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Antibiotic consumption in southern and eastern Mediterranean hospitals: results from the ARMed project

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***Objectives*: The intensity of antibiotic use in hospital settings is recognized as possibly the most important factor for the selection of antimicrobial resistance. Hospitals are therefore being encouraged to undertake surveillance and benchmarking of antimicrobial consumption patterns with a view to identify and rectify possible evidence of overuse or misuse.**

***Methods*: As part of the ARMed project, antibiotic use in 25 hospitals from the southern and eastern Mediterranean countries of Cyprus, Egypt, Jordan, Lebanon, Malta, Tunisia and Turkey was assessed prospectively for 24 months during the years 2004–05. The surveillance focused primarily on systemic antibiotics used in hospital care, aggregated at the level of the active substance, in accordance with the Anatomic Therapeutic Chemical (ATC) classification.**

***Results*: The median total antibiotic use during the study period was 112 defined daily doses per 100 bed-days (DDD/100BD), with an inter-quartile range of 84–428 DDD/100BD. The most common antibiotic groups prescribed were the extended-spectrum and combination penicillins, first- and third-generation cephalosporins and quinolones. Overall, a predominant consumption of wide-spectrum agents was noted, with a significant correlation between the levels of use of third-generation cephalosporins and carbapenems.**

***Conclusions*: Emphasis on wide-spectrum agents could explain one possible factor behind the documented high prevalence of resistance in important pathogens within these same hospitals and suggests the need for improved antibiotic stewardship and prescribing programmes, which may well be applicable to the whole region.**

Keywords: surveillance, resistance, ATC, DDD, carbapenems, cephalosporins, penicillins

Introduction

The causal link between antibiotic resistance and consumption has been well established.[1] Various publications have documented that changes in antimicrobial usage are paralleled, after a variable lag phase, by equivalent changes in the prevalence of antimicrobial resistance.[2] It is common experience in many hospitals that departments that exhibit the highest rates of antimicrobial resistance also invariably have the highest levels of antibiotic use.[3] Such evidence has led to the hypothesis that the selection of resistance during treatment or prophylaxis, rather than transmission from patient to patient, is the key factor in the acquisition of infection caused by a resistant organism.[4] As a result, the intensity of antibiotic use in a population may be the most critical driver in the selection of resistance.[5] Numerous initiatives in recent years have encouraged hospitals to undertake surveillance of antimicrobial consumption patterns with a view to identify and rectify possible overuse and misuse.[6]

The Mediterranean region has been identified as an area of hyper-endemicity for multiresistant hospital pathogens.[7] This is particularly the case for methicillin-resistant *Staphylococcus aureus* (MRSA) and applies to both the European[8] and non-European[9] countries of the region. In recent years, several initiatives have materialized, which aim to collect information on antibiotic prescribing practices within hospital care. Pan-European studies, including 'Development of Strategies for Control and Prevention of Antibiotic Resistance in European Hospitals' (ARPAC)[10] and

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European Surveillance of Antimicrobial Consumption (ESAC)[11] have elucidated the status of hospital antibiotic prescribing in a number of European countries, including those in the Northern Mediterranean. On the other hand, little or no information has been available on the situation in the southern and eastern countries of this region. This lacuna has been addressed by the Antibiotic Resistance Surveillance and Control in the Mediterranean Region (ARMed) project (www.slh.gov.mt/armed) that started in January 2003.[12] Over a 4 year period, this study documented the prevalence of antibiotic resistance in several key pathogens isolated in southern and eastern Mediterranean countries and also attempted to investigate potential influencing factors such as antibiotic consumption and infection control. This publication focuses on the surveillance initiatives on patterns of antibiotic use undertaken within participating hospitals in these countries.

Methods

Participating hospitals collected data on hospital antibiotic consumption for 24 months in the years 2004–05, focusing on systemic antibacterials for hospital care, aggregated at the level of the active substance, in accordance with the Anatomic Therapeutic Chemical (ATC) classification (WHO, version 2005). Data were collected from a point of the distribution chain close to the real antibiotic consumption at the fifth level of the ATC classification and expressed in defined daily doses (DDD). The number of patient-days was deployed as a denominator, as recommended by WHO for drug utilization studies in hospital settings.

