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Patterns of antibiotic use in hospital-acquired infections

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SUMMARY

Background: Monitoring the use of antimicrobials in hospitalized patients is critical owing to the risk of resistance selection. This study aimed to describe the patterns of antimicrobial prescription for the most frequent healthcare-associated infections (HAIs) in France, relating drugs and microbiological data.

Methods: We used data from the 2017 point-prevalence survey of HAI and antimicrobial use in France, a large nationally representative sample survey of inpatients. We sought unambiguous correspondence between individual indications of antibiotic regimen and HAI sites to determine which molecules were directed towards which pathogen, considering its resistance profile.

Results: Among 75,698 adult patients from 401 hospitals, 5.1% had an active HAI and 4.3% were being treated for an HAI. The two most frequent antibiotic indications were lower respiratory tract (LRTI, 27.7%) and urinary tract infections (UTI, 18.4%). For LRTI, the most prescribed antibiotic was amoxicillin-clavulanic acid (27.6%) and most frequently isolated pathogens (each accounting for around 17% of isolates) were *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. Meticillin-resistant *S. aureus* LRTI was more likely to be treated with linezolid. For UTI, ofloxacin, ceftriaxone, amoxicillin/co-amoxiclav were most-prescribed (~13% each) and *E. coli* predominantly isolated (52.0%). Extended-spectrum beta-lactamase-producing *E. coli* UTI were more likely treated by fosfomycin, pivmecillinam or ertapenem.

Conclusions: This study provides a baseline of antimicrobial use in relation to microbiological information in patients with the most common HAIs. These results can serve to direct future efforts in antimicrobial stewardship. Our work could be extended to a broader population, notably in Europe where similar surveys have been conducted.

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Introduction

Exposure to antimicrobial drugs leads to resistance selection, potentially resulting in increased morbidity, mortality and costs [1,2]. Antibiotic pressure is particularly critical in hospitals with 30–50% of inpatients treated in Europe [3]. Hospitals treat numerous chronic illnesses and/or immunocompromised patients, and perform many invasive procedures, with a higher risk of healthcare-associated infections (HAIs), dissemination of resistant micro-organisms and severe outcomes. Moreover, the use of broad-spectrum and last resort agents risks selecting resistant micro-organisms that are responsible for a growing number of potentially untreatable infections.

Improving antimicrobial use is one of several interventions that can reduce the emergence and spread of resistant strains and it requires monitoring antibiotic prescribing patterns in hospitals [4]. At the European level, current data are based on consumption volumes at hospital or specialty level, without clinical context [5]. Since 2012, point-prevalence surveys (PPS) of HAIs include a survey module to characterize antimicrobial consumption among inpatients. This study design has been reproduced in numerous countries to simultaneously monitor the level of infection and antibiotic use [6]. However, except for one pilot study in France [7], we could not find any report from PPS studies jointly analysing the two survey modules. As it appears, antibiotic use has not been related to the prevalent infections and isolated pathogens within European PPSs [3,8] or within similar studies in other countries [9,10].

This study aimed to describe the patterns of antimicrobial prescription for the most frequent HAIs in French hospitals, relating drug selection and potentially resistant micro-organisms, on a large country representative sample. After describing the antibiotic treatments according to the context of acquisition of the infection, we defined which treatment indications could correspond to the sites of reported HAIs. Then we established which molecules, combinations of molecules and classes were used for the main infections. Finally, we examined what were the specific treatments towards resistant micro-organisms.

Material and methods

Cross-sectional data were obtained from the French PPS in 2017 which provided a nationally representative sample of adult inpatients in 401 healthcare facilities [11,12].

In the protocol for European PPSs [6], current individual antimicrobial treatment was characterized by up to four antimicrobial agents prescribed simultaneously. For each agent the prescription context and one of 22 clinical indications were recorded. For this article, we only considered prescription context where the agent is intended for curative treatment of an infection and excluded contexts of surgical or medical prophylaxis. Clinical indications correspond to the anatomical site of the infection targeted by the treatment (in the PPS protocol this variable is termed diagnosis).

Independently of treatment information, the presence of an HAI at study time (active HAI) was recorded for each inpatient. HAI was described by one of 58 possible locations (case definition categories determined by signs and symptoms) and associated micro-organisms if any was isolated. Antimicrobial resistance was evaluated through simplified markers: *Staphylococcus aureus*/meticillin; *Enterococcus faecium* and *E. faecalis*/vancomycin and ampicillin; Enterobacterales/third-generation cephalosporins (including extended-spectrum beta-lactamase (ESBL) production) and carbapenems; *Pseudomonas* spp., *Acinetobacter* spp. and *Stenotrophomonas maltophilia*/ceftazidime and carbapenems.

