Review Article

Addressing the challenge of antibiotic resistance in Maltese healthcare settings

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Abstract

Antimicrobial resistance results in substantial adverse outcomes and negatively impacts mortality, morbidity and economic expenditure. This review focuses on the costs of antibiotic resistance to both patient as well as health-care settings and highlights interventions proven to be effective in curtailing its continued escalation. These concentrate predominantly on initiatives to improve antibiotic prescribing as well as prevent the spread of multi-resistant organisms, amongst which hand hygiene is of paramount importance. With the prevalence of resistance in Malta, amongst the highest in Europe, such interventions need acceptance and implementation by all stakeholders if the current alarming situation is to be controlled and possibly improved.

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Introduction

Antimicrobial resistance is increasing and brings with it the possibility of untreatable infections and a return to the pre-antibiotic era.[1] This phenomenon impinges on the quality of patient care through its associated mortality, morbidity and economic consequences. It also forces upon us the need to resort to more expensive and toxic antibiotics and develop new products to replace those which have been rendered ineffective.[2]

The threat of antimicrobial resistance has been identified as one of the major challenges facing public health by numerous scientific organisations, including the World Health Organization.[3] The challenge of the "Microbial Threat" is even recognised by the European Union (EU) through numerous communications over the past years culminating in the adoption of a community approach titled 'A strategy against the Microbial Threat' which was approved through the EU Council Resolution of the 8th of June 1999.[4]

The impact of antibiotic resistance

Antibiotic resistance impacts adversely on the ability to provide effective management of infectious diseases, whether they arise in the hospital or in the community. A meta-analysis of 31 published studies over 20 years identified an almost two-fold increased risk of mortality in methicillin resistant *Staphylococcus aureus* (MRSA) bacteraemia as opposed to the same infection caused by sensitive strains of the identical organism.[5] One major reason for this finding stems from the need to provide timely and targeted antimicrobial therapy for patients suffering from serious infections. The administration of effectives doses of the correct antibiotic as early as possible in the course of an infection is one of the major predictors of cure.[6] It is much more likely that empiric treatment would fail in an environment where there is a high prevalence of antimicrobial resistance, resulting in significant delay to provide effective therapy and leading to worsened outcomes.[7,8,9] In addition, antimicrobial alternatives for resistant organisms often carry significant side effects. This is particularly the case with glycopeptides used in the treatment of MRSA and both colistin and tobramycin which may be required for resistant Gram-negative organisms.[10,11] Furthermore, scenarios of potentially untreatable infections are already unfolding within both Gram positive bacteria such as enterococci and in Gram-negative bacilli, including pan-resistant *Acinetobacter spp*.[1]

Effect of antimicrobial resistance on healthcare facilities

The repercussions of resistance are not simply restricted to the individual patient. Resistance also has direct impact on health-care facilities.[12] Patients with resistant infections need longer duration of hospitalisation to treat their nosocomial infection.[13] This in turn impacts on the efficient running of hospitals, blocking beds and limiting throughput. Not only do patients with resistant infections utilise precious bed space and require additional expenses related to the hotel functions of a hospital but they invariably require treatment with more expensive antibiotics, which adds another financial element into the equation.[14] It is therefore not surprising that the cost of antibiotic resistance to society as a whole is very significant. In 1995, the national cost of resistance for the United States was estimated to approximate four billion dollars per year.[15] This figure is now likely to be substantially higher.

Antimicrobial resistance and antibiotic use

The direct link between antibiotic use and the subsequent development of resistance in hitherto sensitive strains of bacteria has long been acknowledged. Bacteria can become resistant to an antibiotic during exposure to that drug.[16] The factors that play a role within this process are highly complex and often difficult to predict. *S. aureus* develops resistance to vancomycin at very low frequency yet resistant strains rapidly follow the use of daptomycin, which is reasonably related.[17] Furthermore, it is not only the antibiotic class that appears to be relevant. The total level of antibiotic consumption in an institution also seems to be linked to the development of resistance. This has been shown through meta-analyses that have identified a strong relationship between MRSA prevalence and consumption levels.[18] It is therefore logical to conclude that attempts to reduce resistance should focus on reducing unnecessary use of antibiotics. Since acquisition of resistance in organisms exposed to narrow spectrum drugs is usually low, it is especially important to focus efforts on broad spectrum classes which are known to predispose most to resistance development.[19, 20]

