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Antimicrobial overuse and misuse in the community in Greece and link to antimicrobial resistance using methicillin-resistant *S. aureus* as an example

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ABSTRACT

Both antimicrobial consumption and antimicrobial resistance are very high in Greece, ranking among the highest of Europe. The link between antimicrobial consumption and resistance is well-known. Here, we discuss the reasons of antimicrobial overuse in Greece in the community (such as self-medication, dispersion of antibiotics by pharmacies without prescription, over-prescription by physicians, patient expectations and liability pressure) and we explore the misuse of antibiotics for common community infections. Furthermore, we discuss how such overuse/misuse can drive antimicrobial resistance, using methicillin-resistance in *Staphylococcus aureus* as an example. *S. aureus* is one of the pathogens with high rates of resistance in Greece. Comparing the rate of antimicrobial susceptibility to non-beta lactams between methicillin-resistant and methicillin-sensitive *S. aureus* we highlight the antibiotics that have the potential to drive methicillin-resistance through co-selection. Based on the above we identify targets for intervention in order to reduce antimicrobial overuse/misuse in the community in Greece.

Contents

Introduction

According to the ECDC's (European Centre for Disease Prevention and Control) antimicrobial consumption database (ESAC-Net) antibiotic consumption in Greece ranks among the highest of Europe both in hospitals and in the community (https://ecdc.europa.eu/en/antimicrobial-consumption/database/rates-country). Antimicrobial resistance in Greece is similarly high [1,2].

It is well established that antimicrobial use is a main driver of antimicrobial resistance and limiting antimicrobial use has the potential to reduce resistance [3–5]. Furthermore, co-selection of resistance is possible, i.e., the use of one antibiotic can result in

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selection of strains that are co-resistant to other antibiotics, as has been shown in time-series analyses for several types of resistant pathogens [4,6,7]. Antibiotics of one class may also promote resistance to other antibiotics through enhanced mutagenesis, as is the case with fluoroquinolones [8].

The main aim of this narrative review is to explore the reasons of antimicrobial overuse and misuse in the community in Greece and to assess how rational selection of antibiotics for common infections in the community could reduce the selection pressures driving antimicrobial resistance. Considering the high rate of MRSA (methicillin-resistant *Staphylococcus aureus*) in Greece, *S. aureus* was selected as an example to illustrate the link between inappropriate antibiotic use and development of antimicrobial resistance.

Review methodology

We conducted a narrative review using PubMed (MEDLINE). To find studies reporting the antimicrobial susceptibility of *S. aureus* in Greece we conducted the following search in PubMed: aureus [ti] AND Greece AND (resistance OR resistant OR susceptibility). To find studies regarding antibiotic overuse and misuse in Greece the following search was conducted: (antibiotics OR antibiotic OR antimicrobial OR antimicrobials) AND (consumption OR overuse OR misuse OR inappropriate OR non-prescribed OR self-medication OR prescription) AND Greece. Furthermore, the bibliography of relevant articles was searched to identify more relevant articles.

Brief overview of antimicrobial susceptibility of *S. aureus* in Greece

Resistance of *S. aureus* to methicillin in Greece is among the highest of Europe both in hospitals [2] and in the community [9–13]. According to the latest data (2016) from the European Antimicrobial Resistance Surveillance Network (EARS-Net) (https://ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc) about 40% of invasive (from blood cultures or cerebrospinal fluid) *S. aureus* isolates in Greece are methicillin-resistant. This is in agreement with a national surveillance study conducted in Greece between 2012 and 2016 which showed that 39% of *S. aureus* isolates were MRSA [10]. Several other studies from Greece have described a high percentage of methicillin-resistance in a variety of infections caused by *S. aureus*, ranging from 29% to more than 50% even among children with community-associated *S. aureus* infections [9,11–13].

Of note is that MRSA is co-resistant to several non-beta-lactam antibiotics more often than MSSA. For example, resistance to clindamycin, tetracycline, erythromycin, fluoroquinolones and fusidic acid is significantly higher among MRSA isolates compared to MSSA isolates [9–12]. This is important when considering the antibiotic selection pressures driving methicillin-resistance. Fortunately, the in vitro activity of trimethoprim–sulfamethoxazole, rifampicin, mupirocin, linezolid, tigecycline, daptomycin and ceftaroline remains excellent [9–11,14].

