

# Parenteral versus Oral Administration of Systemic Antimicrobials in European Nursing Homes

## A Point-Prevalence Survey

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### Abstract

**Background:** Residents in long-term care facilities are predisposed to healthcare-associated infections that are likely caused by antimicrobial-resistant microorganisms. Long-term care facilities are increasingly able to offer parenteral antimicrobial treatment but there are few data on the use and appropriateness of such treatment in this setting. Information on the use of parenteral antimicrobials and associated factors in long-term care facilities is necessary to assess the risks and benefits of this treatment and to support the development of antimicrobial policies aimed at minimizing the emergence and spread of antimicrobial resistance.

**Objective:** The aim of this study was to describe the extent of parenteral and oral antimicrobial use in participating European nursing homes (NHs) and to analyse the resident characteristics and determinants associated with route of antimicrobial administration.

**Methods:** Data on resident characteristics and antimicrobials were collected by means of a point-prevalence survey. Logistic regression was used to analyse the data.

**Results:** Based on data from 21 European countries for 2046 antimicrobial prescriptions, an average of 9.0% (range by country: 0.0–66.7%) of treatment was administered parenterally. Multivariate analysis showed that residents receiving parenteral antimicrobials had greater morbidity, such as increased risk of having a urinary catheter ( $p < 0.001$ ), a vascular catheter ( $p < 0.001$ ), impaired mobility ( $p = 0.007$ ) and disorientation ( $p = 0.005$ ). Residents receiving parenteral antimicrobials also had been admitted more recently into the NH ( $p = 0.007$ ). Empirical treatment of respiratory tract infections (RTIs)

accounted for the majority of parenteral antimicrobials, while prophylaxis of urinary tract infection (UTI) was the most common indication for oral antimicrobials. Beta-lactam antibacterials (cephalosporins and aminopenicillins) were the predominant classes used.

**Conclusions:** Our study showed that risk and care-load factors (i.e. the presence of a urinary or vascular catheter, impaired mobility, disorientation and relatively short length of stay) were associated with parenteral administration of antimicrobials in NHs. Furthermore, both the indication and the class of antimicrobial agent used were associated with administration route. For empirical treatment of RTIs, antimicrobials were most often administered parenterally.

## Introduction

Residents in long-term care facilities have predisposing risks for healthcare-associated infections that are likely caused by antimicrobial-resistant micro-organisms.<sup>[1,2]</sup> As well as being given treatment for acute infections, these residents often receive antimicrobials for chronic infection or as prophylaxis. Long-term care facilities are increasingly able to offer parenteral antimicrobial treatments. The use of certain antimicrobial classes can increase the antimicrobial resistance selection pressure.<sup>[1,2]</sup> Any indwelling device is associated with increased risk of infection secondary to colonization with resistant organisms.<sup>[3]</sup> Also, the route of administration, e.g. through a vascular catheter, can increase the propensity for infections.<sup>[1,4]</sup> In contrast, outpatient parenteral antibacterial treatment (i.e. at home) is considered to be safe and effective in older patients, despite a slightly higher incidence of phlebitis at the catheter site.<sup>[5]</sup> Limited data are available on the use of parenteral antimicrobials in long-term care facilities.<sup>[6]</sup> Moreover, the appropriateness of (parenteral) antimicrobial use in long-term care facilities is not yet well studied.<sup>[7]</sup>

The use of parenteral antimicrobials and associated factors in long-term care facilities need to be understood in order to be able to evaluate the risks and benefits of parenteral antimicrobial treatment in these facilities. In turn, this information can support the development of antimicrobial policies for minimizing the emergence and spread of antimicrobial resistance in the future.

The aim of this study was to describe for the first time patterns of parenteral and oral antimicrobial use in participating nursing homes (NHs) in Europe. Furthermore, we analysed resident characteristics relating to and possible determinants of the route of antimicrobial administration in this setting.