Encouraging better use of antibiotics

Although the actual details of antibiotic stewardship programmes differ from one institution to another, two core strategies seem to be most effective.[21] These include Prospective Audit with intervention and feedback as well as a system of Prior Authorisation of antibiotic prescribing. Prospective auditing involves designated and trained members of an antibiotic team, who review patients on antibiotic therapy and provide unsolicited feedback to prescribers as to the appropriateness of their decisions. This approach has been shown to have numerous benefits. It retains the autonomy of prescribers and can be customised to the individual institution. If performed by open-minded individuals, it also stimulates education on antibiotic use and most importantly encourages interaction between colleagues. The disadvantage lies precisely in its voluntary nature; it requires an underlying culture of teamwork in order to succeed. Nevertheless in the right environments it has been shown to be very effective to improve appropriate antibiotic therapy, resulting in diminished use of broad spectrum agents as well as reduced expenditure, all without impacting adversely on patient outcomes.[22]

The second strategy focuses on enforced pre-authorisation of designated wide spectrum antibiotics. In such a programme, infectious disease and microbiology specialists would need to be contacted whenever certain antimicrobials (the span of restricted antibiotic classes differs between institutions) would be requested for treatment. Such a request would then be discussed between prescriber and endorser and if not deemed to be evidence based, replaced by a more appropriate alternative. Efforts to cut down on unnecessary glycopeptides use following outbreaks or significant increases in vancomycin resistant enterococci (VRE) have been shown to be successful.[23] Similar restrictions on the use of third generation cephalosporins in response to outbreaks of ceftazidime resistant *Klebsiella pneumoniae,* resulted in both an immediate as well as sustained reduction in resistant strains.[24]

Nevertheless, simply cutting down on antibiotic use is not a simple panacea for all the problems posed by multi-resistant infections. The most convincing evidence for such initiatives relates to the prevention of *Clostridium difficile* diarrhoea, where a level of sustained improvement has been identified following antibiotic prescribing interventions. On the other hand, out of ten investigated prescribing interventions aimed at reducing resistant Gram-negative bacteria, only one study showed changes that were likely to be clinically relevant. Very limited data are additionally available on the impact of prescribing interventions on Gram positive bacteria, including VRE and MRSA. [25]

The need for infection prevention and control in healthcare settings

These results suggest that antimicrobial control on its own is unlikely to be enough to fully achieve the desired endpoint. It is clear that in order to address the problem of antimicrobial resistance, efforts need to also simultaneously target the spread of resistant organisms within health-care facilities. In fact it has been shown that, except when colonisation pressure is low, antibiotic consumption only has a moderate effect on the prevalence of VRE and possibly other resistant infections.[25] The major predictor of acquisition is actually the number of colonised patients. This is because a greater number of colonised patients will lead to more contacts with the hands of health-care workers and therefore a greater possibility of cross transmission.

As a result, it is important to focus on the possible ways by which resistant organisms can be spread within a health-care facility and utilise this information to implement appropriate prevention and control strategies. The role of hands in the transmission of health-care associated infections has been known since 1847 when Semmelweiss reduced maternal mortality rates from puerperal fever in Vienna by simply forcing doctors to wash their hands before delivery.[26] In the intervening 150 years we have come to understand that hands of health-care

