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Original article

Patients hospitalized abroad as importers of multiresistant bacteria—a cross-sectional study

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ABSTRACT

Objectives: The pandemic spread of multidrug-resistant (MDR) bacteria poses a threat to healthcare worldwide, with highest prevalence in indigent regions of the (sub)tropics. As hospitalization constitutes a major risk factor for colonization, infection control management in low-prevalence countries urgently needs background data on patients hospitalized abroad.

Methods: We collected data on 1122 patients who, after hospitalization abroad, were treated at the Helsinki University Hospital between 2010 and 2013. They were screened for methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE), vancomycin-resistant enterococci, carbapenemase-producing *Enterobacteriaceae* (CPE), multi-resistant *Pseudomonas aeruginosa* and multiresistant *Acinetobacter baumannii*. Risk factors for colonization were explored by multivariate analysis.

Results: MDR colonization rates were higher for those hospitalized in the (sub)tropics (55%; 208/377) compared with temperate zones (17%; 125/745). For ESBL-PE the percentages were 50% (190/377) versus 12% (92/745), CPE 3.2% (12/377) versus 0.4% (3/745) and MRSA 6.6% (25/377) versus 2.4% (18/745). Colonization rates proved highest in those returning from South Asia (77.6%; 38/49), followed by those having visited Latin America (60%; 9/16), Africa (60%; 15/25) and East and Southeast Asia (52.5%; 94/179). Destination, interhospital transfer, short time interval to hospitalization, young age, surgical intervention, residence abroad, visiting friends and relatives, and antimicrobial use proved independent risk factors for colonization.

Conclusions: Post-hospitalization colonization rates proved higher in the (sub)tropics than elsewhere; 11% (38/333) of carriers developed an MDR infection. We identified several independent risk factors for contracting MDR bacteria. The data provide a basis for infection control guidelines in low-prevalence countries **T. Khawaja, Clin Microbiol Infect 2017;23:673.e1–673.e8**

Introduction

Antimicrobial resistance is rapidly increasing in regions with poor hygiene and uncontrolled use of antimicrobials. Multidrug-resistant (MDR) bacteria, particularly multiresistant *Enterobacteriacae*, spreading from there across the globe constitute a universal threat to health care [1,2]. The great number of international arrivals presumably has a major effect on this spread, since travellers act as transporters of the strains [3]: 20%–60% of visitors to these regions become colonized by MDR bacteria, such as extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE) [3–10]. The colonization rates are highest among those returning from South Asia and Southeast Asia, followed by Africa and South America [3,5–10].

The rapid growth of international travel, with over one billion international arrivals annually, is driven by visits to developing

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countries: African and Asian travel have more than doubled during the last 15 years [11]. Hospitalization per se is known to predispose to colonization, and those heading to poor regions are more likely to be hospitalized than those opting for high-income countries [12,13]. The elderly, those visiting friends and relatives (VFR), and those with co-morbidities constitute separate risk groups for travel-related morbidity [4,14,15]. Medical tourism, a growing business, involves elective admittance to a foreign hospital. Of the roughly 500 million annual visitors to developing countries, over a million are likely to be hospitalized there [11,16]. Despite the multitude of reports on ordinary travellers [3–10], we found surprisingly limited data, only seven small studies, of multiresistant bacteria in patients hospitalized abroad [17–23]. Most of them examine only repatriated patients and centre on merely a few MDR types; none provides a detailed geographic distribution or risk factor analysis.

Although patients hospitalized abroad are recognized as a special risk group at hospitals in low-prevalence countries, establishing sound infection control guidelines is difficult in the absence of larger studies that would contain comprehensive risk factor analyses. Most low-prevalence countries only screen for methicillin-resistant *Staphylococcus aureus* (MRSA) and possibly vancomycin-resistant enterococci (VRE), but recently some countries have also begun testing for multiresistant Gram-negative bacteria (MRGN).

A revised screening programme for MRSA and a variety of intestinal MDR strains was implemented in 2010 at our hospital in Helsinki, Finland, which is a low-prevalence country. Since then, we have accumulated data about thousands of patients. The current study focuses on the extent of MDR colonization among patients hospitalized abroad in various geographic regions. Other aims of our investigation were to identify patient-level risk factors for MDR colonization and examine the incidence of symptomatic MDR infection among those colonized.