Hospital antibiotic consumption was divided into eight main antibiotic groups: penicillins (J01C); cephalosporins, carbapenems and monobactams (J01D); tetracyclines (J01A); macrolides + lincosamides + streptogramins (J01F); quinolones (J01M); sulphonamides (J01E); aminoglycosides (J01G); and 'others', including amphenicols, fusidic acid, parenteral nitro-imidazole derivatives and glycopeptides (J01G + J01B + J01X + P01 + J04 + A02 + A07). This system was adapted from the ESAC methodology,[11] but was not identical with it, since ESAC did not include antibacterials outside the J01 ATC group. Penicillins (J01C) were further subdivided into four subclasses: narrow-spectrum penicillins (J01CE); penicillins with extended spectrum, such as ampicillin and amoxicillin (J01CA); combinations with a β-lactamase inhibitor, such as co-amoxiclav (J01CR); and β-lactamase-resistant penicillins (J01CD). Cephalosporins were subdivided into four generations as defined in the 2005 version of the ATC classification: first generation (J01DB), second generation (J01DC), third generation (J01DD) and fourth generation (J01DE). Furthermore, since this project focused on hospital care, we also paid particular attention to antibiotics that are not, or very seldom, used in ambulatory care. These were defined as 'hospital-specific antibiotics' and were analysed separately to explore characteristics in their use. For the purpose of the study, they included third-generation cephalosporins, carbapenems, aminoglycosides and glycopeptides.

A total of 25 hospitals from seven southern and eastern Mediterranean countries—Cyprus (5), Egypt (8), Jordan (1), Lebanon (1), Malta (1), Tunisia (3) and Turkey (6)—participated in this ARMed subproject. Focus group discussion and training among the country coordinators was undertaken during three plenary ARMed meetings. The coordinators then undertook the subsequent instruction of the contact individuals within each study hospital, using the written protocols provided by the project management. They were also responsible for the primary verification of the data before submission to the project management team. Furthermore, prior to the interpretation of the consumption data, we assessed the validity of the information provided through a questionnaire sent to all participating hospitals. Data sets were checked for correctness of coding into the ATC classification. We also investigated data collection bias due to the peculiarities of prescribing systems in individual countries or at the hospital level as well as those due to the characteristics of the individual institution. Elements of bias were identified in the data from Cyprus, where hospital consumption included an element of ambulatory care mix, as well as from single-specialty hospitals in Egypt (two infectious diseases hospitals) and Tunisia (one small bone marrow transplant unit). However, due to the previous total absence of consumption data from these countries, all collected data have been retained, but we clearly indicate the presence of this bias in the text and in the figures and also highlight the instances where any hospital has not been included in the data analysis.

Bed-day statistics were obtained from the individual hospitals' data management units, thus allowing consumption to be reported in DDD per 100 bed-days (DDD/100BD), a standardized figure that provides a degree of comparison among different institutions. Statistical analyses, including Spearman's rank correlation and Mann–Whitney tests, were performed in Medcalc, version 9.2.1.0 (Medcalc Software, Mariakerke, Belgium).

Results

A total of 25 hospitals participated in the study, of which 16 were university teaching hospitals, 6 were general hospitals and the remaining 3 constituted the single-specialty facilities already referred to. The median hospital size was 550 beds [interquartile range (IQR): 208–788]. Two hospitals were unable to provide reliable bed occupancy data, and their results were confined to assessments of proportions of antimicrobial use. Overall antibiotic consumption varied from 45 to 836 DDD/100BD with a median of 112 DDD/100BD and an IQR between 84 and 428 DDD/100BD (Figure 1). One Turkish hospital reported a total consumption of <50 DDD/100BD. Nine hospitals declared a total use between 50 and 100 DDD/100BD, while another five utilized between 100 and 200 DDD/100BD. Eight hospitals reported consumption levels in excess of 200 DDD/100BD. These included all the hospitals from Cyprus, whose consumption data incorporated a substantial (though undefined) quantity of ambulatory care antibiotics, as well as the two single-specialty infectious diseases hospitals in Egypt. We therefore repeated the box and whisker plot, excluding the Cypriot and single-specialty hospitals, and obtained a more homogenous pattern with a median of 97.3 DDD/100BD (IQR: 80–150 DDD/100BD).