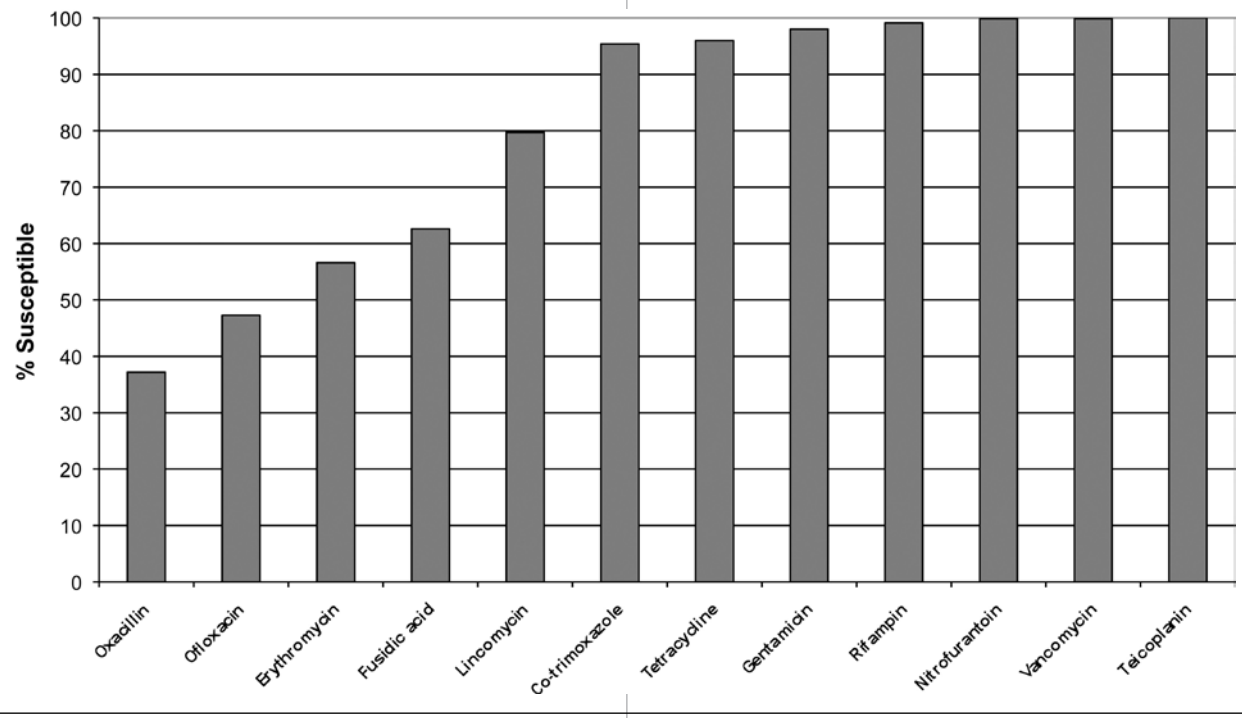
workers regularly become contaminated by micro-organisms which originate from the patients with whom they come into direct contact.[27] Furthermore there is clear evidence that these same organisms can also survive for substantial periods of time in the environment where they would act as a recurrent seed to again contaminate the hands of care providers.[28] Multi-resistant organisms such as MRSA and VRE have been isolated consistently both from the hands of health care workers as well as environmental locations which are subject to regular contact by those same hands.[29]

Efforts to prevent the spread of clonal multi-resistant organisms therefore need to concentrate on breaking the chain of transmission from the colonised or infected patients to other susceptible individuals via hands of health care workers. In theory this can be implemented by isolation precautions for all identified or presumptive patients carrying multi-resistant organisms and stringent compliance with hand hygiene protocols, especially if combined with a proactive screening programme. A three phase intervention has been described by Harbarth *et al.* with an initial period of no control measures, followed by two years of hand hygiene education, audit and feedback and then finally screening and single room isolation. The primary initiative stopped what had previously been an increasing trend of MRSA infections, which then further reduced following the isolation intervention.[30] One of the largest meta-analysis on the subject concluded that concerted efforts which focus on isolation can reduce MRSA levels, even in endemic circumstances.[31] Further expanding on this concept, there are additional studies which suggest that a designated isolation ward to house patients with multi-resistant pathogens provides the most effective results. A retrospective interrupted time series study over more than four years suggested that initial isolation in single rooms and cohorted beds failed to control MRSA spread but a policy change to isolate these cases in a designated separate facility resulted in a reduction in incidence, which was sustained over a prolonged period.[32]