## Methods

The aim of the European Surveillance of Antimicrobial Consumption (ESAC) project<sup>[8]</sup> was to measure antimicrobial consumption in varying healthcare settings, including NHs. A first point-prevalence survey of the NH subproject was performed in April 2009. 'Highly skilled NHs', selected by national representatives of the participating European countries, participated voluntarily in the project. For the purpose of the project, 'highly skilled NHs' were defined as institutions with residents who needed continual supervision and highly skilled nursing care but who did not need invasive medical procedures or constant specialized medical care. The survey had to be performed on a single day that was convenient for the NH staff between 1 and 30 April 2009.

Data were collected either by an internal (NH employee) or external researcher. In some countries, a single researcher (in some cases, the national representative) at the facility collected the data, while in other countries, one external researcher collected data for all participating NHs. Data collectors received a user guide to support

data collection. The researcher categorized the type of infection on the basis of input from nurses, physicians or chart information, or knowledge of the condition of the resident. When data were not collected by a physician, validation of the data was required before submission. Data were transferred by means of optical readable forms or web-based entry (via the ESAC website: <http://www.esac.ua.ac.be>). Every participating NH completed an institutional questionnaire that contained questions on general NH characteristics and denominator data for all eligible residents relating to specific patient characteristics (e.g. the number of residents with wounds or impaired mobility). Eligible residents were those present at 8.00am on the day and admitted for at least 24 hours. Questions on medical care and co-ordination, infection control practices, and antimicrobial consumption were also included. In addition, a resident questionnaire had to be completed for each resident using antimicrobials on the day of the point-prevalence survey. This questionnaire included questions on resident characteristics (e.g. sex, age, use of a urinary catheter, presence of a wound, presence of urinary and/or faecal incontinence) and the antimicrobial treatment (e.g. generic name, indication, administration route). Data were collected according to the Anatomical Therapeutic Chemical (ATC) classification system for anti-infectives for systemic use (antibacterials, antifungals, anti-tuberculous agents) and for nasal mupirocin.<sup>[9]</sup> Antivirals and other topical antimicrobials were not included.

The 'parenteral' route of administration was defined as either intravenous or intramuscular administration. Treatment intent was categorized by the researcher based on specific definitions. When an antimicrobial was prescribed to prevent infections or infectious complications, the indication was classified as 'prophylaxis'. 'Empirical treatment' was defined as antimicrobial use for treatment of infection without documented microbiological results. When microbiology results were available and the pathogen was susceptible to the antimicrobial prescribed, this was classified as a 'documented treatment'.

Analysis of characteristics was performed at the resident level in order to compare the re-

sidents using oral antimicrobials with those using parenteral antimicrobials. Residents for whom at least one variable (e.g. age, hospital admission in the past 3 months, use of a urinary catheter) was missing and residents using only nasal mupirocin were excluded from the analysis. Residents receiving both oral and parenteral treatment were included in the group of parenteral antimicrobial users, this being the more invasive administration route.

Analysis of characteristics (i.e. indication and antimicrobial name) at the drug level for oral and parenteral therapy was performed by analysing all prescribed antimicrobial agents. For residents receiving more than one drug, the characteristics of all treatments were included. Importantly, treatments were excluded for analysis when one or more values were missing. Univariate analysis of resident characteristics was performed to determine any association between single variables (e.g. sex, use of a urinary catheter) and administration route. Age was dichotomized using the median as the separating value. Wheelchair use and being bedridden were analysed together as 'impaired mobility', using mobility as another dichotomous variable in this analysis. In addition, in order to investigate the role of mobility in more depth, the mobility variable was dichotomized in an alternative manner; first, wheelchair use versus the other two categories of mobility, and second, being bedridden versus the other two remaining categories. Next, all resident characteristics were analysed using a multivariable logistic regression and stepwise backward analysis to identify independent factors related to one specific route of administration. A p-value of <0.05 was considered statistically significant. For the calculation of odds ratios, country was added as a separate variable in each model to adjust for any potential cluster effect. All analyses were performed using Stata 10.1 (Stata Corp, College Station, TX, USA).