We also evaluated the most commonly consumed antibiotic groups within each hospital and identified the top five overall groups (Figure 2). The broad-spectrum penicillins, with or without a β-lactamase inhibitor, together with first-generation cephalosporins, were responsible for the bulk of antibiotics prescribed and constituted at least one-third of the total usage in 15 of the 25 hospitals. Interestingly, third-generation cephalosporins were a 'top 5' antibiotic class in nine of the hospitals (four in Egypt, three in Turkey and two in Tunisia).

Consumption of β-lactam antibacterial agents

The average consumption of β-lactam antibiotics in the participating hospitals accounted for more than half of all antibiotics

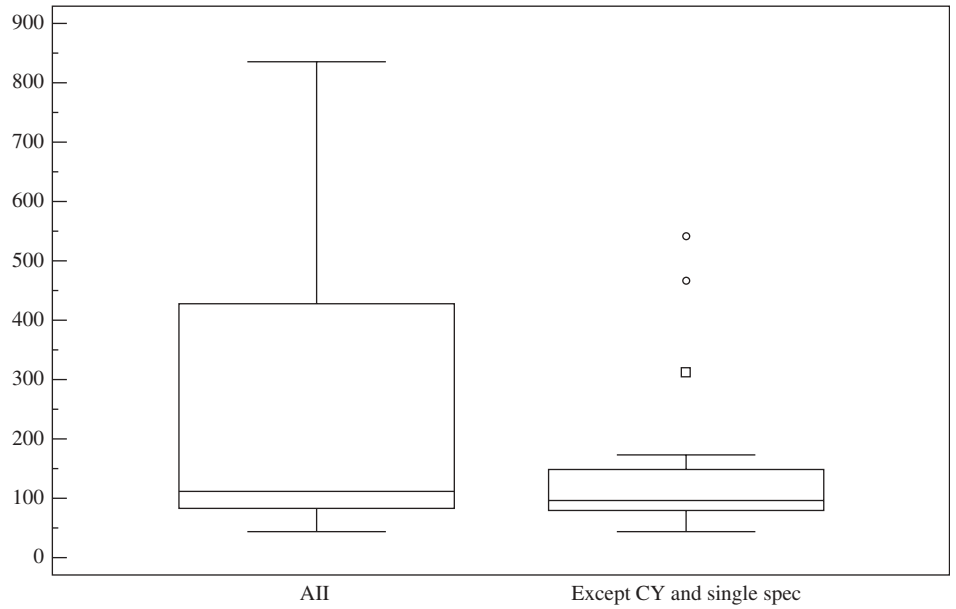

Figure 1. Box and whisker plots of total antibiotic consumption in DDD/100BD for all hospitals and excluding hospitals from Cyprus and single-specialty infectious diseases units from Egypt. Open square and open circle symbols refer to outliers outside 1.5 and 3 interquartile ranges, respectively.