Materials and methods

Study design

Helsinki University Hospital (HUCH) provides secondary and tertiary care for 1.6 million inhabitants of southern Finland. In April 2010 HUCH implemented a screening programme for MDR infections accompanied by guidelines of mandatory contact isolation precautions for all inpatients hospitalized (24 h or longer) or operated upon outside the Nordic countries (within 12 months). These patients are screened for MRSA, VRE, ESBL-PE, carbapenemase-producing *Enterobacteriaceae* (CPE), multiresistant *Acinetobacter baumannii* (MRAB) and multiresistant *Pseudomonas aeruginosa* (MRPA). According to the guidelines, MRSA samples should be taken from nares, throat and either groin or perineum. Rectal swab or stool samples are used for screening for MRGN and VRE. Secreting wounds, indwelling catheters and other spots with increased risk are also sampled.

Using the HUCH laboratory database, we compiled a list of patients with both MRSA and MRGN samples taken between 1 January 2010 and 31 December 2013. We only included patients who had been sampled at least once for both MRSA and all the multiresistant Gram-negative bacteria; VRE cultures were not used as an inclusion criterion, and patients were selected even if the sample was missing. We only included patient charts showing (a) a history of hospitalization or invasive procedure outside the Nordic countries during the past 12 months (henceforth called hospitalization); (b) country of hospitalization; and (c) approximate time frame of travel. Patients treated in more than one geographic region and those having visited another longer than 5 days after hospitalization were excluded.

According to the Finnish Medical Research Act, a review by an ethics committee is only required in research involving intervention. The study protocol was approved by the research board of the Department of Internal Medicine of Helsinki University Hospital.

Collection of patient data, classifications and definitions

Our patient data covered the factors listed in Table S1 (see Supplementary material). Charlson co-morbidity index was calculated. The results of bacterial cultures (blood, urine, stools) were recorded. Countries were grouped into seven geographic regions (see Supplementary material, Table S1, Fig. S1). Patients treated in two countries were categorized by the one last visited.

To enable a rough comparison between emerging and advanced economies, the regions were further grouped by climate zones into temperate (North America, Oceania and Europe) and (sub)tropical (others).

The patients were classified by purpose of travel: (a) ordinary travellers (tourist and business journeys; mostly Finnish citizens), (b) VFR, and (c) those living abroad for more than 6 months a year.

Multidrug resistance detected in clinical specimens within 30 days of presentation was considered to indicate an MDR infection only if the findings were viewed as relevant by the clinicians. To keep the definition strict, patients given empiric MDR treatment and those with microbiological samples taken abroad were not classified as having a clinical MDR infection.

Microbiological methods

Methicillin-resistant *S. aureus* was screened after overnight enrichment on chromID™ MRSA (bioMérieux, Marcy-l'Étoile, France), or CHROMagar™ MRSA (CHROMagar, Paris, France), and confirmed with *S. aureus*-specific nuclease and *mecA* gene quantitative PCR. VRE was screened using enrichment Enterococcosel broth (BBL, Cockeysville, MD, USA) followed by in-house selective media as previously described [24], or CHROMagar™ VRE media. Positive findings were confirmed by in-house PCR as described by Suppola *et al.* [24].

Extended spectrum β-lactamase-PE and CPE were analysed by plating directly on CHROMagar™ ESBL and CHROMagar™ KPC, respectively. ESBL species identification was confirmed by matrix-assisted laser desorption/ionization time-of fight (MALDI-TOF; Vitek-MS, bioMérieux) and resistance was confirmed by standard CLSI method [3]. CPE species were confirmed with in-house carbapenemase gene PCR [25].

Multidrug resistant *P. aeruginosa* (strain is resistant to both ceftatzidime and meropenem) and MRAB (resistant to meropenem) were screened from ESBL and KPC plates. Cultures were tested by C-390, VITEK-GN or MALDI-TOF for species identification. Isolates resistant to meropenem for *Acinetobacter*, and both meropenem and ceftatzidime for *Pseudomomas*, were analysed by PCR for carbapenemase genes as previously described [25].

The ESBL and CPE isolates of the same species were considered separate strains if their susceptibility profiles differed substantially.

Statistics

Univariate analyses were conducted using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). For categorical variables, we used chi-squared test or one-sample binomial test, for continuous variables the Mann–Whitney *U* test or binary logistic regression was used. All tests were two-sided. Factors with a p value <0.2 in the univariate analysis were chosen for further analysis by the multivariable model with binary logistic regression; of the strongly correlating risk factors only one was picked. When selecting the

variables for the final model, the Akaike information criteria were used. Multivariable analyses were carried out with SPSS 21.0.0.1 (IBM Corp.).