## Results

Data were available for 323 NHs and 31 691 residents from 21 European countries (Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania,

Malta, the Netherlands, Norway, Poland, Russian Federation, Slovenia, Sweden and three UK administrations: England, Northern Ireland and Scotland). A total of 1966 residents were prescribed a total of 2046 antimicrobials on the day of the point-prevalence survey. The mean overall prevalence of antimicrobial use was 6.5%.<sup>[10]</sup> Overall, parenteral antimicrobials accounted for 9.0% (n=183) of treatments whilst oral drugs accounted for 90.2% (n=1844) and nasal treatment 0.9% (n=18) [data for one resident were not available]. These proportions differed considerably between (range by country: 0.0–66.7%) [figure 1] and within countries. Indeed, in nine of the 21 participating countries, only oral antimicrobials were used. When countries without parenteral antimicrobial use and Latvia (in which only two parenteral treatments were observed) were excluded, the range between countries was 0.8–55.1%.

#### Resident Characteristics

At the resident level, an analysis was performed on the data for 1773 individuals. Ten residents

received oral and parenteral antimicrobials simultaneously. The results of the univariate logistic regression showed that sex and length of NH stay were significantly associated with the antimicrobial administration route (oral or parenteral) [table I]. Residents with a urinary catheter, vascular catheter and/or a wound had higher percentages of use of parenteral antimicrobials than of oral agents. Parenteral administration was also significantly associated with the risk factors disorientation and/or impaired mobility. Further analysis of the role of mobility revealed that the proportion of wheelchair-dependent residents was only slightly higher among users of parenteral antimicrobials compared with those taking oral agents (45.0% vs 41.7%,  $p=0.4$ ). In contrast, the proportion of bedridden residents was significantly higher among those taking parenteral antimicrobials compared with those taking oral antimicrobials (36.1% vs 15.8%,  $p<0.001$ ). When the univariate analysis clustered by country was compared with the crude univariate analysis, the only significant difference was for hospital admission in the past 3 months (crude  $p=0.03$  vs cluster-adjusted  $p=0.14$ ). Stepwise backward multivariate logistic regression of

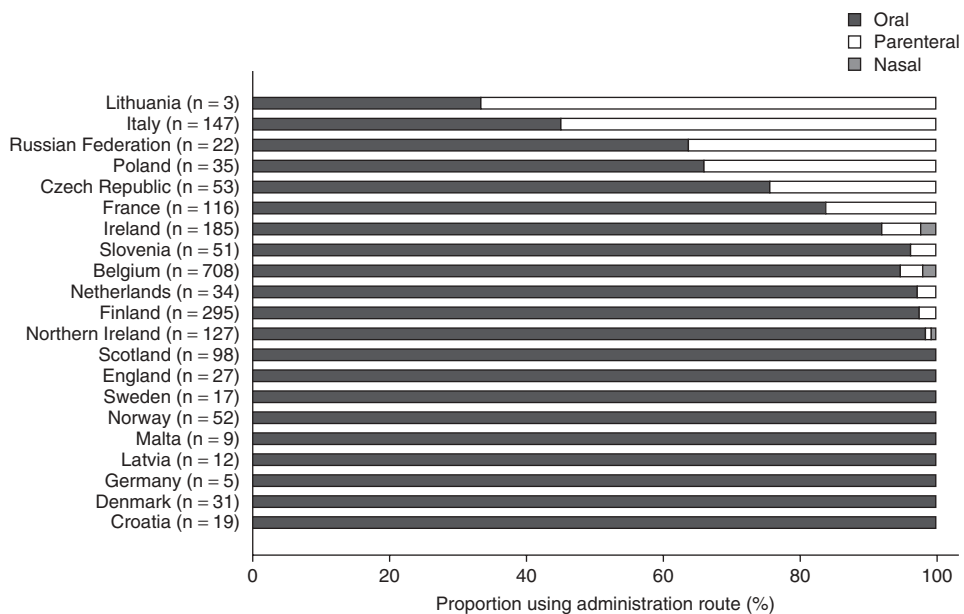


Fig. 1. Frequency of use of antimicrobial administration route in nursing homes by country.