Hand hygiene

Emphasis on improved hand hygiene compliance within health care facilities remains a paramount component for all infection control programmes and various models have been proposed to achieve the desired results. The study that is most often quoted in the literature is the one undertaken by Pittet *at al.* in Geneva, Switzerland where improvement in hand hygiene compliance through the introduction of alcoholic hand rub resulted in an increase of hand hygiene rates from 48% to 66% and a concurrent reduction in both overall rates of health care associated infections and specifically MRSA transmission.[33] Based to a certain degree on the results of Pittet's work, alcohol hand rub has become the mainstay of the latest recommendations, including those issued by the World Health Organization in its *Clean Care is Safer Care* campaign.[34] Significant reductions in MRSA have been reported following alcohol rub introduction and promotion in hospitals.[35] In addition to providing more convenient facilities, many institutions have also focused their efforts to encourage their staff to use those same facilities more appropriately and regularly. One way in which this has been done is through audits of hand hygiene compliance and feedback to the staff being observed. Decrease in health-care associated infection prevalence and increase in hand hygiene compliance has been reported using such an approach as part of a multi-modal intervention strategy.[36]

Figure 1: *Overall proportions of resistance within S. aureus strains isolated at the Microbiology Laboratory of Mater Dei Hospital during the year 2008*



Local antimicrobial resistance epidemiology

The local state of affairs in Malta appears to be quite alarming with various drug-bug combinations exhibiting considerable levels of resistance, particularly within healthcare settings. A review of the antimicrobial susceptibility data of pathogens isolated at the Microbiology Laboratory of Mater Dei Hospital in the year 2008, indicates that the overall oxacillin (methicillin) sensitivity of *S. aureus* strains was only 37% (Figure 1). In addition, only about half of these isolates were sensitive to macrolides, quinolones and fusidic acid, the latter almost certainly the consequence of acknowledged abuse of topical preparations in the community. Ironically it is the older and less popular pharmaceuticals such as tetracyclines, lincosamides, nitrofurantoin and co-trimoxazole that show the best susceptibility profiles as well as antimicrobials whose availability is restricted (glycopeptides and rifampicin).

The situation is just as serious for *Pseudomonas aeruginosa*, typically associated with the most immunocompromised patients. Ceftazidime, piperacillin-tazobactam and ciprofloxacin – all commonly used agents for such infections – are effective for less than 70% of local isolates (Figure 2). Carbapenems, so often the final resort, are only marginally superior in terms of susceptibility. The preparations that can offer best microbiological optimism (tobramycin, amikacin and colistin) are in turn characterised by toxic side effects that preclude widespread use. Even in the case of *Escherichia coli*, a pathogen not commonly associated with acquired resistance, various therapeutic challenges exist. Indeed local strains are already substantially unresponsive to commonly used agents, including penicillin derivates and fluoroquinolones (Figure 3).

A potential criticism of such data is that it includes pooled strains, a proportion of which are likely to be colonisers and contaminants and therefore clinically insignificant. It is for this reason that more attention is being placed upon blood culture isolates which, if taken properly, are guaranteed to be relevant. Indeed the European Antimicrobial Resistance Surveillance System (EARSS: available from www.rivm.nl/earss) utilises only such data to provide an epidemiological picture of antimicrobial resistance in the European region. Unfortunately, the most recent EARSS report highlights Malta as the country having the highest proportion of MRSA within the whole European network; more than 50% of *S. aureus* blood culture isolates tested methicillin resistant in 2007.[37] Furthermore trend analysis over the past 8 years suggests a consistent and statistically significant increase over this time period (Figure 4). Quinolone resistance in *E. coli* bacteraemia isolates has – like MRSA – also increased unabated in the past years, reaching levels around 35% in 2007 (Figure 5). Equally worrying is the novel appearance, and apparent escalation, of *E. coli* strains that test non-susceptible to third generation cephalosporins. This would strongly suggest that highly pathogenic strains are rapidly developing extended-spectrum beta-lactamase (ESBL) activity, which further decreases therapeutic options in serious infections such as septicaemia.

These results are not in themselves genuinely surprising since the risk factors identified by this review have already been shown to be prevalent in healthcare facilities in this country. Per capita antibiotic consumption within tertiary care is one of the highest in Europe. Use of wide spectrum penicillins, cephalosporins and quinolones is significantly higher than equivalent medians at both pan-European and even Mediterranean comparison.[38] These three groups have been implicated as drivers of MRSA as well as ESBL and quinolone resistance in Gram-negatives.[39] In addition, published data support a hypothesis that cross-transmission of resistant organisms is being facilitated through inadequate compliance with infection control protocols, especially in terms of lack of hand hygiene. A recent study reported that overall hand hygiene compliance amongst doctors before patient contact was only 22.7% and ranged as low as 9.9% in some specialties.[40]

Conclusion

It is therefore critical to address this escalating situation if we are not to be faced with impossible restricted therapeutic choices in the treatment of serious infections in the near future. This is not the first time that such a call to arms has been made.