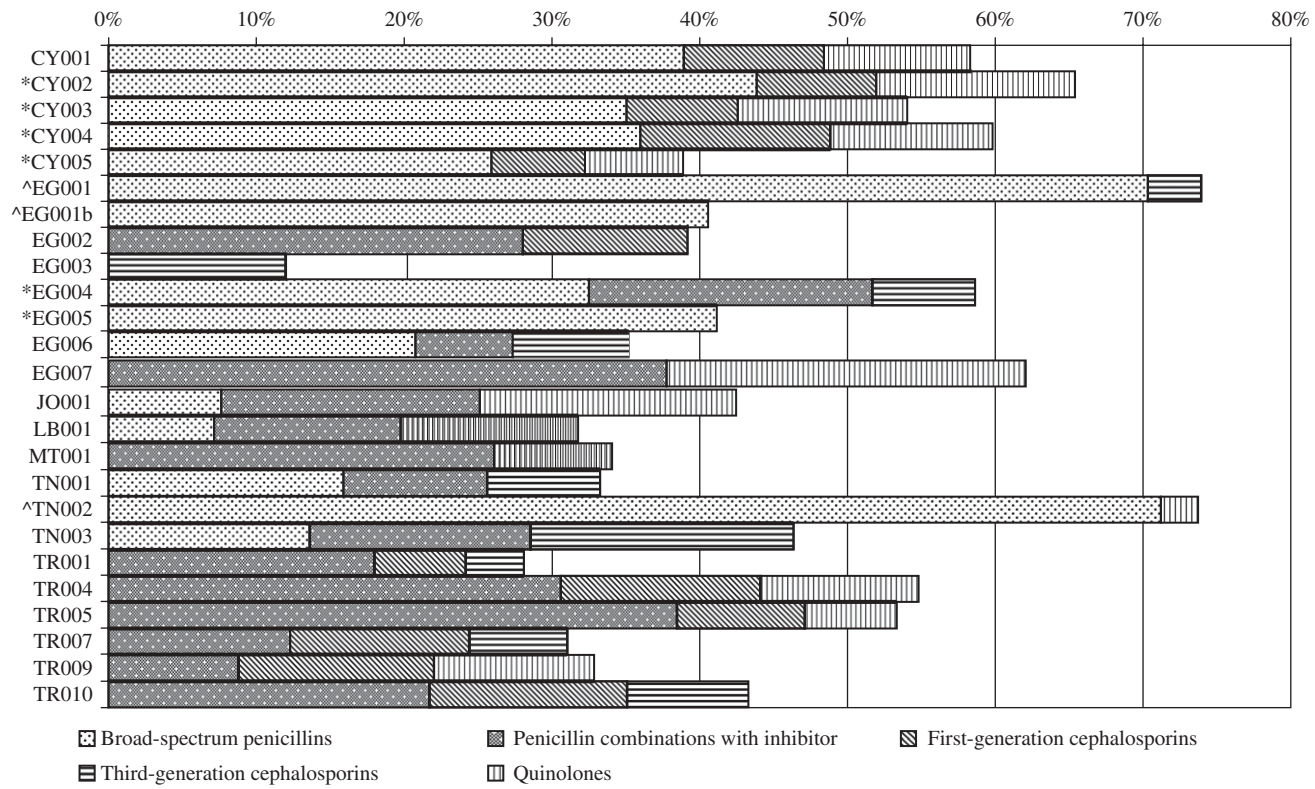

Figure 2. Proportional consumption of the five most commonly utilized antibiotic classes among the participating hospitals. *Secondary care hospitals. ^Single-specialty facilities. CY, Cyprus; EG, Egypt; JO, Jordan; LB, Lebanon; MT, Malta; TN, Tunisia; TR, Turkey.

prescribed (39% for penicillins and 18% for cephalosporins). Throughout all of the participating hospitals, a very low use of narrow-spectrum penicillins was evident. In fact, with the exception of two hospitals in Tunisia, the use of β-lactamase-sensitive (e.g. benzylpenicillin) and β-lactamase-resistant (e.g. flucloxacillin) penicillins did not exceed 1% of total antibiotic consumption. β-Lactam use concentrated predominantly on extended-spectrum penicillins, with or without a β-lactamase inhibitor. An almost