Results

Patient characteristics

The medical charts of the 2756 patients tested for MDR bacteria in HUSLAB (HUCH Laboratories) were screened. A total of 1122 persons met the inclusion criteria and thus constituted the final study population (see Supplementary material, Table S1). The median age was 51 years; those visiting the (sub)tropics (median age 45 years) were younger than those travelling in Europe (median age 55 years) ($p < 0.001$).

The vast majority of the patients had been hospitalized in Europe (64%; 717/1122), mainly in Spain (196), Estonia (159) and Russia (69). The second most common region was East and Southeast Asia, with Thailand (72%; 128/179) as the destination most visited.

Nearly a quarter of all patients (24.2%; 272/1122) had lived abroad for at least part of the year, while 11.2% (126/1122) were VFR travellers. Almost one-quarter (23%; 255/1122) had been transferred directly from a foreign hospital. For the remaining 867 patients, the median stay in Finland before presentation was 11 days (interquartile range 54 days). More than one-tenth (11.9%; 133/1122) had been at an intensive care unit. A history of intensive care was recorded less frequently for visitors to South Asia (4.1%; 2/49) or the Middle East and North Africa (8.3%; 9/109) than those travelling in Europe (13.0%; 93/717) or East and Southeast Asia (13.4%; 24/179). An invasive procedure abroad was recorded for 26.2% (294/1122) and antibiotic use for 35.3% (396/1122) of patients (see Supplementary material, Table S1).

MDR findings

Nearly one-third of the patients carried at least one MDR strain (333/1122; 29.7%) (Table 1): ESBL-PE was detected in 25.1% (282/1122), MRSA in 3.8% (43/1122) and CPE in 1.3% (15/1122). Only 1.3% (15/1122) had VRE, yet 10.2% (114/1122) were not sampled for it. MRAB was carried by 1.7% (19/1122) and MRPA by 1.0% (11/1122). At least two MDR strains were found in 109 patients (9.7%) (Table 2).

Patients hospitalized in the (sub)tropics carried MDR significantly ($p < 0.001$) more often (55.2%; 208/377) than those treated in temperate regions (16.8%; 125/745). The difference was considerable for ESBL-PE, CPE and MRSA, whereas the carriage rates varied less for VRE, MRPA and MRAB (Table 3).

Analysed by geographic region (Fig 1), the greatest frequency of MDR carriers was seen among those who had visited South Asia (77.6%; 38/49), followed by South America (60%; 9/15), sub-Saharan Africa (60%; 15/25), and East and Southeast Asia (52.5%; 94/179).

Risk factors for colonization

The risk of MDR colonization mostly reflected the probability of being colonized with ESBL-PE, as 282 (85%) of 333 affected patients had contracted at least one ESBL-PE strain (Table 3).

Univariate analysis

In the univariate analysis (Table 2) destination proved a strong risk factor: compared with Europe, patients returning from any region other than North America were significantly more likely to be colonized. Those hospitalized in South Asia had the highest colonization rates. Male gender, young age, ICU stay, invasive procedures, VFR status, direct transfer from a foreign hospital, and antibiotic use were all identified as risk factors (Table 2). The shorter the time since hospitalization abroad, the greater the probability of being colonized. General health (Charlson comorbidity index) and alcohol abuse had no predictive value.

Multivariate analysis

In the multivariate analysis hospitalization in areas other than Europe or North America and Oceania remained a significant predictor of colonization. Other independent risk factors were age <6 years, VFR travel or residence abroad, antibiotic use or invasive procedure in a foreign hospital, direct inter-hospital transfer, and short time between hospitalization abroad and sampling. Only male sex and intensive care abroad as predictors of colonization were explained by other risk factors (Table 2). Fig. 2 shows the differences in colonization rates with respect to two well-known risk factors, destination and antibiotic use.

MDR infections

Thirty-eight of the 333 (11.4%) colonized patients had a clinical MDR infection within 30 days of presentation (see Supplementary

Table 1
Number of multidrug-resistant carriers by geographic region visited, data shown as *n* (%)