**Table I.** Characteristics of residents receiving oral and parenteral antimicrobial treatments in European nursing homes (NHs)<sup>a</sup>

Variable	Route of administration (%) <sup>b</sup>		Univariate analysis			Cluster-adjusted stepwise backward multivariate analysis (country as cluster)		
	oral (n = 1604)	parenteral (n = 169)	OR	95% CI	p-value	OR	95% CI	p-value
Age (y, median)	85	84	0.85	0.61, 1.17	0.31	–	–	–
Male	26.9	40.2	1.83	1.32, 2.53	<0.001	–	–	–
NH stay <1 year	29.7	44.4	1.89	1.37, 2.60	<0.001	1.48	1.11, 1.98	0.007
Hospital admission (past 3 months)	21.8	29.0	1.47	1.03, 2.09	0.03	–	–	–
Urinary catheter	13.0	37.9	4.09	2.90, 5.77	<0.001	2.16	1.50, 3.10	<0.001
Vascular catheter	1.8	20.7	14.70	8.68, 24.91	<0.001	7.77	3.24, 18.63	<0.001
Wound	21.6	39.1	2.32	1.67, 3.23	<0.001	–	–	–
Urinary and/or faecal incontinence	74.9	79.3	1.28	0.87, 1.89	0.21	–	–	–
Disorientation	61.5	73.4	1.73	1.21, 2.46	0.003	1.53	1.14, 2.05	0.005
Impaired mobility	57.5	81.1	3.16	2.12, 4.70	<0.001	2.15	1.23, 3.73	0.007

a Coding scheme: oral=0; parenteral=1; age: ≤ median=0; ≥ median=1; all remaining variables: no=0; yes=1.

b Values are percentage of study population unless otherwise stated.

OR=odds ratio; – indicates exclusion of non-significant variables during stepwise backward analysis.

resident characteristics showed that the presence of a urinary catheter and/or a vascular catheter and impaired mobility were significantly associated with route of administration. Including country as a cluster in the model resulted in length of NH stay and disorientation also being significant variables in addition to the variables identified using the model with country excluded (table I).

### Treatment Characteristics

Analysis of treatment characteristics was performed on the data for a total of 1959 antimicrobial prescriptions. Empirical treatments comprised the majority of both oral and parenteral administrations. However, the proportion of treatments used for prophylaxis was much greater for oral treatments than for parenteral treatments. Culture samples were taken more often for oral treatments. The majority of parenterally administered antimicrobials were used to treat respiratory tract infections (RTIs), whereas the majority of oral treatments were utilized for urinary tract infections (UTIs).

The majority of parenteral treatments consisted of ATC code J01D 'Other beta-lactam antibacterials', of which most were cephalosporins

(tables II and III). In addition, the percentage of 'other β-lactam antibacterials' used was much higher for parenteral than for oral administration. The largest proportion of orally administered compounds consisted of antimicrobials from the ATC code J01C 'Beta-lactam antibacterials, penicillins' category. The proportion of penicillin β-lactam antibacterials was also relatively high for parenteral antimicrobials but smaller than that for oral antimicrobials. In the univariate analysis, the proportions of J01M 'Quinolone antibacterials' and J01X 'Other antibacterials' (i.e. not included in any other categories) were significantly higher in the orally administered drugs than in the parenterally administered drugs. The difference in the proportions of J01F 'Macrolides, lincosamides and streptogramins' between the oral and parenterally administered drugs was not significant. J01G 'Aminoglycosides' were prescribed for parenteral use only, while J01E 'Sulfonamides and trimethoprim' and J01A 'Tetracyclines' were administered orally only. The treatment characteristics of parenteral and oral antimicrobial administrations in European NHs are shown in table II.