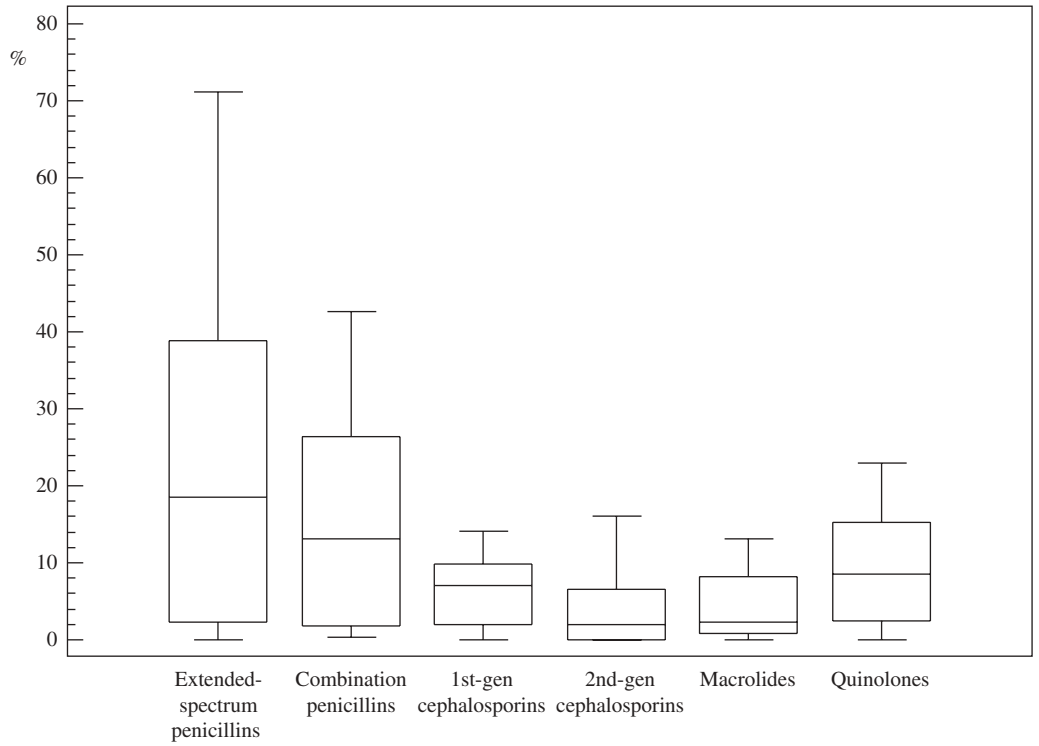

Figure 3. Box and whisker plots for proportional consumption of first-line antibiotic groups.

equal preference for these two categories was discerned within the participants. Where combination penicillin consumption was high, the equivalent use of their extended-spectrum counterparts was relatively low and vice versa. In other words, hospitals tended to concentrate their penicillin consumption on just one of these two subclasses. As evident in Figure 3, there was no significant difference in median percentage consumption between these two subgroups: extended-spectrum penicillins exhibited a median proportion of 18.6%, while combination penicillins had a median of 13.1% ($P = 0.4$, not significant). Nevertheless, some interesting geographical patterns could be discerned. Hospitals from Cyprus and Tunisia prescribed mainly extended-spectrum penicillins, whereas those in Turkey predominantly utilized combination penicillins (on average more than a quarter of all antibiotics).

Cephalosporin consumption lagged behind penicillin use in all but four participating hospitals (one in Egypt, one in Lebanon and two in Turkey). The combined use of first- and second-generation classes, on average, accounted for ~10% of the total consumption. Quite remarkable was the difference in the consumption between second-generation (median: 2%; IQR: 0% to 7%) and third-generation (median: 6.2%; IQR: 3% to 11%) cephalosporins (Mann–Whitney $P = 0.004$). When single-specialty hospitals were excluded, the use of third-generation cephalosporins actually exceeded the sum of the consumption of first- and second-generation components in 7 of the 22 hospitals. This occurred primarily in hospitals located in Tunisia and Egypt.

Hospital-specific antibiotics

A substantial use of the J01DD group was clearly evident and accounted for more than half of the consumption of 'hospital antibiotics' in at least 10 institutions. The emphasis on third-generation cephalosporins was particularly striking when contrasted with other antibiotic groups normally associated with hospital care, namely carbapenems, glycopeptides and aminoglycosides (Figure 4). This was confirmed by a significant difference (Mann–Whitney $P = 0.001$) in overall consumption compared with carbapenems (median: 1.4%; IQR: 0.6% to 3%) and glycopeptides (median: 1.1%; IQR: 0.2% to 3%). The latter two antimicrobials showed reasonably homogeneous patterns of consumption throughout the study group, rarely exceeding 5% in any hospital. Furthermore, in five of the Egyptian hospitals, neither of these two antibiotic groups was utilized in any appreciable quantities. These institutions depended considerably on donations, and neither class was part of the respective hospital formularies. We also identified a correlation between the proportion of use of third-generation cephalosporins with carbapenems (Spearman's $\rho = 0.454$; $P = 0.03$), suggesting that hospitals with above-average use of third-generation cephalosporins also tended to be higher consumers of carbapenems (Figure 5).