Microbe	Europe ($n = 717$)	North America and Oceania ($n = 28$)	Latin America ($n = 15$)	Sub-Saharan Africa ($n = 25$)	North Africa and Middle-East ($n = 109$)	South Asia ($n = 49$)	East and Southeast Asia ($n = 179$)	Total ($n = 1122$)
Any MDR	121 (16.9)	4 (14.3)	9 (60.0)	15 (60.0)	52 (47.7)	38 (77.6)	94 (52.5)	333 (29.7)
MRSA	17 (2.4)	1 (3.6)	2 (13.3)	1 (4.0)	9 (8.3)	4 (8.2)	9 (5.0)	43 (3.8)
ESBL-PE	90 (12.6)	2 (7.1)	7 (46.7)	13 (52.0)	46 (42.2)	37 (75.5)	87 (48.6)	282 (25.1)
VRE	10 (1.4)	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.1)	0 (0.0)	15 (1.3)
MRAB	11 (1.5)	0 (0.0)	1 (6.7)	0 (0.0)	1 (0.9)	0 (0.0)	6 (3.4)	19 (1.7)
MRPA	8 (1.1)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	2 (1.1)	11 (1.0)
CPE	3 (0.4)	0 (0.0)	2 (13.3)	0 (0.0)	4 (3.7)	4 (8.2)	2 (1.1)	15 (1.3)
Multiple MDR carriers								
≥2 classes of MDR[a]	13 (1.8)	1 (3.6)	3 (20.0)	0 (0.0)	7 (6.4)	8 (16.3)	10 (5.6)	42 (3.7)
≥2 MDR strains[b]	28 (3.9)	1 (3.6)	4 (26.7)	6 (24.0)	17 (15.6)	15 (30.6)	38 (21.2)	109 (9.7)
≥4 MDR strains[b]	3 (0.4)	0 (0.0)	1 (6.7)	1 (4.0)	0 (0.0)	3 (6.1)	4 (2.2)	12 (1.1)

Figures in parentheses are percentages of patients who were treated in the geographic region in question.
Abbreviations: MDR, multidrug-resistant bacteria; MRSA, methicillin resistant *Staphylococcus aureus*; ESPL-PE, extended-spectrum β-lactamase-producing *Enterobacteriaceae*; VRE, vancomycin-resistant enterococci; CPE, carbapenemase-producing *Enterobacteriaceae*; MRPA, multiresistant *Pseudomonas aeruginosa*; MRAB, multidrug-resistant *Acinetobacter baumannii*.
[a] Patients with more than one of the bacteria MRSA, ESBL-PE, VRE, MRAB, MRPA and CPE.
[b] Either different multidrug-resistant bacterial species or having significantly differing susceptibility profile.

Table 2
Patient characteristics and results of univariate and multivariate risk factor analyses