We studied patients, aged 15 years or more, diagnosed with at least one HAI and receiving at least one antibiotic as therapy for an HAI. The study population was restricted to adult patients as antibiotics used in children may be different to those in adults.

Because records of patients' treatment and their infection status were independent, we assumed an agent (or combination of agents) was aimed at treating the HAI if the treatment indication corresponded to the recorded infection site. Because the list of possible indications differed from that of possible locations, some correspondences could not be inferred [6]. For instance, there was no specific treatment indication strictly attributable to surgical site infections which can affect a wide spectrum of organs and tissues.

In the absence of isolated micro-organisms, treatment was considered empirical. We assessed whether those empirical treatment regimens were included in the respective lists of recommended indications from national prescription guidelines of the French National Agency for Medicines and Health Products (ANSM) and the French Infectious Diseases Society (SPILF) available at the study period [15,16]. We also examined the frequency of prescription of molecules particularly at risk of generating resistance and last resort molecules, as defined in the list of 'critical' antibiotics by the ANSM [17].

To account for differences between sample survey data and target population, design effect due to clustering, and to propagate uncertainty, we calculated weighted proportions, stratified by type of healthcare facilities and region with survey R package [13]. Proportions are given with 95% confidence intervals. Comparisons were tested by weighted chi-squared and *t*-tests.

Results

Among 75,698 adult patients from 401 hospitals, 4.3% [3.9; 4.6] received therapy for an HAI. The most frequent clinical indications were lower respiratory tract infections (LRTIs) (27.7% [25.4; 30.0]) and urinary tract infections (UTIs) (18.4% [16.3; 20.5]). Conversely, 5.1% [4.8; 5.5] of adult patients were reported to have an active HAI at sampling time. The most common HAIs were UTIs (29.2% [27.2; 31.1]), surgical site infections (16.4% [14.8; 18.1]) and LRTIs (15.8% [14.1; 17.5]).

Individual-based correspondences between therapeutic indications (diagnosis) and HAI site are shown in Supplementary Figure S1. The two most frequent therapeutic indications can be matched with corresponding HAI sites and we next focused our study on hospital-acquired LRTIs and UTIs.

Distribution of isolated pathogens

One or several pathogens were isolated for most UTIs (90.7% [88.0; 93.4]) and almost half of reported LRTIs (48.2% [41.3; 55.1]). *E. coli* was the most common cause of UTI (52.0%; Figure 1). For LRTI, a greater variety of bacterial species were isolated with *S. aureus*, *P. aeruginosa* and *E. coli* each accounting for 16–18% of all isolates.

Antimicrobial agents

Most patients with an LRTI received a single antimicrobial agent (68.2% [64.5; 72.0]), 24.4% received from two to four agents and 7.3% were not treated. More than half of treatments were with a penicillin as monotherapy, most frequently amoxicillin-clavulanic acid (27.3%), followed by piperacillin-tazobactam and amoxicillin (Table I). The second most prescribed class was third-generation cephalosporins, alone or in association with metronidazole. Carbapenems were used in 10.4% of LRTI treatments.

Patients with UTI also predominantly received a single agent (71.7%); 9.1% received two or three agents and 19.2% were not treated. Penicillins (amoxicillin with or without clavulanic acid), fluoroquinolones and third-generation cephalosporins were most commonly prescribed. Less than 2% of UTIs were treated with carbapenems.

Examining treatments for the main isolated pathogens by antibiotic class, for penicillins were the the most frequently used agents for *S. aureus* (44%), *E. coli* (40%) and *P. aeruginosa* (30%) (Figure 2a); carbapenems were the most common agents used for *K. pneumoniae* (39%). Penicillins were also the most frequently used class for *E. coli* UTI, whereas fluoroquinolones and trimethoprim-sulfamethoxazole were used more frequently for other urinary pathogens (Figure 2b).

Treatment of resistant pathogens

Figure 3 shows the proportion of prescription per meticillin-susceptible or -resistant *S. aureus* and extended spectrum beta-lactamases (ESBL) producing, or not, *E. coli*.

It provides an understanding of the preferential antimicrobial choices for treating a strain known to be sensitive or resistant to this class.