Other antibiotics

Use of macrolides was relatively low (median: 2.7%; IQR: 1% to 8.4%), with the highest consumption (13% of total use) registered in the Maltese hospital. However, substantial quinolone consumption was evident (median: 8.9%; IQR: 2.2% to 16%), especially in the Cypriot hospitals and the single institutions from Jordan and Lebanon where it exceeded 15% of total use. Tetracyclines and chloramphenicol were rarely used, with the majority of hospitals reporting negligible consumption.

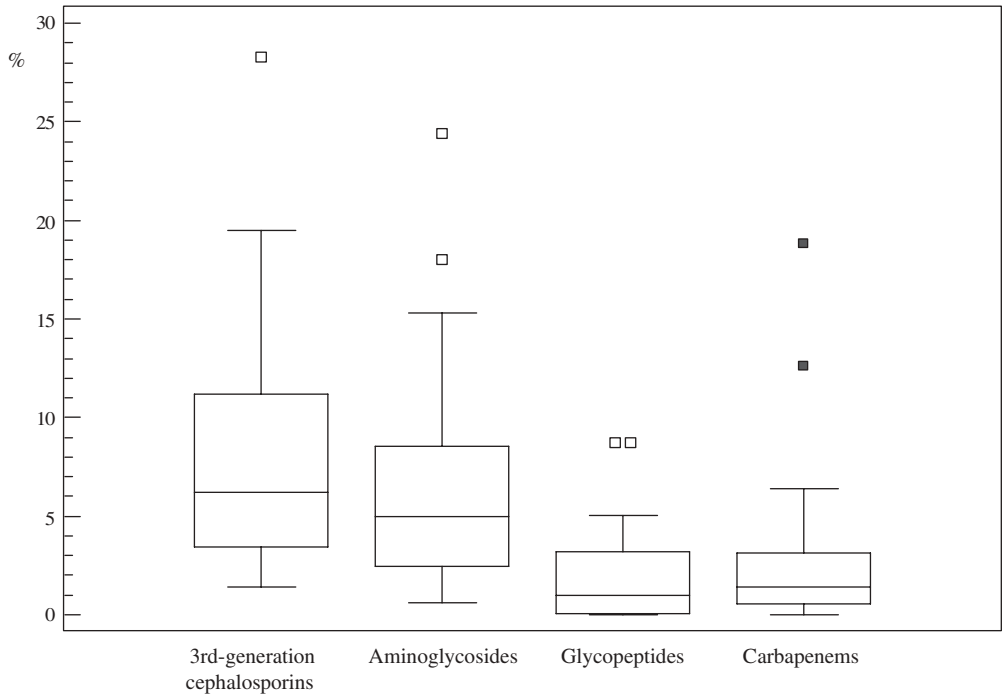

Figure 4. Box and whisker plots for proportional consumption of 'hospital antibiotic' groups. Open square and filled square symbols refer to outliers outside 1.5 and 3 interquartile ranges, respectively.