Risk factor	Patients ($n = 1122$) n	MDR carriers ($n = 333$) n (%)	Non-carriers ($n = 789$) n (%)	OR (95% CI) in univariate analysis	p value in univariate analysis	Adjusted OR (95% CI) in multivariate analysis[a]	p value in multivariate analysis
Sex							
Female	497	128 (26)	369 (74)	1.0	—	—	—
Male	625	205 (33)	420 (67)	1.4 (1.1–1.8)	0.010	—	—
Age group (years)					0.008		0.054
0–5	108	49 (45)	59 (55)	1.0	—	1.0	—
6–17	54	12 (22)	42 (78)	0.3 (0.2–0.7)[b]	0.004	0.3 (0.1–0.8)[b]	0.014
18–30	148	45 (30)	103 (70)	0.5 (0.3–0.9)[b]	0.014	0.4 (0.2–0.9)[b]	0.014
31–50	243	65 (27)	178 (73)	0.4 (0.3–0.7)[b]	0.001	0.4 (0.2–0.7)[b]	0.003
51–65	255	73 (29)	182 (71)	0.5 (0.3–0.8)[b]	0.002	0.5 (0.3–0.9)[b]	0.020
>65	314	89 (28)	225 (72)	0.5 (0.3–0.7)[b]	0.001	0.5 (0.3–1.0)[b]	0.033
Geographic region					<0.001		<0.001
Europe	717	121 (17)	596 (83)	1.0	—	1.0	—
North America and Oceania	28	4 (14)	24 (86)	0.8 (0.3–2.4)[c]	0.719	1.0 (0.3–3.0)[c]	0.945
Latin America	15	9 (60)	6 (40)	7.4 (2.6–21.1)[c]	<0.001	10.4 (3.3–32.5)[c]	<0.001
Sub-Saharan Africa	25	15 (60)	10 (40)	7.4 (3.2–16.9)[c]	<0.001	7.0 (2.9–17.1)[c]	<0.001
North Africa and Middle East	109	52 (48)	57 (52)	4.5 (2.9–6.9)[c]	<0.001	5.6 (3.5–9.0)[c]	<0.001
South Asia	49	38 (78)	11 (22)	17.0 (8.5–34.2)[c]	<0.001	19.0 (9.0–40.0)[c]	<0.001
East and Southeast Asia	179	94 (53)	85 (48)	5.4 (3.8–7.7)[c]	<0.001	5.7 (3.8–8.4)[c]	<0.001
Type of journey					0.025		0.021
Other (i.e. tourism, business)	724	201 (28)	523 (72)	1.0	—	1.0	—
Residence abroad	272	82 (30)	190 (70)	1.1 (0.8–1.5)[d]	0.457	1.6 (1.0–2.4)[d]	0.029
VFR	126	50 (40)	76 (60)	1.7 (1.2–2.5)[d]	0.007	1.8 (1.1–2.9)[d]	0.022
Interhospital transfer							
No or not specified	867	238 (27)	629 (73)	1.0	—	1.0	—
Yes	255	95 (37)	160 (63)	1.6 (1.2–2.1)	0.003	1.8 (1.2–2.6)	0.004
ICU stay abroad							
No or not specified	989	274 (28)	715 (72)	1.0	—	—	—
Yes	133	59 (44)	74 (56)	2.1 (1.4–3.0)	<0.001	—	—
Invasive procedure abroad							
No or not specified	828	227 (27)	601 (73)	1.0	—	1.0	—
Yes	294	106 (36)	188 (64)	1.5 (1.2–2.0)	0.005	1.9 (1.4–2.7)	<0.001
Antibacterial medication					<0.001		<0.001
Not specified	726	145 (20)	581 (80)	1.0	—	1.0	—
Parenteral	313	150 (48)	163 (52)	3.7 (2.8–4.9)[e]	<0.001	3.2 (2.3–4.5)[e]	<0.001
Yes, but parenteral not specified	83	38 (46)	45 (54)	3.4 (2.1–5.4)[e]	<0.001	2.8 (1.6–4.9)[e]	<0.001
Time from discharge to first sample (days. mean)[f]	59.6 (SD 87)	49.6 (SD 80)	63.8 (SD 89)	0.94 (0.90–0.99)[f]	0.013	0.92 (0.86–0.97)[f]	0.006
Alcohol abuse							
No	1004	298 (30)	706 (70)	1.0	—		
Yes	118	35 (30)	83 (70)	1.0 (0.7–1.5)	0.996		
Charlson co-morbidity index (points)					0.911		
0	623	185 (30)	438 (70)	1.0	—		
1	155	48 (31)	107 (69)	1.1 (0.7–1.6)[g]	0.757		
2–3	229	63 (28)	166 (72)	0.9 (0.6–1.3)[g]	0.534		
4–5	63	20 (32)	43 (68)	1.1 (0.6–1.9)[g]	0.735		
>5	52	17 (33)	35 (67)	1.2 (0.6–2.1)[g]	0.650		

Abbreviations: ICU, intensive care unit; MDR, multidrug-resistant bacteria; –, not applicable; SD, standard deviation; VFR, visiting friends and relatives.
[a] Alcohol abuse and Charlson co-morbidity index were not used in the multivariate analyses. Sex and ICU stay abroad were included in the model, but eliminated by backward selection before the final step.
[b] Compared to the youngest age group.
[c] Compared to Europe.
[d] Compared to 'other'.
[e] Compared to 'not specified'.
[f] Analysed as a continuous variable, OR and adjusted OR given per 30 days.
[g] Compared to those with 0 points.

material, Table S1). Six (1.8% of carriers) had positive blood cultures (three for ESBL-PE, one for MRSA, MRAB and MRPA each). Wound infections and UTI proved the most common non-bacteraemic infections. Three deaths were directly attributed to MDR infections.

Discussion

Our results show that hospitalization in the (sub)tropics tends to incur high proportions of colonized patients, whereas the figures for temperate regions remained fairly low. Apart from destination, the multivariate analysis revealed several other risk factors. These data can be applied when drawing up infection control guidelines in low-prevalence countries.

MDR colonization rates

In our research 29.7% (333) of the 1122 patients were colonized with an MDR, which agrees with previous investigations [17,18,22,23]. The proportion is, however, unexpectedly low compared with the 20%–60% found in a number of studies

Table 3
Number of multidrug-resistant carriers in the (sub)tropics and temperate regions