Figure 2: *Overall proportions of resistance within P. aeruginosa strains isolated at the Microbiology Laboratory of Mater Dei Hospital during the year 2008*

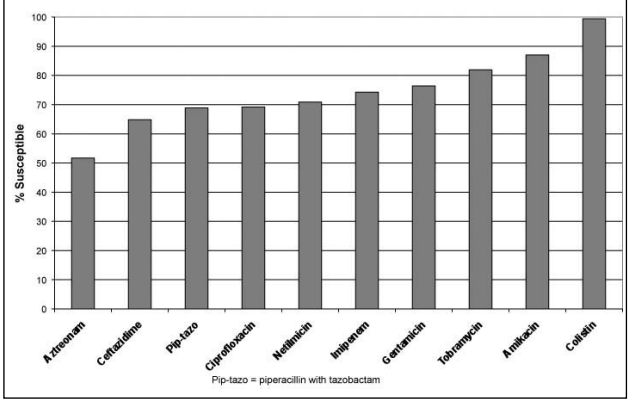


Figure 3: *Overall proportions of resistance within E. coli strains isolated at the Microbiology Laboratory of Mater Dei Hospital during the year 2008*

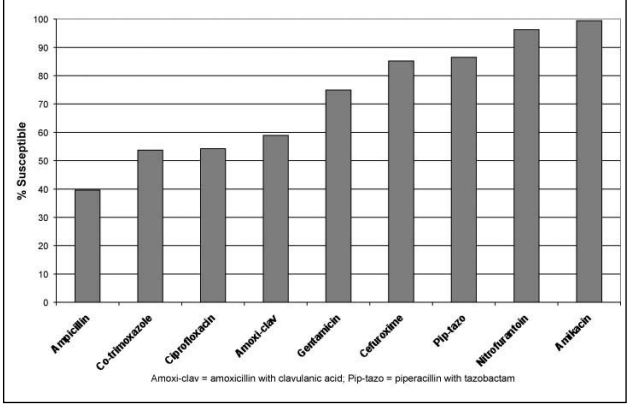


Figure 4: *Proportions of methicillin resistance in S. aureus isolates (MRSA) from blood cultures, as reported to the European Antimicrobial Resistance Surveillance System network by European countries from 1999 to 2007 (Malta = MT); reproduced with permission from EARSS Annual Report 2007. [Only European countries that reported 20 isolates or more per year for at least three years are included. The arrows indicate significant trends. The asterisks indicate significant trends in the overall national data that were, non-significantly, supported by data from laboratories reporting all nine years]*