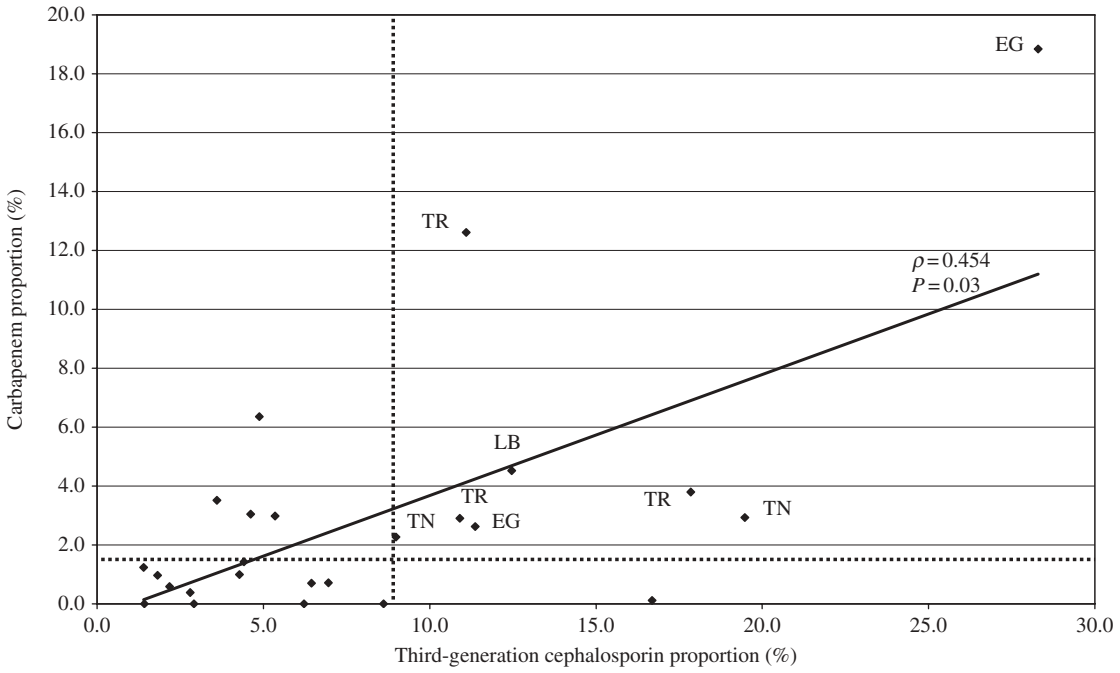

Figure 5. Correlation plot for proportional consumption of carbapenems and third-generation cephalosporins including median (dotted) lines as well as line of best fit and Spearman's ρ. EG, Egypt; LB, Lebanon; TN, Tunisia; TR, Turkey.

Discussion

The ARMed project marks the first attempt to identify patterns of antibiotic consumption in hospitals within the southern and eastern Mediterranean region using a standard methodology. The previous void in available data is not surprising since antibiotic consumption information at the hospital level is lacking on a worldwide basis, even in more developed countries. It is therefore difficult to benchmark the results obtained by the ARMed hospitals with other institutions within the region and beyond. An international multicentre study of 15 hospitals from 14 countries undertaken by Westh *et al.*[13] in 1996 reported that the total antibiotic consumption among its participants ranged from 30 to 111 DDD/100BD. More relevant, due to its geographic

proximity, was the ARPAC study that analysed consumption data from 139 hospitals in 30 European and neighbouring countries and reported a median consumption level of 49.6 DDD/100BD (IQR: 37.1–65.4).[14] At face value, therefore, the ARMed results would appear to be significantly higher. However, ARPAC reported considerable heterogeneity among different European regions. The highest consumption was, in fact, registered within the hospitals in the southern European area, which reported a substantially higher median of 72.2 DDD/100BD (IQR: 46.8–89.7). A publication from a single hospital in Israel established its total consumption to be 124 DDD/100BD.[15] As a consequence, the results of the hospitals in the ARMed study do not appear to differ considerably from those identified within other countries bordering the Mediterranean.

Antibiotic consumption has been cited as an important driver for the advent and proliferation of antimicrobial resistance in hospitals.[16] However, based on the above arguments, our results would not seem to explain the significant levels of resistance previously identified by the ARMed project within the countries of the region, particularly for MRSA,[9] as well as *Escherichia coli* resistant to quinolones and third-generation cephalosporins.[17] One possible hypothesis could stem from our evidence of a significant level of consumption of wider spectrum formulations. These are known to pose a greater risk of the development of resistance than alternatives with a narrower antibacterial spectrum of activity.[18] Crowcroft *et al.*[19] showed, through multivariate analysis, a correlation between the incidence of nosocomial MRSA and use of co-amoxiclav in Belgian hospitals. Monnet *et al.*[16] also identified dynamic, temporal relationships between monthly %MRSA and quinolone use. Data by Rahal *et al.*[20] suggest that a major factor for dissemination of ESBL-producing Enterobacteriaceae is antibiotic exposure by ceftazidime. More recently, the same conclusion was reported by Lin *et al.*[21] We believe that the ARMed data suggest a substantial emphasis on these wide-spectrum agents within the participating hospitals, particularly third-generation cephalosporins and quinolones. The significant correlation between the consumption of third-generation cephalosporins and carbapenems is a case in point. Both agents are normally reserved for serious healthcare-associated infections. The fact that hospitals tended to show concurrent levels of use for both agents could be interpreted at face value to indicate that, in the higher consuming institutions, this was a natural consequence of a prevalence of multiresistant Gram-negative pathogens. However, the hospitals with above-median use were actually not the ones that registered highest resistance proportions. This could suggest that these agents were widely used as a first-line empirical treatment, despite possible narrower spectrum alternatives being adequate. Such a situation would not be surprising as we have already reported the lack of antibiotic policies and initiatives within the southern and eastern Mediterranean hospitals of the project.[22] It is, of course, well established that other factors, especially those that promote the spread of microorganisms within hospitals, are equally relevant in the epidemiology of resistance.[23] Even here, inadequately developed infection control programmes and heavy bed occupancy have already been identified as widespread, and they could equally be important contributors to the prevalence of nosocomial-resistant infections within the region.[22]