Microbe	Temperate regions[a] ($n = 745$) n (%)	(Sub)tropics[b] ($n = 377$) n (%)	p value	Total ($n = 1122$) n (%)
Any MDR	125 (16.8)	208 (55.2)	<0.0001	333 (29.7)
MRSA	18 (2.4)	25 (6.6)	<0.0001	43 (3.8)
ESBL-PE	92 (12.4)	190 (50.4)	<0.0001	282 (25.1)
VRE	12 (1.6)	3 (0.8)	0.2616	15 (1.3)
MRAB	11 (1.5)	8 (2.1)	0.4286	19 (1.7)
MRPA	8 (1.1)	3 (0.8)	0.6552	11 (1.0)
CPE	3 (0.4)	12 (3.2)	0.0001	15 (1.3)
Multiple MDR carriers				
≥2 classes of MDR[c]	14 (1.9)	28 (7.4)	<0.0001	42 (3.7)
≥2 MDR strains[d]	29 (3.9)	80 (21.2)	<0.0001	109 (9.7)
≥4 MDR strains[d]	3 (0.4)	9 (2.4)	0.0023	12 (1.1)

Figures in parentheses are percentages of patients who had been treated in the geographic area in question.
Abbreviations: MDR, multidrug-resistant bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; ESPL-PE, extended-spectrum β-lactamase-producing *Enterobacteriaceae*; VRE, vancomycin-resistant enterococci; CPE, carbapenemase-producing *Enterobacteriaceae*; MRPA, multiresistant *Pseudomonas aeruginosa*; MRAB multiresistant *Acinetobacter baumannii*.
[a] Defined as Europe, North America and Oceania.
[b] Defined as Asia (excluding the former Soviet Union), Africa and Latin America.
[c] Patients with more than one of the bacteria MRSA, ESBL-PE, VRE, MRAB, MRPA and CPE.
[d] Either different multidrug-resistant bacterial species or having significantly differing susceptibility profile.

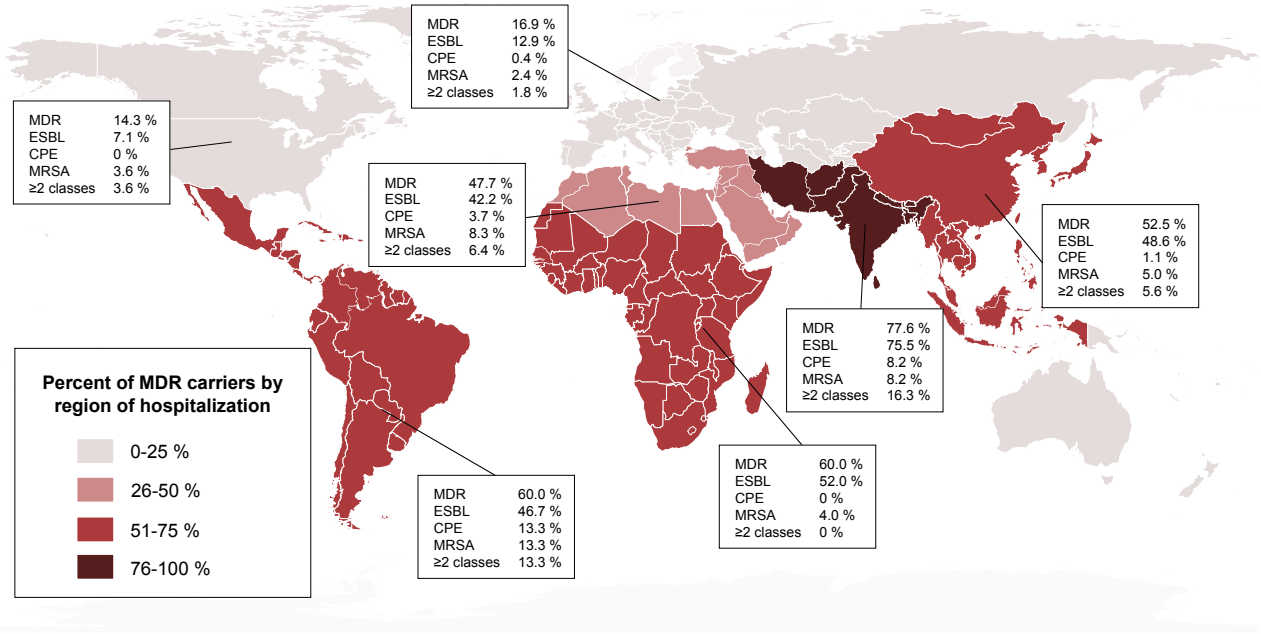

Fig. 1. Prevalence of multidrug-resistant bacteria carriage in returning patients according to the geographic region of their prior hospitalization. Abbreviations: MDR, multidrug-resistant bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; ESPL-PE, extended-spectrum β-lactamase-producing *Enterobacteriaceae*; CPE, carbapenemase-producing *Enterobacteriaceae*.

