number of HIV/AIDS patients in 2007 on the *y*-axis (no data available for Italy, Russia and Austria). Use in (b) DDD per 1000 inhabitants per day and (c) as a percentage of the total use of antivirals used for the treatment of HIV/AIDS. °2007 use for Belgium. *Outpatient use only for Austria, the Netherlands, Norway and Portugal.

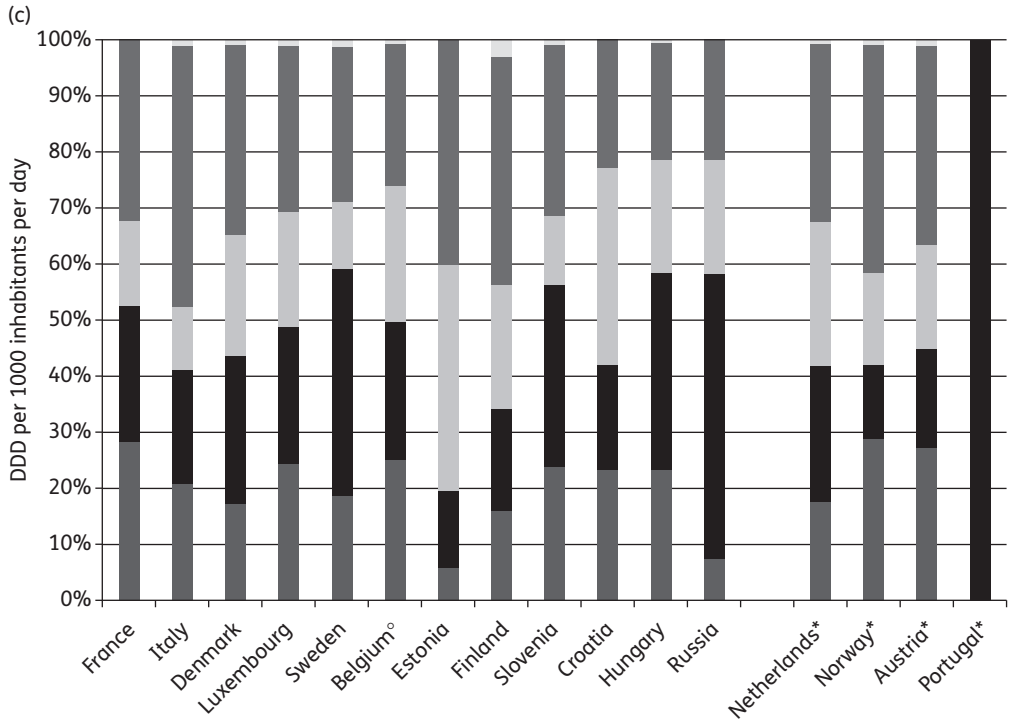

Figure 2. (Continued).

and regulatory practices, and knowledge on antimicrobials). For example, the Netherlands ranks among the lowest for per capita use of antibiotics, but also (with outpatient data only) has among the highest antiviral consumption. For a better understanding of this and other observations, grouping the antiviral substances into categories according to their main indication allowed a more clinically relevant description of their use. In most countries, substances used in HIV/AIDS treatment represented more than 50% of the total use, and therefore their use will strongly determine the variation between countries. The strong correlation between their use in DDD and the total number of HIV/AIDS patients (Figure 2a) suggests that these substances are indeed mainly used for HIV/AIDS treatment, that most registered HIV/AIDS patients will receive treatment and that the ESAC use data are valid. The number of HIV/AIDS patients actually treated will determine antiviral consumption. This consumption may vary considerably, as the population of HIV/AIDS patients typically consists of minority groups or even suppressed subcultures (e.g. drug users, homosexuals and immigrants). The Netherlands, among some other countries, has been trying to organize the care for these groups by an efficient nationwide programme that is fully reimbursed and rather successful, leading to higher consumption of antivirals.[15] Moreover, most antiviral substances to treat HIV-positive patients are used for several years, even decades, whereas antibiotics, antimycotics and antifungals are mainly used to treat incidental infections. In addition, with the increased prevalence of HIV infections and decreased mortality, we can expect a yearly increase in antiviral consumption.

However, despite international recommendations on antiretroviral therapy for HIV infection by the WHO,[16] differences in the relative use of antiviral classes can be observed. Differences in national guidelines for HIV/AIDS treatment and compliance with these guidelines may partially explain this variation, together with differences in reimbursement systems of antiviral classes between countries.