Exploring the reasons of antibiotics overuse in the community in Greece

Although systemic antibiotics are prescription-only medications, self-medication is common in Greece both in urban and rural areas [15–18]. The major source of self-medication in Greece is acquisition from pharmacies without prescription and to a much lesser extent use of left-over antibiotics at home or from friends or relatives [16,17,19]. Illegal access to antibiotics without a prescription has also been described in other countries [20,21], however the percentage of systemic antibiotics sold at pharmacies without a prescription is higher in Greece compared to most other European countries [22]. Amoxicillin-clavulanate and second generation cephalosporins (i.e., medications that have the potential to select methicillin-resistant strains) are among the most common antibiotics dispensed without prescription [16], but even fluoroquinolones, which according to Greek law require a separate specific prescription, are often dispensed by pharmacies without prescription when requested by patients [15]. Of note is that, according to the authors' experience in primary care in rural areas, prescription of antibiotics are often requested by patients or even their pharmacists retrospectively, i.e. after the antibiotic has already been dispensed without physician consultation. This observation may not be generalizable to other areas but is in agreement with observation from Spain [23]. It nevertheless warrants exploration in future studies of antimicrobial overuse in the community in Greece.

Potential determinants of antibiotic dispensing without a medical prescription have been studied in another Mediterranean country (Spain) where self-medication is also prevalent, similar to Greece [24]. According to this study, antibiotics are often prescribed by pharmacists when the patient is known to have difficulty in gaining access to a doctor (a common problem in rural Greece). Furthermore, dispensing of antibiotics without prescription is motivated by the fear of losing a regular customer, as patients may try to obtain antibiotics without prescription at another pharmacy. Insufficient knowledge (such as not recognizing antibiotic resistance as a major health problem) and the belief that new antibiotics will be developed to solve the resistance issue are other attitudes that were found to be associated with dispensing antibiotics without prescription.

However, self-medication is not the only factor contributing to antibiotic overuse in Greece. Over-prescription of antibiotics by Greek physicians is also a major driver of antimicrobial over-consumption [19]. Similar to other countries [25–27], unnecessary prescription of antibiotics, especially for respiratory tract infections, is common in Greece [28]. Factors, such as patient expectations, liability pressure, fear of treatment failure without antibiotics, insufficient knowledge, influence by pharmaceutical companies [23,29], and potentially even financial incentives by pharma companies to doctors may contribute to over-prescription of antibiotics by physicians although the extent to which each of the above contribute to antibiotic over-prescription in Greece is unclear.

Especially in pediatric populations self-medication (administration of antibiotics by parents or pharmacists without consultation from a physician) is uncommon [17,28,30], suggesting that over-prescription by physicians is the main driver of antibiotic consumption among pediatric patients. Although one could speculate that parental pressure may be a major factor leading to over-prescription, this may not be the case in Greece [28,31]. The majority of Greek parents understand that most upper respiratory tract infections are self-limited, and although many would request an antibiotic prescription only a minority would be dissatisfied and would consider consulting another pediatrician if antibiotics were not prescribed [28,31]. Therefore, perceived patient expectations by physicians rather than actual patient expectations may drive antimicrobial prescriptions, as has been shown in studies from other countries [29].

Examples of incorrect antimicrobial prescription practices in Greece

As discussed above, antimicrobial resistance rates for several non-beta lactam antibiotics is higher in MRSA compared to MSSA. Furthermore, while MRSA is resistant to beta-lactams, MSSA