exploring non-hospitalized healthy travellers [3–10]; after all, colonization rates are expected to be higher among those hospitalized than those with no healthcare contacts [12]. The difference is readily explained by two points. First, studies of ordinary travellers comprise almost exclusively visitors to developing countries, whereas our patients had mostly returned from places within Europe. Indeed, the colonization rate among patients hospitalized in the (sub)tropical regions was as high as 55.2% (208/377) (Table 3). Three-quarters (77.6%) of our patients visiting South Asia were colonized by MDR bacteria—a rate higher than reported for non-hospitalized travellers returning from the same region [3,6,7,9,10]. Second, non-hospitalized travellers are mostly sampled on return or soon after it, whereas our patients had come home up to 12 months before screening. At least for ESBL-PE, the colonization rate has been shown to drop within months [7–10]. Consistent with this, in our data, a short duration since hospitalization abroad predicted a positive colonization status (Table 2). Had the patients been sampled immediately on arrival in Finland, the colonization rates would probably have been higher.

As expected, ESBL-PE were the most common MDR bacteria (282/1122), followed by MRSA (53/1122). Those hospitalized in the (sub)tropics were substantially more likely to carry these pathogens than those hospitalized in Europe, North America and Oceania. The difference in colonization rates was also highly significant for CPE (12/377 versus 3/745). Colonization by MRAB, MRPA and VRE was rare (19, 15 and 11 carriers, respectively); for these bacteria no difference was seen between the (sub)tropics and temperate regions. Our data can be applied to determining which bacteria to screen for when admitting patients previously hospitalized in the various geographic regions.

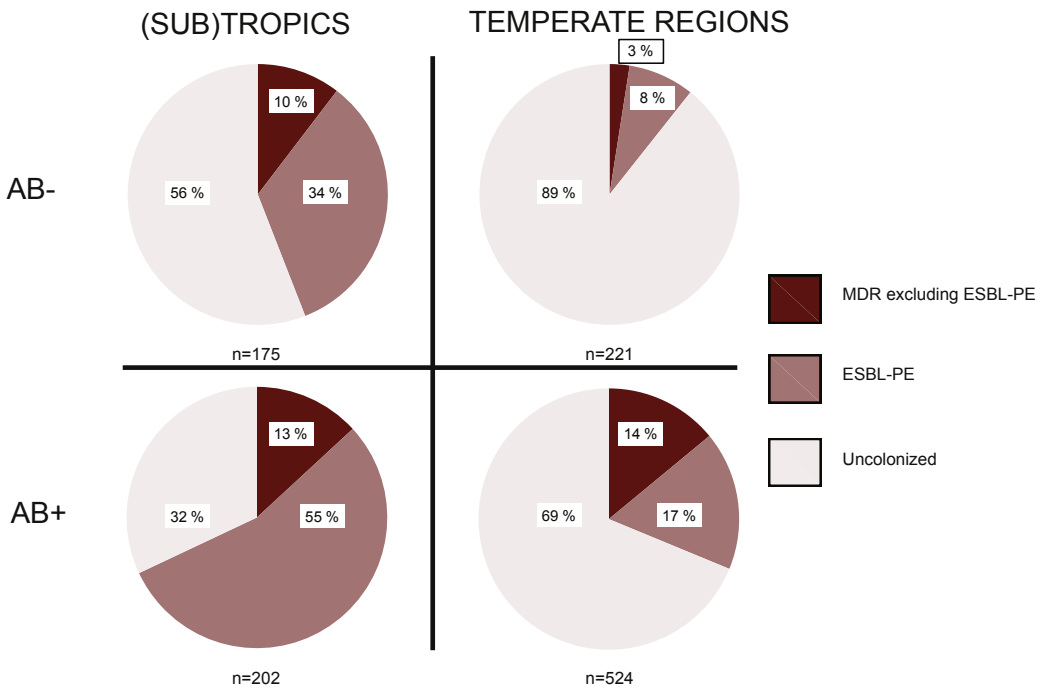

Fig. 2. Proportion of patients carrying multidrug-resistant bacteria by area visited and by use of antibiotics. Abbreviations and definitions: AB+, patients recorded as having received antibiotics either parenterally or orally while abroad; AB−, patients with no antibiotic use abroad; (Sub)tropics, Asia (excluding the former Soviet Union), Africa and Latin America; Temperate regions, Europe, North America and Oceania; MDR, multidrug-resistant bacteria; ESPL-PE, extended-spectrum β-lactamase-producing *Enterobacteriaceae*.