The five most frequently orally prescribed agents overall were amoxicillin and enzyme inhibitor (14.8%), nitrofurantoin (10.7%), amoxicillin (8.6%),

**Table II.** Treatment characteristics of parenteral and oral antimicrobial administrations in European nursing homes

Variable	Route of administration (%)	
	oral (n = 1784)	parenteral (n = 175)
Prophylaxis	30.9	5.1
Empirical treatment	52.9	77.1
Documented treatment	16.2	17.7
Urinary tract infection	52.5	21.7
Respiratory tract infection	29.8	58.3
Surgical site infection	3.3	5.1
Unspecified infection	4.3	6.9
Other infection	8.5	5.1
Bloodstream infection	0.5	2.3
Gastrointestinal infection	1.2	0.6
Culture sample	30.5	21.1
<b>ATC code</b>		
J01A: Tetracyclines	2.9	0
J01C: Beta-lactam antibacterials, penicillins	28.6	22.9
J01D: Other beta-lactam antibacterials	7.0	53.7
J01E: Sulfonamides and trimethoprim	11.4	0
J01F: Macrolides, lincosamides and streptogramins	4.6	4.0
J01G: Aminoglycosides	0	13.7
J01M: Quinolone antibacterials	14.6	3.4
J01X: Other antibacterials	26.8	2.3
Other ATC classes than J01	4.2	0

**ATC** = Anatomical Therapeutic Chemical classification (see table III).

methenamine (8.0%) and trimethoprim (7.9%). In contrast, in Finland and Norway, methenamine (49.3%) and pivmecillinam (30.3%) were the most frequently prescribed agents for oral use. Among antimicrobials for parenteral use, the three most frequently administered antimicrobials were ceftriaxone (39.4%), gentamicin (9.7%) and amoxicillin (6.9%).

## Discussion

In two studies performed in northern American NHs, the proportion of parenteral antimicrobials relative to total antimicrobials administered was 7%<sup>[1]</sup> and 11%.<sup>[11]</sup> This is comparable with our findings (9%). A Norwegian study reported a prevalence of only 1% for parenteral antimicrobials

among all antibacterial prescriptions in NHs.<sup>[6]</sup> Most studies have focused on specific infection types or patient groups, mainly residents suffering from lower RTIs. A cross-national analysis comparing the results of Dutch and American studies showed that parenteral antimicrobials were administered less often for lower RTIs in Dutch NHs than in US NHs (12.8% vs 32.6%).<sup>[12]</sup> In the Dutch study, most parenteral treatments were administered intramuscularly, whereas in the US, most parenteral treatments were given intravenously.<sup>[13]</sup> Another study in the US of NH residents with advanced dementia and pneumonia showed that 59.1% of the antimicrobial treatments were administered parentally: 27.4% intramuscularly and 31.7% intravenously.<sup>[14]</sup> In our study, subdividing parenteral administration in this way was not possible because of the design of the study. Moreover, since the number of parenteral treatments was small, making this distinction would not have been useful.

A wide difference in the proportion of parenteral antimicrobial use was observed among European countries. Several explanations can be given for these findings based on the literature. In primary healthcare, southern European countries traditionally prescribe newer antimicrobials more

**Table III.** Anatomical Therapeutic Chemical (ATC) classification codes of antimicrobials (source: WHO Collaborating Centre for Drug Statistics Methodology<sup>[9]</sup>)

Antimicrobial class/name	ATC code
Tetracyclines	J01A
Beta-lactam antibacterials, penicillins	J01C
amoxicillin	J01CA04
pivmecillinam	J01CA08
amoxicillin and enzyme inhibitor	J01CR02
Other beta-lactam antibacterials	J01D
ceftriaxone	J01DD04
Sulfonamides and trimethoprim	J01E
trimethoprim	J01EA01
Macrolides, lincosamides and streptogramins	J01F
Aminoglycoside antibacterials	J01G
gentamicin	J01GB03
Quinolone antibacterials	J01M
Other antibacterials	J01X
nitrofurantoin	J01XE01
methenamine	J01XX05

often than northern European countries.<sup>[15]</sup> In addition, not all countries or NHs might be equally able or allowed to administer parenteral antimicrobials.<sup>[2]</sup> Additionally, inappropriate use of oral compounds can promote the development of antimicrobial resistance against certain oral antimicrobials, leading to a mandatory use of parenteral alternatives.<sup>[2]</sup>