Amoxicillin-clavulanic acid was approximately 10 times more prescribed for LRTI with susceptible *S. aureus* than for the meticillin-resistant strain (Figure 3a). Conversely, linezolid was 100 times more frequently prescribed for meticillin-resistant *S. aureus*.

For UTI treatment, amoxicillin, ceftriaxone and fluoroquinolones were the preferred agents for susceptible *E. coli* while fosfomycin, pivmecillinam, trimethoprim-sulfamethoxazole and ertapenem use was mainly for ESBL-producing *E. coli*.

Compliance with prescribing guidelines

Considering only empiric prescriptions we found that 73% of LRTI treatments and 77% of UTI treatments were consistent with national guidelines.

Discussion

Combining individual data that are typically collected in point prevalence surveys we were able to describe antimicrobial use for the most frequent hospital-acquired infections. This use could be defined as empirical when microbial aetiology and resistance are only presumptive, or targeted according to specific isolated bacteria and their resistance profile. We chose the two most frequently treated HAIs in the French context in the 2017 PPS, LRTI and UTI. We found that treatments were coherently related to isolated organisms. For instance, regardless of the resistance profile, we identified patterns of treatment for LRTI: *S. aureus* and *E. coli* infections mostly treated by co-amoxiclav whereas *P. aeruginosa* infections were predominantly treated by piperacillin-tazobactam and *K. pneumoniae* infections by carbapenems. These prescribing patterns are in line with the background bacterial epidemiology for France at the study time where 29% of *K. pneumoniae* vs 10% of *E. coli* strains were resistant to third-generation cephalosporins [14]. We also found that therapies were strongly related to the resistance profile. Compared with infections with susceptible strains, ertapenem use increased ten-fold for UTI with ESBL-producing *E. coli*. For LRTI, we measured a hundred-fold increased linezolid use for meticillin-resistant *S. aureus* (MRSA) infection.and a seven-fold meropenem increase for resistant strains.

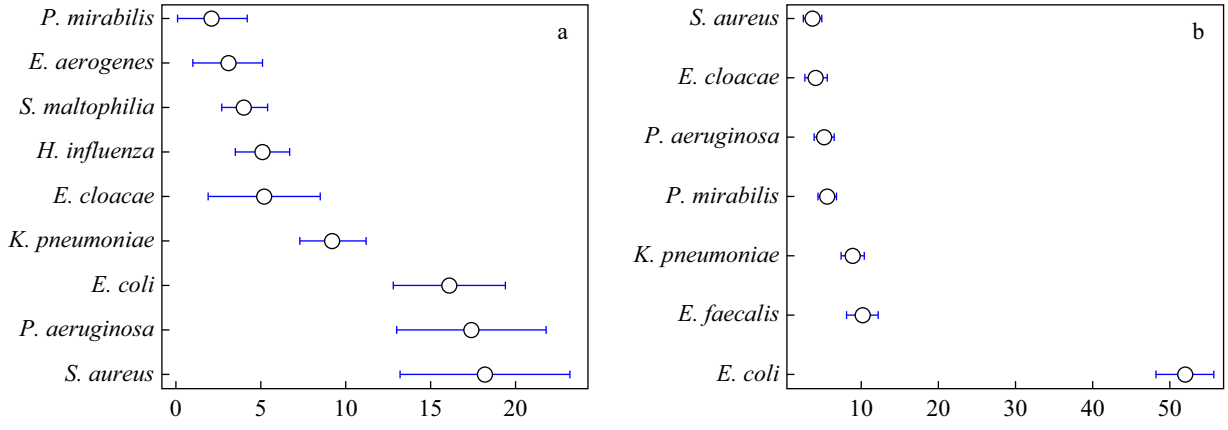

Figure 1. Proportion of pathogens isolated in LRTI (a) and UTI (b). Species found in less than 1% of isolates are not represented.