Risk factors for colonization

Multivariate analysis revealed the following independent risk factors for colonization: destination, antimicrobial use, age <6 years, VFR travel, foreign residence, invasive procedure abroad, interhospital transfer and short time interval between foreign hospitalization and sampling. These findings also accord with some previous studies, e.g. with respect to antibiotic use [3,8,10,12] VFR travel [4,8] and invasive treatment [12]. Antibiotics break colonization resistance, and make space for resistant newcomers [3,10,26,27] whereas VFR travel and invasive treatment presumably involve increased exposure.

MDR colonization in hospitalized children

In research conducted among non-hospitalized travellers, young age has been associated with less frequent ESBL-PE carriage [3,6]. In our data the youngest patients were colonized more often than the others; however, probably because coming from the (sub)tropics and receiving intensive care was significantly more common among them than the other age groups (data not shown). A large proportion of our youngest patients were natives of developing countries adopted into Finland or children with congenital heart defects treated here (mostly citizens of Estonia). Indeed, foreign residence or VFR was recorded for 82.4% (89/108) of the patients in this age group, and only for 30.5% (309/1014) in the others.

Infections with MDR

A total of 38 (11.4%) of the 333 colonized patients had an infection caused by an MDR within 30 days of presentation at our hospital; bacteraemia was detected in six (1.8%). Previous non-traveller data indicate even higher infection rates in various settings: ESBL-PE bloodstream infection was diagnosed in 8.5% and 15.4% of colonized inpatients in the USA [28] and Israel [29], respectively. These data highlight the risk of infection for patients colonized with MDR bacteria and support screening of high-risk patients.

Limitations

The data of our retrospective study were, by definition, restricted to those recorded in patient files, and prospective studies are needed to confirm many of the findings. As ICU stay or antibiotic use may have been under-recorded, the differences between the various groups might even be greater than those observed. Due to lack of pre-travel samples, we could not verify that the strains detected had been contracted abroad. Hence, it is possible that part of our subjects had contracted the MDR strain after arriving in Finland. However, with the low Finnish resistance rates, this should be of marginal significance: in a previous report, ESBL-PE was only found in 1.2% of pre-travel stools of 430 healthy Finnish travellers and CPE in none [3]. ECDC statistics show that only 7.4% of the *Escherichia coli* in blood cultures proved resistant to third-generation cephalosporins [30]. In our hospital district, ESBL-PE accounted for 7.9% of the *E. coli* blood isolates and MRSA only for 3% of the clinical *S. aureus* isolates in 2013 [31].

Implications for guidelines in low-prevalence countries

As a result of the lack of research data, infection control guidelines in low-prevalence countries have been based on educated assumptions. These policies have a considerable practical impact both on decisions concerning the use of resources (e.g. single rooms, personnel) and economics (costs of contact precautions and screening). Even a single epidemic by an MDR strain can prove extremely expensive for the hospital. Our data suggest new approaches to infection control for travellers. The present data indicate that, where there is a lack of other risk factors, less rigorous

screening and isolation practices might suffice for patients returning from regions with lower prevalence of MDR. At the same time, the high carriage rates among non-hospitalized travellers [3–10] imply that cost-effectiveness is best achieved by risk-based screening and patient isolation. As regards the risk factors, our data suggest that destination is the most important one, whereas previous hospitalization, along with antibiotic use and travellers' diarrhoea, also deserves special attention [3,10].

Conclusions

We found a high rate of MDR colonization among patients previously hospitalized in the (sub)tropics, whereas the figures for temperate regions were low. In multivariate analysis several independent risk factors were identified: destination, invasive procedure or antimicrobial use abroad, age <6 years, VFR travel or foreign residence, direct interhospital transfer, and short time since hospitalization. We suggest that with limited resources, infection control practices targeting all patients with a prior hospitalization abroad may not be the most effective approach. Instead, a risk-based evaluation would be a practicable solution, focusing on travellers returning from regions with poor hygiene and uncontrolled use of antimicrobials. Not only prior hospitalization but also other factors such as antibiotic use should be taken into consideration. A symptomatic MDR infection developed in 11% of all carriers, which further attests to the usefulness of screening high-risk patients

Transparency declaration

A. Kantele reports personal fees as a member of the board from Valneva 2016 Stockholm, and personal fees from lectures for Baxter, Crucell, GSK, Pfizer, PaxVax, MSD, Valneva; none are relevant for the present study. All other authors have no conflicts of interests to declare.

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Appendix A. Supporting information

Additional Supporting Information may be found in the online version of this article at http://dx.doi.org/10.1016/j.cmi.2017.02.003.

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