Furthermore, the case-mix of residents can vary between facilities and countries.<sup>[2,16]</sup> A study from the US showed a trend towards correlation of the incidence of antimicrobial use with the case-mix within an NH.<sup>[17]</sup> An NH with a high proportion of high-dependency residents might be inclined to use a higher proportion of parenteral antimicrobials. This highlights the relevance of taking case-mix into account when comparing the proportions of antimicrobials being used, particularly those administered parenterally. Additionally, comparable (in terms of health status) NH residents in different countries might receive treatments characterized by different degrees of aggressiveness.<sup>[12]</sup> Another study that compared antimicrobial use in the US and the Netherlands revealed international discrepancies in attitudes (based on the decision-making environment, societal norms, ethical standards and legal procedures) towards the use of parenteral administration.<sup>[18]</sup> Although this study compared data from the US with data from only one European country, it is likely that these variations in attitudes also apply to other European countries.<sup>[15]</sup>

It should be noted that dissimilarities in the proportions of parenteral antimicrobial use cannot be interpreted as being representative for a country since the number of participating NHs included in the study was small. Moreover, because of the convenience sampling design utilized in this pilot phase, selection of participants might not have been representative of (parenteral) antimicrobial use on a national level.

A study in the US showed that residents receiving parenteral antimicrobial treatments were on average younger and had a mean length of NH stay of less than 3 years.<sup>[14]</sup> Consistent with this finding, univariate analysis in our study showed that parenteral antimicrobials were sig-

nificantly more often prescribed in residents with a length of stay of less than 1 year than in those with a longer stay.

Our results showed that a higher percentage of residents receiving parenteral antimicrobials were disoriented with respect to time and/or space compared with residents who received oral antimicrobials. This could possibly be explained by the fact that such residents could be physically unable to take oral medication or might be less compliant because of their inability or unwillingness to swallow tablets.

The significant difference in impaired mobility between residents using oral and parenteral antibacterials can most likely be attributed to the residents who were bedridden. It is also likely that bedridden patients were frailer and had more comorbidities. Furthermore, these patients would have been prone to pressure sores, which often become infected.

Of all residents, 2.0% (35 of 1773) had a vascular catheter and received parenteral antimicrobial treatment. Of all residents with a vascular catheter, 55.5% (35 of 63) received parenteral antimicrobials. Of all residents receiving parenteral antimicrobials, 20.7% (35 of 169) had a vascular catheter. The different proportions of vascular catheter use between residents receiving oral treatment and those receiving parenteral treatment might have been due to the fact that the catheter could serve as an administration route for parenteral antimicrobials. However, parenteral administration in our study also included intramuscular injections. Furthermore, a Canadian and US study found no significant relationship between the percentage of residents with intravenous catheters and antimicrobial use in general in NHs.<sup>[19]</sup>

In general, residents receiving parenteral antimicrobials suffered from more severe conditions in comparison with residents receiving oral antimicrobials. Our data were unable to provide insight into the direction of this association.

Including country as a cluster in the multivariate analysis of resident characteristics resulted in an increase in the number of significant variables. When compared with the crude univariate analysis, the country cluster analysis found associations between parenteral administration and length of

NH stay and disorientation only. The first finding was likely due to a wide variation in length of stay (short-term vs long-term care) across countries, but both findings deserve further investigation.