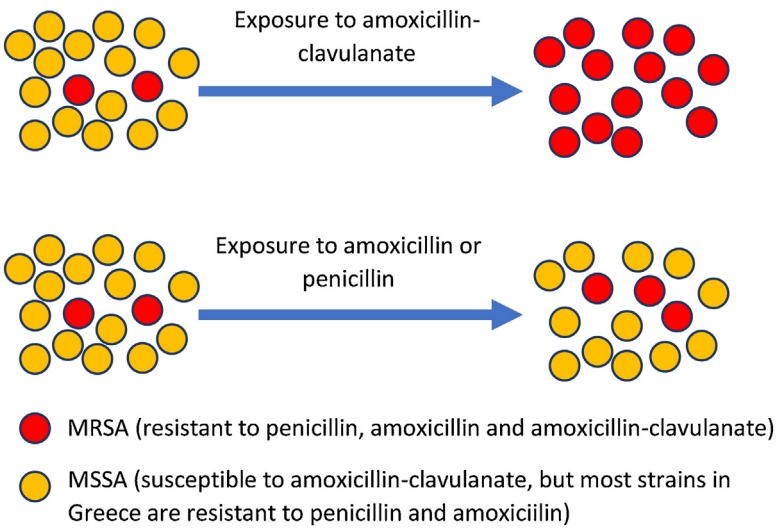

Fig. 1. Antibiotic selection pressure leading to methicillin-resistance.
Exposure to amoxicillin-clavulanate may allow the emergence of MRSA (methicillin-resistant *S. aureus*) over MSSA (methicillin-sensitive *S. aureus*). Similarly, exposure to other antibiotics (cephalosporins, clindamycin, macrolides, fluoroquinolones and fusidic acid) to which MRSA is more likely to be resistant compared to MSSA may also favor the emergence of MRSA. On the contrary, exposure to antibiotics to which both MSSA and MRSA strains are resistant (e.g. amoxicillin or penicillin) is not expected to select MRSA strains.

remains susceptible to cephalosporins (such as cefuroxime) and beta-lactam-combinations with beta-lactamase inhibitors (such as amoxicillin/clavulanate). Therefore, use of the above-mentioned antimicrobials has the potential to promote methicillin-resistance through co-selection (Fig. 1). Of note is that topical agents such as fusidic acid may also promote the rise of MRSA in the community through co-selection [32]. In this context it is worth mentioning that, according to the authors' experience, fusidic acid is commonly used by Greek patients without prescription for a variety of non-infectious skin conditions (even for mosquito bites). The latter observation warrants confirmation in prospective studies.

A good example of irrational antibiotic use in the community in Greece is the use of amoxicillin-clavulanate or other antimicrobials (such as macrolides and 2nd generation cephalosporins) for infections such as acute otitis media in children or tonsillopharyngitis [19,30,33–35] for which amoxicillin (or penicillin for tonsillopharyngitis) alone would be the recommended first choice [36,37]. Addition of clavulanate to amoxicillin, a common practice for the outpatient treatment of community-acquired pneumonia in Greece [33], may also be unnecessary as high-dose amoxicillin is sufficient according to guidelines [38,39]. The potential of amoxicillin-driven selection of MRSA is low, as both MRSA and most MSSA in Greece are resistant to penicillin and amoxicillin [11]. On the contrary, provided that staphylococcal coverage is not required, the unnecessary addition of clavulanate to amoxicillin or using alternative antimicrobials to which MRSA is more likely to be resistant than MSSA, can promote methicillin-resistance (Fig. 1). Of note is that despite the availability of national Greek guidelines, compliance with first-line antibiotics remains low among primary care physicians [33,34], although compliance among younger physicians may be higher [34], indicating the need for continuous educational courses to update practicing physicians.

Regarding skin and soft tissue infections, when coverage of *S. aureus* is indicated, empirical coverage of MRSA is necessary considering the high-rate of methicillin-resistance in Greece. Although clindamycin is often used for the empirical coverage of MRSA for skin and soft tissue, resistance of MRSA to clindamycin is high in Greece [9–11], and considering the higher rate of resistance to clindamycin in MRSA compared to MSSA this has the potential to co-select methicillin-resistance. On the contrary, resistance to trimethoprim-sulfamethoxazole remains low in both MSSA and MRSA [9–11] and clindamycin has not been found to be superior for the treatment of uncomplicated skin infections [40]. Therefore, trimethoprim-sulfamethoxazole may be a better first-line choice for the treatment of uncomplicated skin and soft tissue infections when coverage of MRSA is considered and may reduce antibiotic selection pressure favoring MRSA.