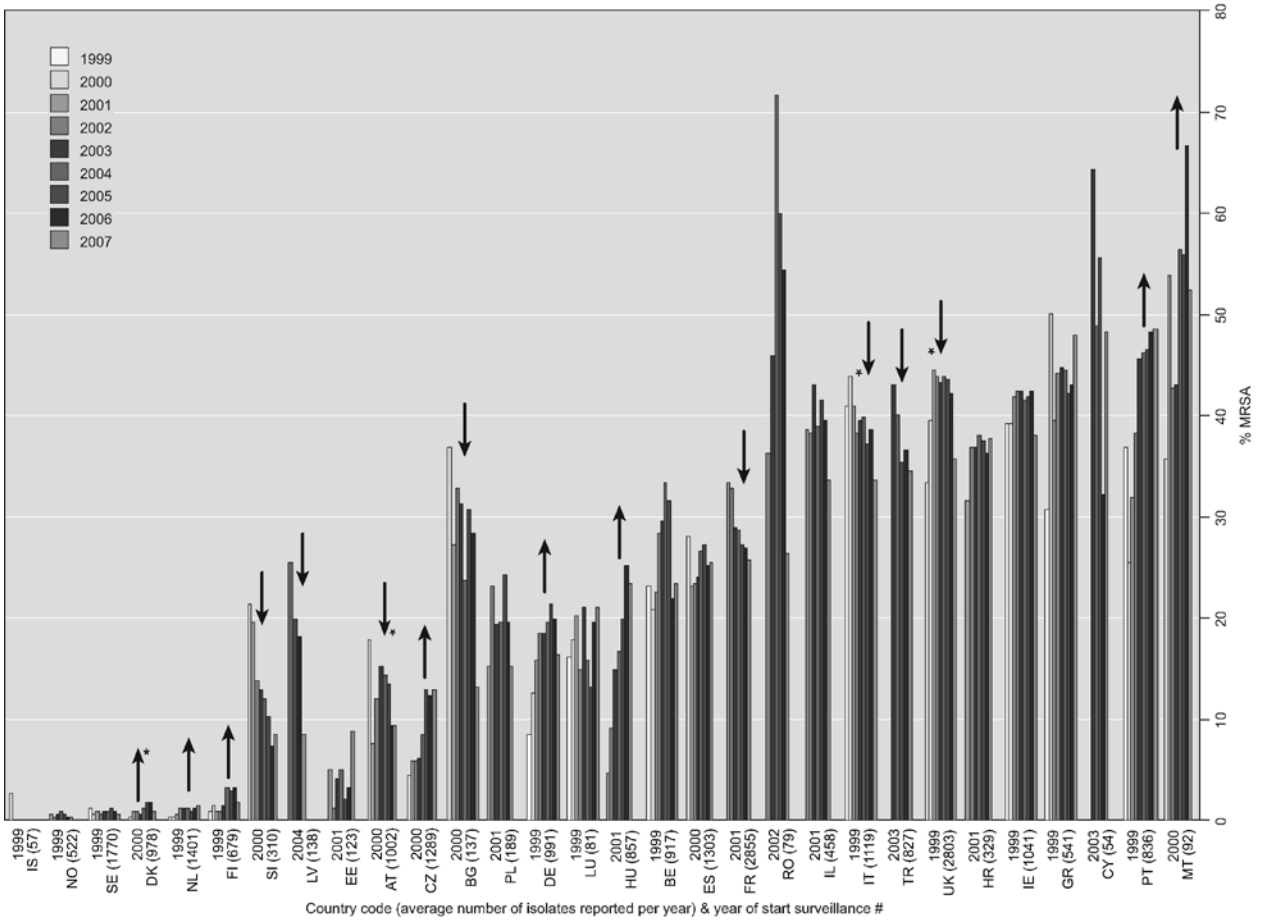
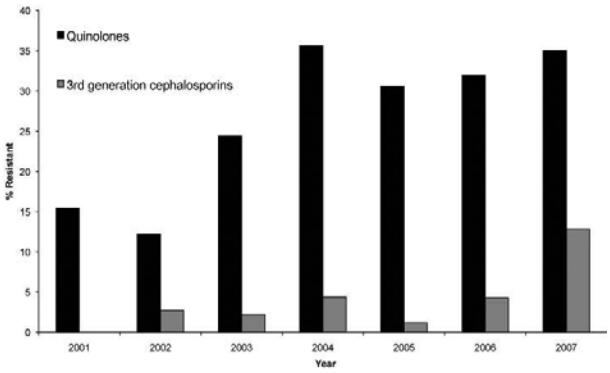


Figure 5: *Yearly proportions of quinolone and third generation cephalosporin resistance in blood culture E. coli isolates reported by Malta to the European Antimicrobial Resistance Surveillance System network between 2000 and 2007; as accessed from the EARSS interactive database [www.rivm.nl/earss]*



Very similar conclusions were included in a comprehensive multi-stakeholder report issued almost a decade ago.[41] The recent establishment of a National Antibiotic Committee, with legislative backing, promises to provide a base from which to kick-start effective interventions aimed at halting, and hopefully reversing, this consistent trend of rising antimicrobial resistance.

There is no doubt what those interventions need to be: more judicious antibiotic prescribing attitudes together with greater ownership and accountability of infection control policies and procedures. The way forward is quite obvious; the only uncertainty lies in getting all stakeholders to buy into it and thereby translate words into day-to-day practice.

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