Table I
Ten most common treatments of lower respiratory tract (LRTIs) and urinary tract infections (UTIs), by antimicrobial class and molecules comprising combinations

Class	LRTI		UTI
	[95%CI]		[95%CI]
Penicillins	54.1 [50; 57.6]	Penicillins	31.0 [27.3; 34.6]
Cephalosporins 3 G	24.8 [21.1; 28.5]	Fluoroquinolones	27.7 [24.2; 31.2]
Carbapenems	10.4 [8.2; 12.7]	Cephalosporins 3 G	24.4 [20.1; 28.8]
Fluoroquinolones	10.3 [8.6; 12.1]	Sulfonamides	6.2 [4.4; 8.1]
Aminoglycosides	8.0 [5.4; 10.6]	Carbapenems	1.5 [0.8; 2.3]
Nitroimidazoles	7.2 [4.8; 9.5]	Aminoglycosides	1.2 [0.2; 2.2]
Macrolides	3.7 [2.1; 5.2]	Glycopeptides	1.1 [0.5; 1.6]
Glycopeptides	2.1 [0.7; 3.5]	Cephalosporins 2 G	0.7 [0.0; 1.5]
Sulfonamides	1.6 [0.7; 2.6]	Nitroimidazoles	0.6 [0.1; 1.2]
Antimycobacterial	0.0 [0; 0.0]	Macrolides	0.3 [0.0; 0.6]
Others	7.6 [NA; NA]	Others	8.8 [NA; NA]
Molecules			
Amoxicillin-clavulanic acid	27.6 [24.4; 30.9]	Ofloxacin	13.9 [11.2; 16.6]
Ceftriaxone	9.1 [6.2; 12.1]	Amoxicillin	13.6 [10.3; 16.8]
Piperacillin-tazobactam	8.9 [7.1; 10.7]	Amoxicillin-clavulanic acid	13.1 [10.4; 15.8]
Cefotaxime	4.7 [2.0; 7.5]	Ceftriaxone	12.6 [10.0; 15.3]
Amoxicillin	4.0 [2.2; 5.8]	Ciprofloxacin	8.1 [5.5; 10.6]
Imipenem-relebactam	3.3 [1.8; 4.8]	Nitrofurantoin	6.8 [4.6; 9.0]
Ceftriaxone, metronidazole	2.3 [1.2; 3.3]	Cefixime	6.6 [4.2; 9.1]
Piperacillin	2.1 [0.9; 3.2]	Trimethoprim-sulfamethoxazole	6.0 [4.2; 7.8]
Levofloxacin	1.9 [1.0; 2.7]	Levofloxacin	2.6 [0.7; 4.5]
Cefotaxime; metronidazole	0.6 [0.3; 0.8]	Norfloxacin	1.6 [0.6; 2.6]
Others	36.0 [NA; NA]	Others	15.0 [NA; NA]

95%CI, 95% confidence interval.

However, we observed some disturbing results warranting some caution in interpreting the data. For instance, the relatively high number of MRSA HAIs receiving amoxycillin/clavulanate, a drug with cross-resistance to meticillin, shows either a lack of knowledge from the prescribers, or that the drug was prescribed for another indication than the MRSA HAI. Also, we hypothesized that the presence of isolated germs implied a targeted treatment, but we cannot exclude that some therapies initially prescribed as empirical were not yet re-evaluated according to microbiological results at the study time. On the UTI front, many of the prescriptions concern drugs used for cystitis that are often overprescribed, mainly for urinary tract colonization.

This type of survey data cannot directly address antibiotic prescribing appropriateness as necessary detailed diagnosis, clinical or radiological information is lacking. However our results can be looked at in the context of current recommendations for antimicrobial use. This study suggests that most empirical treatment regimens were in line with national prescription guidelines and that most last-resort antibiotics were adequately prescribed and restricted to resistant pathogens. Still, antibiotics particularly at risk of generating resistance, including amoxicillin/clavulanic acid, third-generation cephalosporins and fluoroquinolones [17] were widely prescribed (see Table I). This study has two further major limitations. First, antibiotic use could only be related to a specific infection in a limited number of cases. As illustrated in Supplementary Figure S1, we could establish a correspondence between diagnosis associated to antibiotic use and site of HAI only when these two items were identically specified and specifically associated at patient level. As described in the European protocol for PPSs, the two variables are not defined with the same list, making certain correspondences impossible [6]. Second, although the initial survey sample size ensured a good precision for the main outcomes of prevalences of both HAI and antimicrobial use at a national and regional level, the number of infections for which a bacterium was isolated with a resistance profile was limited in our study. Notably treatment of infections caused by less frequent potentially resistant pathogens could not be studied. We addressed these two limitations by analysing the most frequently reported HAIs and their most frequent pathogens.

Potential perspective from our study is two-fold. Firstly, numerous PPSs have been conducted in past years on which a similar analysis could be performed, potentially revealing contrasting patterns of antibiotic use to treat HAIs, at least within Europe. Secondly, the design of future PPSs could allow us to explicitly relate infections (including those community-acquired) and treatments.