Over the project duration, the collection of reliable antibiotic consumption data proved to be more challenging than equivalent attempts to elucidate antimicrobial resistance in the same institutions. Several hospitals in the project were unable to source antibiotic consumption documentation, even when hospital pharmacies existed. Data acquisition proved impossible in facilities where antibiotics were purchased independently by the patients before their admission or where the patient's relatives usually buy antibiotics from a pharmacy or organization outside the hospital. Another interesting issue observed among many participants was the fact that drug formulations were procured by tender. As a result, bulk amounts of one particular drug tended to be obtained in one instance. In the case of interchangeable drugs (e.g. amoxicillin and ampicillin, co-amoxiclav and ampicillin/sulbactam etc.), when a tender expired, it was not uncommon to have a different active substance (not just a different brand name) replacing the previous one. This could give rise to otherwise unexplainable sudden total shifts from one drug to a similar one, from one period to the next, if consumption surveillance is undertaken over shorter periods of time. In addition, drug donations were reasonably widespread in a number of the Mediterranean hospitals. One of the hospitals totally relied on antibiotics being donated or procured independently for one-quarter of a year, with normal procurement re-established in the next quarter. Dependence on availability of donated antibiotics would therefore substantially influence antibiotic prescribing patterns in different time periods. Hospital specialists prescribing for clients of outpatient clinics, or providing initial doses of a post-discharge prescription, affected the ambulatory-to-hospital consumption mix in Cyprus. Some hospitals in the project also found it challenging to obtain valid and comparable information on hospital bed-days. These data were at times only available on a yearly basis and with considerable delay.

As in any sentinel surveillance study, one potential limitation related to the representativeness of the participating hospitals. This difficulty is always a particular problem in developing countries, where the pool of hospitals capable of partaking in a research project, especially one of a resource intensive nature like this study, is more restricted. The identification and recruitment of ARMed hospitals were exclusively the decision of the country coordinators who were deemed to be best qualified to identify adequate representativeness in the circumstances.

Despite the challenges and limitations, we conclude that the ARMed results have shed, for the first time, an insight into the prescribing patterns of a substantial cohort of hospitals in seven southern and eastern Mediterranean countries. The data obtained suggest that while the total quantity of antibiotic use in these hospitals may not differ excessively from neighbouring countries, an emphasis on wide-spectrum agents is evident. This may be extrapolated to suggest that reliance on broad-spectrum antibiotics could be a relevant driver behind the region's well-documented antimicrobial resistance problems. Monnet[24] has proposed, through mathematical modelling, that in environments where there are both a high prevalence of resistance as well as evidence of heavy antibiotic consumption, the area of improvement that is likely to have the biggest impact on resistance is the control of antibiotic use. Such improvement can be obtained through antibiotic stewardship programmes that aim to ensure that the use of antibiotics in hospitals is commensurate with the clinical circumstances and the local resistance epidemiology.[25] Like in many other hospitals worldwide, these stewardship programmes appear to be urgently required in institutions within the southern and eastern Mediterranean.

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Transparency declarations

None to declare.

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