Prophylactic antimicrobials were more likely than empirical antimicrobials to be administered only orally. Conversely, the proportion of empirical treatments was much higher for parenteral treatments than for oral treatments. However, a bias arising from smaller absolute numbers could result in proportional differences. The majority of oral antimicrobials were used for prophylaxis of UTIs, which was the most frequent indication in terms of absolute numbers ( $n=936$ ). In contrast, more than half of the parenteral antimicrobials administered were utilized for empirical treatment of RTIs, although this indication was much less frequent in terms of absolute numbers ( $n=102$ ). Two Scandinavian studies have confirmed that the majority of infections in NHs are UTIs.<sup>[20,21]</sup>

Parenteral prophylactic treatments might be chosen based on the general condition of the resident. Prophylaxis is intended as a non-aggressive therapy. Parenteral administration might cause more burden in the frail elderly, particularly when administration is performed through a vascular catheter, which is considered a risk factor for infection.<sup>[16]</sup> However, daily intramuscular administration is probably even less pleasant for the recipient, especially when it is repeated on a long-term basis.

The proportion of samples obtained for culture and sensitivity was inexplicably slightly higher among residents receiving oral treatment compared with those receiving parenteral treatment. This is remarkable since the decision to use a parenteral treatment should be a conscious choice based on clinical severity and preferably confirmed by microbiological diagnosis.

The differences between the proportions of ATC classes used could be attributed to the fact that some antimicrobial agents were only available either orally or parenterally in various countries. However, when both indication and the ATC class were considered, it transpired, from the results of our own study and those of others,<sup>[2,22]</sup> that different classes of antimicrobials were ad-

ministered either orally or parenterally for similar or identical indications without any obvious reason for selection of a particular route of administration.

A possible limitation of this analysis was the inclusion of residents receiving both oral and parenteral antimicrobials in the group of parenteral antimicrobial users. However, the number of residents receiving both routes of administration was too small for meaningful separate analysis. In order not to exclude these residents, they were categorized according to the most invasive therapy. A limitation of a point-prevalence survey is that data are known only for the day of measurement. The length of parenteral antimicrobial use is unknown. Also, switches from oral to parenteral treatment are not detected. Another limitation is that our data do not allow for thorough investigation of associations between resident or treatment characteristics and the route of administration; only the existence of an association could be indicated. Furthermore, obtaining data on several confounding factors, such as dosage forms, health insurance coverage decisions in different countries and physician practice patterns, was not an objective of this study.

Another constraint inherent in the study design is the difference in the amount of available data from different countries. Selection bias is present because of over-representation and under-representation of NHs from some countries. This overrepresentation is exemplified by the high ranking of methenamine, a drug that is used only in some northern European countries exclusively as UTI prophylaxis. Representative data for European NHs as a whole and in most cases at the country level have not been collected. The aim of the ESAC survey was to create an overview of data, not to generate a representative sample.

Future investigation using representative data could enable the development of models to help further understand the differences in antimicrobial prescribing in NHs among countries. The associations found should be further investigated in order to define trends towards existing relationships. The extensive utilization of



prophylaxis for UTIs in long-term care facilities deserves further attention and future investigation. The factors determining the decision of prescribers to offer either oral or parenteral antimicrobials also need further investigation.<sup>[22]</sup> Additionally, reaching consensus on the preferred types of antimicrobial and administration route for certain infectious disease indications deserves further attention at a European or even global level.

## Conclusions

Our survey showed that, in NHs, a relatively small proportion (9%) of antimicrobials were given parenterally. Residents taking parenteral antimicrobials required more medical care. A larger proportion of these residents had one or more of the following: a urinary catheter, a vascular catheter, impaired mobility, disorientation or had been admitted to the NH for less than 1 year. Parenteral antimicrobials were mainly used as an empirical treatment for RTIs, whereas the majority of oral antimicrobials were given for uroprophylaxis. Cephalosporins (mainly ceftriaxone) were the most frequently administered parenteral agents, whereas amoxicillin plus enzyme inhibitor therapy was the most frequently administered oral antimicrobial.

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