In this study, we provided nationally representative patterns of antimicrobial use in relation to microbiological information in patients with the most common HAI. Our results can serve to direct future effort of antimicrobial stewardship. Also, we leveraged a type of data that is available in many countries

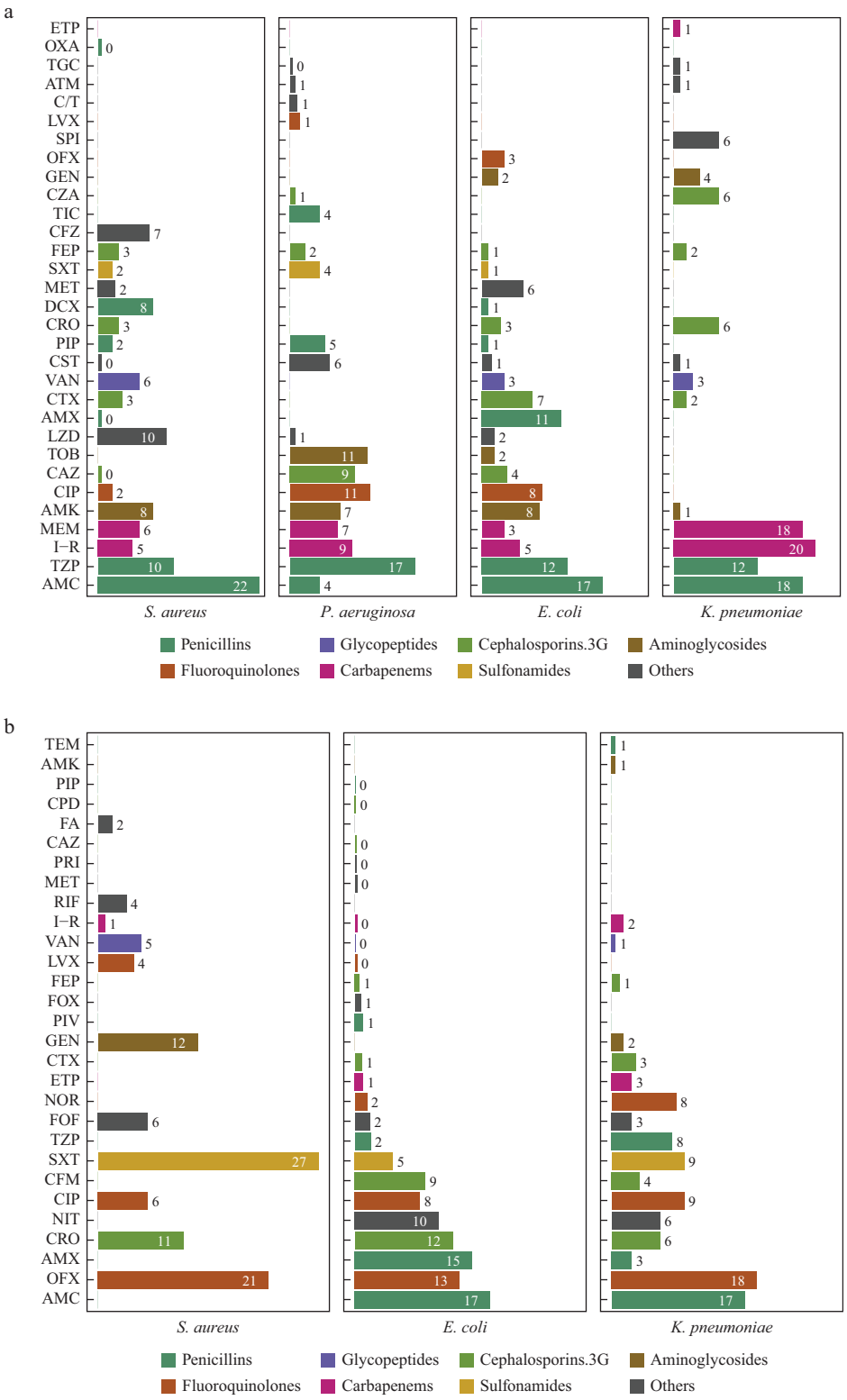

Figure 2. Antimicrobials prescribed for lower respiratory tract infection (LRTI) (a) and urinary tract infection (UTI) (b), by most common pathogens. Numbers are proportion of drug prescription for a pathogen ('0' stands for values between 0 and 1 and blank rows represent no prescription). AMC, amoxicillin-clavulanic acid; AMK, amikacin; AMX, amoxicillin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CFM, cefixime; CFZ, cefazolin; CIP, ciprofloxacin; CPD, cefpodoxime; CRO, ceftriaxone; CST, colistin; CTX, cefotaxime; CZA, ceftazidime-avibactam; DCX, dicloxacillin; ETP, ertapenem; FA, fusidic acid; FEP, cefepim; FOF, fosfomycin; FOX, cefoxitine; GEN, gentamicin; I-R, imipenem-relectam; LVX, levofloxacin; LZD, linezolid; MEM, meropenem; MET, metronidazole; NIT, nitrofurantoin; NOR, norfloxacin; OFX, ofloxacin; OXA, oxacillin; PIP, piperacillin; PIV, pivmecillinam; PRI, pristinamycin; RIF, rifampin; SPI, spiramycin; SXT, trimethoprim-sulfamethoxazole; TEM, temocillin; TGC, tigecycline; TIC, ticarcillin; TOB, tobramycin; TZP, piperacillin-tazobactam; VAN, vancomycin.