Could interventions and rational selection of antibiotics reduce methicillin-resistance?

Considering the above, interventions targeting patients, physicians and pharmacists are necessary. It has been shown that such interventions in Greek areas have the potential to at least rationalize the selection of antimicrobials [31]. However, there is a need for continuous (or at least repetitive) educational initiatives, as antibiotic use tended to revert back to previous levels at the end of the antimicrobial stewardship campaign [31]. Furthermore, it is important to expand such interventions to a national level. Using algorithms based on Centor criteria and rapid antigen detection testing also has the potential to reduce unnecessary antibiotic prescription for sore throat [41], however the test is often not available to public primary care physicians in Greece. Finally, a stricter enforcement of the Greek law, according to which all antibiotics are prescription-only drugs, is necessary to tackle the problem of over the counter antimicrobial sales by pharmacies.

Several studies have demonstrated the potential of antimicrobial stewardship to reduce methicillin-resistance [5,7,42,43]. Removal of key antibiotic selection pressures by restricting the use of the so-called "4C" (cephalosporins, co-amoxiclav, clindamycin and ciprofloxacin or more generally fluoroquinolones) and macrolides has been shown to reduce the rate of both hospital-associated and community-associated MRSA infections [5]. Interventions to rationalize the selection of antibiotics for common respiratory infections have been conducted successfully in parts of Greece resulting in a decrease in consumption of macrolides, 2nd generation cephalosporins, fluoroquinolones and the combination amoxicillin clavulanate [31], i.e. drugs that can drive the selection of methicillin-resistant *S. aureus* strains. This was achieved by replacing the above antibiotics with narrower-spectrum antibiotics (amoxicillin or penicillin) [31] that are less

likely to promote methicillin resistance considering that the majority of MSSA are non-susceptible to the latter antibiotics [11].

Examples of rationalization in selection of empirical regimens by primary care physicians that may help reduce antibiotic selection pressures favoring MRSA are the following: (1) limiting the unnecessary addition of beta-lactamase inhibitors and reducing the use of 2nd generation cephalosporins, macrolides or other alternatives when amoxicillin or penicillin alone are the guideline-recommended first-line treatments (such as for acute streptococcal pharyngitis, acute otitis media in children without risk factors for beta-lactam resistance or for community-acquired pneumonia when outpatient management is appropriate [36–39]), (2) favoring the use of trimethoprim-sulfamethoxazole (instead of clindamycin) as a first line agent for the treatment of uncomplicated skin and soft tissue infections that require coverage for MRSA [40]. Prospective studies are needed to demonstrate whether these suggestions can result in a reduction of methicillin-resistance in Greece.

Link between antimicrobial overuse in the community and rates of methicillin resistance in nosocomial infections

Antimicrobial use in the community could reasonably result in a higher rate of antimicrobial resistance in hospitals and vice-versa, considering the proven bi-directional spread of resistance between the community and hospitals. Furthermore, community-strains of *S. aureus* may actually be responsible for many hospital-onset infections, considering the well-established association between nasal carriage at admission and *S. aureus* infection with the same strain during hospital stay [44]. Finally, several studies have demonstrated the potential of antimicrobial stewardship to reduce methicillin-resistance, both in hospitals and in the community [5,7,42,43]. Based on the above, interventions that target antimicrobial consumption in the community have the potential to reduce methicillin-resistance both in the community and in nosocomial *S. aureus* infections. However, prospective studies are needed to confirm the validity of these assumptions.

Conclusion

The proportion of methicillin-resistance in *S. aureus* infections in Greece is among the highest of Europe, and co-resistance of MRSA to non-beta lactam antibiotics is very common. Antibiotic overuse, both in the community and in hospitals, is a major driver of high antimicrobial resistance in Greece. Both self-medication by patients and over-prescribing of antibiotics by physicians contribute to the problem. Moreover, irrational selection of antibiotics may further contribute to the selection of methicillin-resistant strains. National interventions are needed to reduce the dispensing of antibiotics by pharmacies without prescription, to limit unnecessary prescriptions of antibiotics by educating both patients and physicians, and to rationalize the selection of antibiotics for common bacterial infections.

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Competing interests

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Ethical approval

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