Surveillance data on the prevalence of hepatitis B and C are difficult to compare across countries due to differences in system structures, reporting practices, data collection methods and case definitions.[17–19] Moreover, for hepatitis B, the ESAC use data without links to indication do not allow for the assessment of use for hepatitis B without bias of the 'HIV/hepatitis B antivirals', which represent the major part in most countries in comparison with the 'Hepatitis B antivirals'.

Hepatitis C, however, is nearly universally treated with (peg)interferon in combination with ribavirin (J05AB04) for 6 months to 1 year.[20] This treatment is also applied in Croatia, but ribavirin is obtained through donation by pharmaceutical companies selling (peg)interferon, and therefore ribavirin use is not registered in the Croatian wholesale data. Monitoring ribavirin use could serve as an indicator of the prevalence of hepatitis C and help validate surveillance data. Alternatively, differences in compliance with recommended treatment strategies could be identified.

The intercountry variation in anti-herpetic substances is smaller compared with the other categories, but still considerable (factor 7.99). These substances are mainly used for the treatment or suppression of herpes simplex and herpes zoster infection and their variation can be explained by differences between national treatment guidelines, different reimbursement systems and drug cost. The use of ganciclovir and valganciclovir, indicated to treat cytomegalovirus, is less common, clearly

related to the limitation of treatment to immunocompromised patients.

For the prevention and/or treatment of influenza, Russia is the only country that reports extensive use of cyclic amines. Amantadine (ATC N04BB01), a cyclic amine originally developed for the treatment of early influenza A viral infection, is not included in the ESAC data. Amantadine is currently used in the treatment of Parkinson's disease and drug-induced extrapyramidal reactions, as well as off-label use in combating the fatigue associated with multiple sclerosis. Amantadine is no longer recommended for the treatment or prevention of influenza, but it might still be used for this indication. For example, in Norway, amantadine is only reimbursed for chronic infections. However, less than half of the sold DDDs were reimbursed, suggesting amantadine is used for other indications, such as influenza. Data linking prescriptions with indication are necessary to reveal actual use. In the meantime, we suggest including amantadine in the antiviral database. The use of neuraminidase inhibitors is not particularly widespread, representing 4.5% in Finland to 0.02% in Luxembourg. In Belgium and Portugal, oseltamivir and zanamivir are not reimbursed, and for that reason they are not included in the data. Quarterly data covering several years rather than calendar years will be helpful in interpreting the use of antivirals for the prevention and/or treatment of influenza.

During the outbreak of the A/H1N1 pandemic in 2009, stockpiles of neuraminidase inhibitors, primarily oseltamivir, were used to provide primary healthcare professionals with neuraminidase inhibitors for distribution without prescription in Belgium. Several European countries also had a stock of oseltamivir already purchased, e.g. in 2005 during the avian flu pandemic.[21,22] Stockpiling and distribution without prescription might represent an important obstacle to monitoring actual antiviral consumption. In countries providing reimbursement data (Austria, Belgium, Hungary, Italy and Luxembourg) and countries providing sales data from community pharmacists (the Netherlands and Sweden), the use of stockpiles and distribution without prescription by primary healthcare professionals are not monitored. In countries providing distribution data (Denmark, Finland, France, Norway and Slovenia), stockpiles can be monitored, but these do not necessarily reflect actual consumption.

We have shown that differences in outpatient antibiotic selection pressure account for geographical variation of antibiotic resistance in Europe.[3] However, antiviral resistance, except for HIV and hepatitis B virus, has only been reported in specific patient groups (e.g. in immunocompromised patients) and has not been reported to spread in the community.[7] HIV treatment may well induce resistance, but this is largely a problem in individual patients who receive suboptimal treatment regimens, although such resistance can also, to some extent, be transmitted. In addition, resistance sometimes appears to occur unrelated to antiviral consumption, as observed with the influenza drugs amantadine and oseltamivir (2007–08 H1N1).[23–26]

In conclusion, the ESAC project represents the first set of publicly available standardized and validated supranational data on systemic antiviral use in Europe. The variation is mainly determined by the use of HIV/AIDS antivirals. These observations should stimulate further analysis of the variation of specific antiviral substances. ESAC data will facilitate auditing of antiviral prescribing and evaluation of the implementation of guidelines and public health policies.

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Transparency declarations

None to declare.

Disclaimer

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Supplementary data

Tables S1 and S2 and Figures S1, S2 and S3 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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