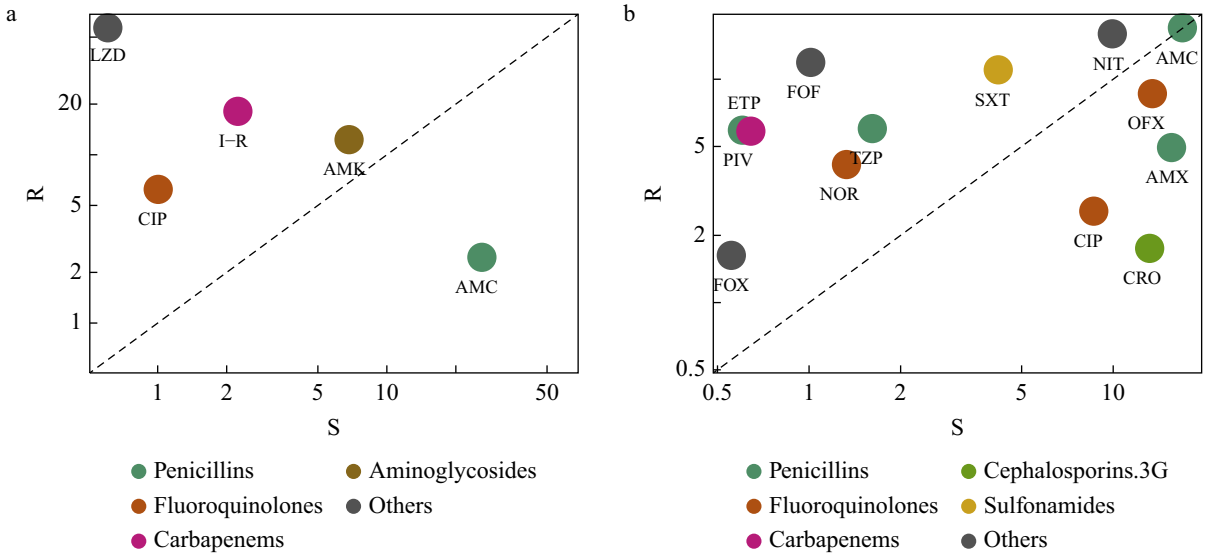

Figure 3. Proportion of antimicrobial prescription according to pathogen resistance for meticillin-resistant *Staphylococcus aureus* (MRSA) lower respiratory tract infection (LRTI) (a) and extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli urinary tract infection (UTI) (b). (a) x-axis (respectively y-axis) in log scale represents proportion of prescription when pathogen is deemed sensitive (resistant). (b) x-axis (respectively y-axis) in log scale represents proportion of prescription when pathogen is deemed sensitive (resistant). AMC, amoxicillin-clavulanic acid; AMK, amikacin; AMX, amoxicillin; CIP, ciprofloxacin; CIP, ciprofloxacin; CRO, ceftriaxone; ETP, ertapenem; FOF, fosfomycin; FOX, cefoxitin; I-R, imipenem-relebactam; LZD, linezolid; NIT, nitrofurantoin; NOR, norfloxacin; OFX, ofloxacin; PIV, pivmecillinam; SXT, trimethoprim-sulfamethoxazole; TZP, piperacillin-tazobactam.

where similar surveys have been conducted, notably in Europe, and as such our work could be extended to a broader population.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.05.008.

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